Conversion of Some Pyrimidine 2'-Deoxyribonucleosides into the Corresponding 2',3'-Didehydro-2',3'-dideoxynucleosides

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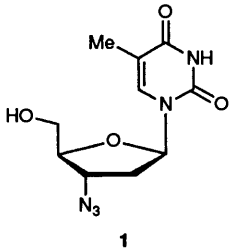
Thymidine **4b** was converted into 2,3'-anhydro-1-(2'-deoxy-β-D-*threo*-pentofuranosyl)thymine **7b** in ~65% isolated yield by being heated at 155 °C with an excess of diphenyl sulfite and 1-methylimidazole in *N,N*-dimethylacetamide solution. 2'-Deoxyuridine **4a**, 2'-deoxy-5-ethyluridine **4c** and 2'-deoxy-5-fluorouridine **4d** were similarly converted into 2,3'-anhydronucleosides which were isolated as their 5'-*O*-(*tert*-butyldimethylsilyl) derivatives **8a**, **8c** and **8d** in 51, 50 and 59% yield, respectively. When the oxetane derivatives **5a–d**, prepared by the literature procedure from the parent 2'-deoxynucleosides **4a–d**, were heated with an excess of sodium hydride in *N,N*-dimethylacetamide solution at 100 °C, they were converted into the corresponding 2',3'-didehydro-2',3'-dideoxynucleosides **6a–d** in 68, 76, 69 and 74% isolated yield, respectively. The latter compounds were similarly prepared from the 2,3'-anhydronucleosides **7a–d** in 71, 81, 69 and 74% isolated yield, respectively. 2,3'-Anhydro-5'-*O*-(*tert*-butyldimethylsilyl)-2'-deoxy-5-(trifluoromethyl)- and -5-iodo-1-(β-D-*threo*-pentofuranosyl)uracil **8e** and **8f**, which were themselves prepared from the parent 2'-deoxynucleosides **4e** and **4f**, respectively, in ~60 and 50% yield, were converted by a three-step procedure *via* the intermediate 2'-deoxy-3'-(phenylseleno) derivatives **10e** and **10f** into the corresponding 2',3'-didehydro-2',3'-dideoxynucleosides **6e** and **6f** in 52 and 49% overall yield, respectively. Compound **8e** was also converted into 2',3'-dideoxy-5-(trifluoromethyl)uridine **11b** and 3'-azido-2',3'-dideoxy-5-(trifluoromethyl)uridine **11c** in 49 and 66% overall yield, respectively.

The discovery that 3'-azido-3'-deoxythymidine (AZT, **1**) and a number of related 2',3'-dideoxynucleoside derivatives possess high anti-HIV activity[1,2] has led, in the past few years, to a considerable increase in research in this area of nucleoside chemistry. The 2',3'-didehydro-2',3'-dideoxynucleosides comprise one group of nucleoside analogues which has been investigated in this connection and indeed 2',3'-didehydro-3'-deoxythymidine **2** and 2',3'-didehydro-2',3'-dideoxycytidine **3** have both been found[1] to be powerful anti-HIV agents.



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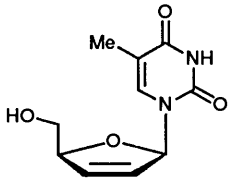

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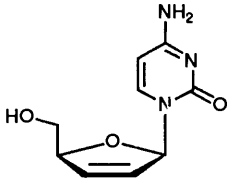

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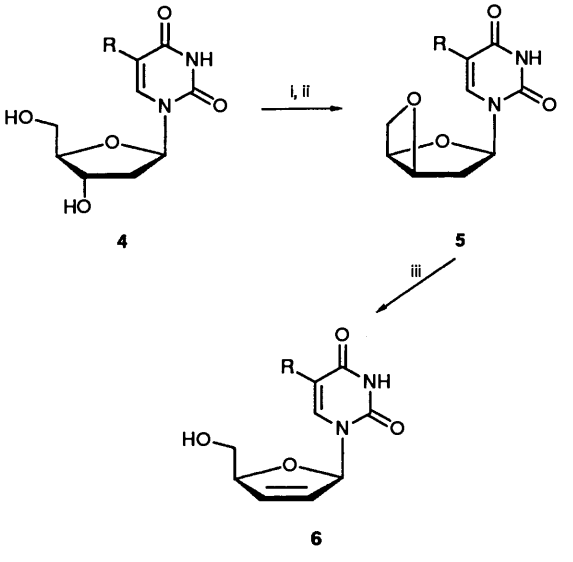
2',3'-Didehydro-2',3'-dideoxynucleosides of general formula **6** can be prepared from the corresponding 2'-deoxynucleosides[3–9] or ribonucleosides.[10–14] The present study is concerned with the conversion of 2'-deoxyribonucleosides **4** into 2',3'-didehydro-2',3'-dideoxynucleosides **6**. The most straightforward procedures involve subjecting either the corresponding nucleoside oxetane derivatives (**5**, Scheme 1) or the 2,3'-anhydronucleosides (**7**, Scheme 2) to base-promoted eliminations. However, if the base residues themselves are sensitive to the strong bases required to effect these eliminations, an alternative procedure (see below) is required.



a; R = H; **b**; R = Me; **c**; R = Et; **d**; R = F (**6b≡2**)

Scheme 1 *Reagents and conditions:* i, $MeSO_2Cl$, C_5H_5N; ii, aq. NaOH, reflux, 1 h; iii, NaH, DMA, 100 °C, 35–45 min

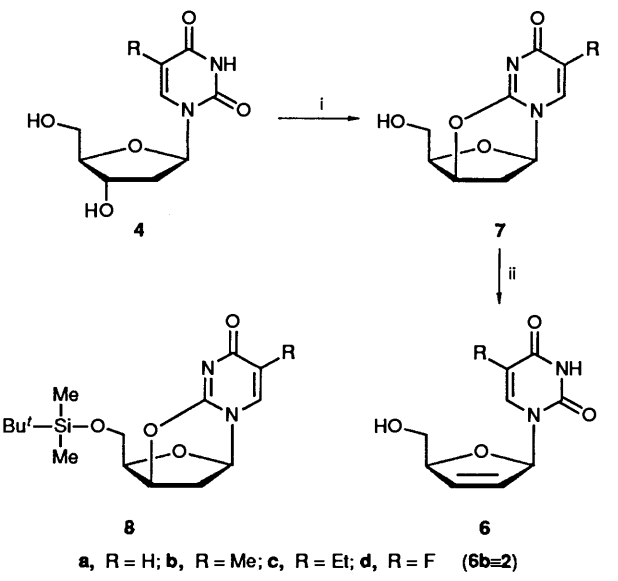
Almost thirty years ago, Horwitz *et al.* showed[3c] that 2'-deoxyuridine **4a** and thymidine **4b** could readily be converted into 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-uracil and -thymine (**5a** and **5b**; Scheme 1), respectively, by converting them first into their 3',5'-di-*O*-mesyl derivatives and then by heating the crude products, under reflux, with an excess of aq. sodium hydroxide. Following this procedure, we have converted 2'-deoxyuridine **4a**, thymidine **4b**, 2'-deoxy-5-

ethyluridine **4c** and 2′-deoxy-5-fluorouridine **4d** into the corresponding oxetane derivatives (**5a**, **5b**, **5c** and **5d**, respectively) in 65, 68, 62 and 49% isolated yield. Horwitz *et al.* further showed[3c] that when anhydro compounds **5a** and **5b** were in turn allowed to react with 2.0 mol equiv. of potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) solution at room temperature, 2′,3′-didehydro-2′,3′-dideoxyuridine **6a** and 2′,3′-didehydro-3′-deoxythymidine (d4T) **2**, respectively, were obtained in good yield. As d4T **2** has been found to be a highly potent and selective anti-HIV agent,[1] the reaction between the oxetane **5b** and potassium *tert*-butoxide (1.6 mol. equiv.) in DMSO solution at room temperature has recently been scaled up,[5] and d4T **2** was obtained in 57% isolated yield. We believe that this key elimination reaction (*i.e.*, the conversion of oxetanes **5** into unsaturated furanosides **6**; Scheme 1) can be effected more efficiently with sodium hydride (~ 3.0 mol equiv.) in *N*,*N*-dimethylacetamide (DMA) solution at 100 °C, and we now report that substrates **5a**, **5b**, **5c** and **5d** were converted in this way into compounds **6a**, **2**, **6c** and **6d**, respectively, in 68, 76, 69 and 74% isolated yield. The sodium hydride-promoted conversion of compound **5b** into d4T **2** (in 76% isolated yield) was carried out on a 0.03 molar scale while the potassium *tert*-butoxide-promoted conversion of compound **5b** into d4T **2** (in 57% isolated yield) was carried out on a 0.4 molar scale. It can be seen that the overall yield of d4T **2** obtained *via* the oxetane route (Scheme 1) with sodium hydride as base was almost 52% for the three steps, starting from thymidine **4b**.

We recently reported[15] that thymidine **4b** could be converted into 2,3′-anhydro-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)thymine **7b** (Scheme 2) by being heated with an excess of diphenyl sulfite[16] (see Experimental section for preparation) in the presence of 1-methylimidazole in DMA solution at ~155 °C, and that anhydro compound **7b** could easily be isolated from the products in almost 65% yield. Other workers[17] have recently converted **4b** into **7b** by a three-step process, also in ~65% yield. We now report that when unprotected compound **7b** was heated (Scheme 2) with ~3.0 mol. equiv. of sodium hydride in DMA at 100 °C for 30 min, d4T **2** was obtained in 81% isolated yield. Therefore, using this approach, it is possible to convert thymidine **4b** into d4T **2** in two steps in ~52.5% overall yield. Horwitz *et al.*[3c] had previously reported that when the 5′-*O*-trityl derivative of compound **7a** was treated with potassium *tert*-butoxide in DMSO at room temperature, the 5′-*O*-trityl derivative of compound **6a** was obtained in good yield. Khwaja and Heidelberger[4] subsequently used the same procedure to convert the unprotected anhydro compound **7d** into compound **6d**, also in good yield.

Although unprotected 2′-deoxyuridine **4a**, 2′-deoxy-5-ethyluridine **4c** and 2′-deoxy-5-fluorouridine **4d** also underwent cyclization when they were heated with diphenyl sulfite under the above conditions (Scheme 2), attempts to isolate the resulting 2,3′-anhydronucleosides **7a**, **7c** and **7d** in a pure state were unsuccessful. The crude products of the cyclization reactions were therefore treated with *tert*-butylchlorodimethylsilane (TBDMSCl) and imidazole in acetonitrile to give their 5′-*O*-(*tert*-butyldimethylsilyl) derivatives **8a**, **8c** and **8d**, which were easily isolated as crystalline solids in yields of 51, 50 and 59%, respectively. Desilylation of the latter compounds **8a**, **8c** and **8d** was readily effected by treating them with ~2 mol equiv. of tetraethylammonium fluoride (TEAF) in acetonitrile at room temperature for 2 h, and the unprotected 2,3′-anhydronucleosides **7a**, **7c** and **7d** were thereby obtained as crystalline solids in yields of 65, 64 and 67%, respectively. Treatment of these anhydronucleosides **7a**, **7c** and **7d** with ~3 mol equiv. of sodium hydride in DMA at 100 °C for 30 min (Scheme 2) gave the corresponding 2′,3′-didehydro-2′,3′-dideoxynucleosides **6a**, **6c** and **6d** in isolated yields of 71, 69 and 74%, respectively.

While the 2,3′-anhydronucleoside route (Scheme 2) appears

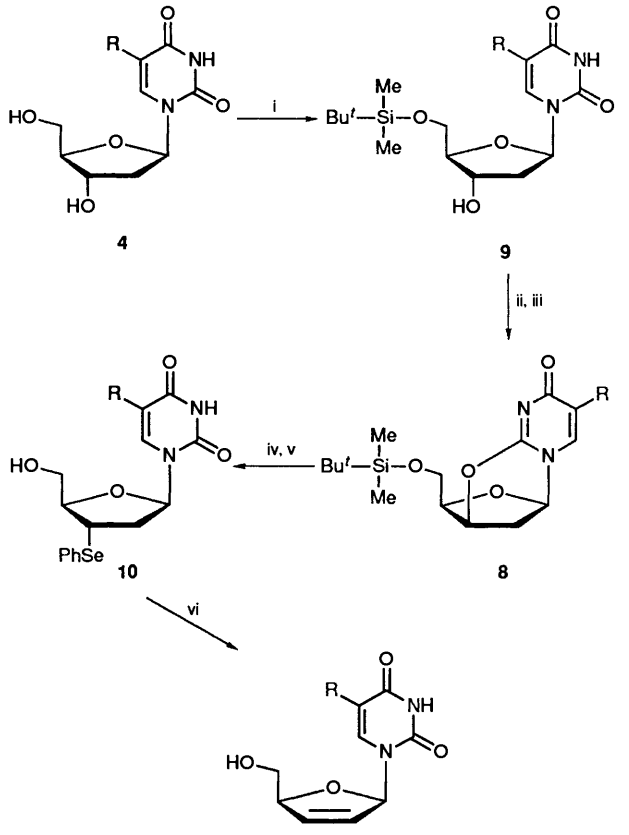


Scheme 2 *Reagents and conditions:* i, $(PhO)_2SO$, 1-methylimidazole, DMA, 155 °C, 20–45 min; ii, NaH, DMA, 100 °C, 30 min

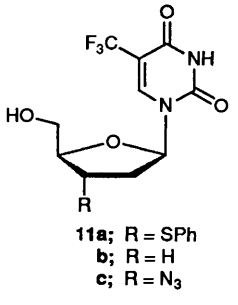
to be both a convenient and relatively efficient procedure for the conversion of thymidine **4b** into d4T **2**, the extra two steps (*i.e.*, silylation and desilylation) needed in the isolation of the other pure 2,3′-anhydronucleosides **7a**, **7c** and **7d** make this route less convenient for the preparation of the other 2′,3′-didehydro-2′,3′-dideoxynucleosides **6a**, **6c** and **6d**. It would seem that the latter compounds are better prepared by the oxetane route (see Scheme 1 and above). However, as both the oxetane and the 2,3′-anhydronucleoside routes (Schemes 1 and 2) involve the use of a strong base (*i.e.*, sodium hydride or potassium *tert*-butoxide), neither of them is suitable for the preparation of 2′,3′-didehydro-2′,3′-dideoxynucleosides in which the base residues are themselves base sensitive. Therefore, as both 2′-deoxy-5-(trifluoromethyl)uridine **4e** and 2′-deoxy-5-iodouridine **4f** decomposed when treated either with sodium hydride in DMA at 100 °C or with potassium *tert*-butoxide in DMSO at room temperature, a third route was required for the conversion of the latter 2′-deoxynucleosides **4e** and **4f** into the corresponding 2′,3′-didehydro-2′,3′-dideoxynucleosides **6e** and **6f**, respectively.

The six-step procedure used for the conversion of unprotected diols **4e** and **4f** into unsaturated furanosides **6e** and **6f**, respectively, is indicated in outline in Scheme 3. The parent 2′-deoxynucleosides **4e** and **4f** were first converted into their 5′-*O*-(*tert*-butyldimethylsilyl) derivatives **9e** and **9f**, which were isolated as crystalline solids in 88 and 76% yield, respectively. The latter compounds were then converted into the corresponding 2,3′-anhydronucleoside derivatives **8e** and **8f** by a two-step process (mesylation with methanesulfonyl chloride in pyridine solution, followed by cyclization with diisopropylethylamine in propan-1-ol solution) in 73 and 68% isolated yield, respectively.

Compounds **8e** and **8f** were then allowed to react with an excess of sodium phenyl selenide, prepared[18] from diphenyl diselenide and sodium metal in hexamethylphosphoric triamide (HMPA)–tetrahydrofuran (THF), and the products thereby obtained were treated with TEAF in acetonitrile to give the corresponding 2′-deoxy-3′-(phenylseleno)nucleoside derivatives **10e** and **10f**. These phenylseleno derivatives were then treated with a large excess of hydrogen peroxide in THF–water at 0 °C to give the target 2′,3′-didehydro-2′,3′-dideoxynucleosides **6e** and **6f**. These compounds which, to the best of our knowledge, have not previously been reported in the literature, were obtained in 52 and 49% overall isolated yield for the three steps starting from anhydrido compounds **8e** and **8f**, respectively. Unfortunately,



Scheme 3 *Reagents and conditions:* i, TBDMSCl, C_5H_5N; ii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; iii, Pr^i_2NEt, PrOH, reflux; iv, PhSeNa, HMPA, THF, 50 °C; v, Et_4NF, MeCN; vi, H_2O_2, aq. THF, 0 °C



neither compound **6e** nor compound **6f** showed significant anti-HIV activity in *in vitro* tests. After the completion of our studies, two other groups [8,9] described the use of sodium phenyl selenide in the conversion of 2,3′-anhydro-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)thymine derivatives into d4T **2** by procedures closely similar to that indicated above in Scheme 3.

The protected 2,3′-anhydronucleoside derivative **8e** also proved to be a useful intermediate in the preparation of 2′,3′-dideoxy-5-(trifluoromethyl)uridine [19] **11b** and 3′-azido-2′,3′-dideoxy-5-(trifluoromethyl)uridine [20] **11c** (trifluoro-AZT). First, the anhydro compound **8e** was heated with an excess each of thiophenol and tripropylamine in DMA at 120 °C for 6 h, and the products were treated with TEAF in acetonitrile to give the putative phenylthio derivative **11a**. When the latter compound was heated with Raney nickel in ethanol solution, under reflux, compound **11b** was obtained and was isolated as a crystalline solid in 49% overall yield for the three steps. Finally, when compound **8e** was heated with ~3 mol equiv. of lithium azide in DMA [15] at 120 °C for 2 h, and the products treated with TEAF in acetonitrile, the azide **11c** was obtained and isolated in 66% overall yield for the two steps.

Experimental

M.p.s were measured with a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra, unless otherwise stated, were measured at 360 MHz with a Bruker AM 360 spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Tetramethylsilane was used as an internal standard, and *J*-values are given in Hz. UV spectra were measured with a Perkin-Elmer Lambda-3 spectrophotometer. Merck silica gel 60 F_{254} TLC plates were developed in solvent systems A [chloroform–methanol (9:1 v/v)] and B [butan-1-ol–acetic acid–water (5:2:3 v/v)]. Merck silica gel H was used for short-column chromatography. Acetonitrile, THF, triethylamine, pyridine, and diisopropylethylamine were dried by heating, under reflux, over calcium hydride and were then distilled; DMA, 1-methylimidazole and HMPA were dried by distillation over calcium hydride under reduced (water-pump) pressure; diethyl ether was dried over sodium wire before distillation.

1-(3,5-*Anhydro*-2-*deoxy*-β-D-threo-*pentofuranosyl*)*uracil* **5a**.—Methanesulfonyl chloride (0.47 cm^3, 6.0 mmol) was added to a stirred solution of 2′-deoxyuridine **4a** (0.456 g, 2.0 mmol) in anhydrous pyridine (5 cm^3) at 0 °C (ice–water-bath) and the resulting solution was stirred for a further period of 30 min at room temperature. The products were then poured into ice–water (~50 g), and the resulting precipitate was washed with ice-cold water. The latter material and aq. sodium hydroxide (0.28 g, 7.0 mmol in 25 cm^3) were heated together, under gentle reflux, for 1 h. The solution obtained was cooled, neutralized with 1.0 mol dm^{-3} hydrochloric acid, and then concentrated to dryness under reduced pressure. The residue was extracted with boiling acetone (2 × 50 cm^3), the combined extracts were evaporated under reduced pressure, and the residue was fractionated by chromatography on silica gel. Elution of the column with chloroform–ethanol (9:1 v/v), concentration of the appropriate fractions, and crystallization from ethanol gave 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)uracil **5a** (0.273 g, 65%), m.p. 215 °C (lit.,[3c] 206–210 °C); R_f 0.43 (system A); δ_H[$(CD_3)_2SO$] 2.50 (2 H, m), 4.02 (1 H, dd, *J* 1.8 and 8.1), 4.70 (1 H, dd, *J* 4.1 and 8.2), 4.92 (1 H, m), 5.49 (1 H, m), 5.72 (1 H, dd, *J* 2.1 and 8.1), 6.52 (1 H, t, *J* 5.2), 8.18 (1 H, d, *J* 8.2) and 11.39 (1 H, br s); δ_C[$(CD_3)_2SO$] 37.10, 75.11, 80.06, 86.87, 88.45, 102.10, 141.08, 151.14 and 163.09.

1-(3,5-*Anhydro*-2-*deoxy*-β-D-threo-*pentofuranosyl*)*thymine* **5b**.—Thymidine **4b** (0.968 g, 4.0 mmol) was treated as above with methanesulfonyl chloride (0.94 cm^3, 12.0 mmol) in anhydrous pyridine (10 cm^3) and, after work-up, the crude 3′,5′-di-*O*-mesyl derivative was heated for 1 h, under reflux, with aq. sodium hydroxide (0.56 g, 14.0 mmol in 50 cm^3). Work-up and purification of the products gave, after crystallization from ethanol, 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)thymine **5b** (0.613 g, 68%), m.p. 187 °C (lit.,[5] 188–190 °C); R_f 0.42 (system A); δ_H[$(CD_3)_2SO$] 1.79 (3 H, d, *J* 0.9), 2.47 (2 H, m), 4.04 (1 H, dd, *J* 1.6 and 8.0), 4.69 (1 H, dd, *J* 4.0 and 8.1), 4.89 (1 H, m), 5.48 (1 H, m), 6.51 (1 H, t, *J* 5.4), 8.02 (1 H, m) and 11.34 (1 H, br s); δ_C[$(CD_3)_2SO$] 12.41, 37.22, 75.25, 79.93, 86.97, 88.33, 109.75, 136.61, 151.21 and 163.74.

1-(3,5-*Anhydro*-2-*deoxy*-β-D-threo-*pentofuranosyl*)-5-*ethyluracil* **5c**.—2′-Deoxy-5-ethyluridine **4c** (0.512 g, 2.0 mmol) was treated as above with methanesulfonyl chloride (0.47 cm^3, 6.0

mmol) in anhydrous pyridine (5 cm^3) and, after work-up, the crude 3′,5′-di-*O*-mesyl derivative was heated for 1 h, under reflux, with aq. sodium hydroxide (0.28 g, 7.0 mmol in 25 cm^3). Work-up and purification of the products gave, after crystallization from ethanol, the title compound (0.295 g, 62%) (Found: C, 55.1; H, 6.1; N, 11.5. Calc. for $C_{11}H_{14}N_2O_4$: C, 55.5; H, 5.9; N, 11.8%), m.p. 173 °C (lit.,[21] 174–175 °C); R_f 0.41 (system A); $\delta_H[(CD_3)_2SO]$ 1.03 (3 H, t, *J* 7.4), 2.23 (2 H, m), 2.50 (2 H, m), 4.02 (1 H, dd, *J* 1.7 and 8.1), 4.72 (1 H, dd, *J* 4.1 and 8.1), 4.91 (1 H, m), 5.50 (1 H, m), 6.57 (1 H, t, *J* 5.3), 8.04 (1 H, m) and 11.35 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 12.38, 19.54, 37.08, 75.23, 79.99, 87.10, 88.30, 115.55, 136.02, 151.05 and 163.29.

1-(3,5-*Anhydro*-2-*deoxy*-β-D-threo-*pentofuranosyl*)-5-*fluorouracil* **5d**.—2′-Deoxy-5-fluorouridine **4d** (0.984 g, 4.0 mmol) was treated as above with methanesulfonyl chloride (0.94 cm^3, 12.0 mmol) in anhydrous pyridine (10 cm^3) and, after work-up, the crude 3′,5′-di-*O*-mesyl derivative was heated for 1 h, under reflux, with aq. sodium hydroxide (0.56 g, 14.0 mmol in 50 cm^3). Work-up and purification of the products gave, after crystallization from ethanol, the *title compound* (0.446 g, 49%) (Found: C, 47.55; H, 3.8; N, 12.0. $C_9H_9FN_2O_4$ requires C, 47.4; H, 4.0; N, 12.3%), m.p. 188 °C; R_f 0.40 (system A); $\delta_H[(CD_3)_2SO]$ 2.46 (1 H, m), 2.59 (1 H, m), 4.07 (1 H, dd, *J* 1.5 and 8.2), 4.72 (1 H, dd, *J* 4.1 and 8.2), 4.92 (1 H, m), 5.51 (1 H, m), 6.53 (1 H, m), 8.42 (1 H, d, $J_{F,H}$ 7.4) and 11.92 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 36.85, 75.32, 80.28, 87.03, 89.01, 125.60 (d, $J_{C,F}$ 34.7), 139.95 (d, $J_{C,F}$ 230.6), 149.89 and 157.09 (d, $J_{C,F}$ 26.3).

Diphenyl Sulfite.[16]—A solution of freshly distilled thionyl dichloride (49.04 cm^3, 0.672 mol) in dry diethyl ether (50 cm^3) was added during 20 min to a stirred, dry solution of phenol (131 g, 1.39 mol) and pyridine (109.4 cm^3, 1.35 mol) in diethyl ether (200 cm^3) at 0 °C (ice–water-bath). The reaction flask was then shaken thoroughly and the products were filtered. The residue was washed with diethyl ether (200 cm^3), and the combined filtrate and washings were evaporated under reduced pressure. Distillation of the residue gave diphenyl sulfite (97.6 g, 62%) as a liquid, b.p. 135 °C/0.7 mmHg (lit.,[16] 178 °C/15 mmHg).

2,3′-*Anhydro*-1-(2′-*deoxy*-β-D-threo-*pentofuranosyl*)*thymine* **7b**.—A flask containing a stirred mixture of thymidine **4b** (5.0 g, 20.6 mmol), diphenyl sulfite (19.34 g, 82.6 mmol), 1-methylimidazole (0.34 cm^3, 4.27 mmol) and DMA (50 cm^3) was immersed in an oil-bath maintained at 156 ± 1 °C. After 45 min, the products were cooled to 0 °C and were then poured into a stirred, cooled (to 0 °C) mixture of triethylamine (50 cm^3) and water (90 cm^3). After 40 min, by which time it had warmed up almost to room temperature, the resulting solution was extracted with chloroform (4 × 50 cm^3). The remaining aqueous layer was concentrated under reduced pressure and the viscous oil thus obtained was dissolved in absolute ethanol (30 cm^3), and the solution was re-evaporated. After one further evaporation from absolute ethanol (30 cm^3) solution, the residue was triturated with diethyl ether (3 × 30 cm^3). Dichloromethane (50 cm^3) was then added and the resulting solid precipitate was collected by filtration and washed with dichloromethane (2 × 10 cm^3). After the combined filtrate and washings had been concentrated to ~30 cm^3, light petroleum (boiling range 30–40 °C; 15 cm^3) was added, and the resulting mixture was refrigerated (4 °C) for 24 h. A second crop of solid was obtained; it was collected by filtration and was washed with dichloromethane (2 × 5 cm^3). The two crops of solid were combined and dried over P_2O_5 *in vacuo* at 75 °C to give virtually pure 2,3′-*anhydro compound* **7b**[22] (3.0 g, 64.8%) [Found, after recrystallization from ethanol–water (9:1 v/v) and drying *in vacuo* at 100 °C over P_2O_5: C, 49.6; H, 5.7; N, 11.6. Calc. for $C_{10}H_{12}N_2O_4 \cdot H_2O$: C, 49.6; H, 5.8; N, 11.6%]; R_f 0.38 (system B); λ_{max}(95% EtOH)/nm 247.5 (ε 7760); λ_{min}/nm 219 (4750); $\delta_H[(CD_3)_2SO]$ 1.75 (3 H, d, *J* 0.8), 2.4–2.6 (2 H, m), 3.48 (2 H, m), 4.19 (1 H, dt, *J* 2.3 and 6.5), 5.04 (1 H, m), 5.82 (1 H, d, *J* 3.8) and 7.57 (1 H, m); $\delta_C[(CD_3)_2SO]$ 13.03, 32.72, 59.69, 76.93, 85.32, 86.74, 115.99, 136.80, 153.69 and 171.02.

2,3′-*Anhydro*-1-(2′-*deoxy*-β-D-threo-*pentofuranosyl*)*uracil* **7a**.—A solution of 2′-deoxyuridine **4a** (0.456 g, 2.0 mmol), diphenyl sulfite (1.404 g, 6.0 mmol) and 1-methylimidazole (0.31 cm^3, 0.4 mmol) in DMA (10 cm^3) was heated at 155 °C, in an atmosphere of nitrogen, for 30 min. The cooled products were poured into a mixture of triethylamine (5 cm^3) and water (5 cm^3) and the resulting mixture was stirred at 0 °C (ice–water-bath) for 30 min. The products were partitioned between water (25 cm^3) and chloroform (25 cm^3). The aqueous layer was separated, extracted with chloroform (3 × 25 cm^3), and then evaporated under reduced pressure. After the residue had been evaporated with toluene, it was dissolved in acetonitrile (5 cm^3) and TBDMSCl (0.455 g, 3.0 mmol) and imidazole (0.408 g, 6.0 mmol) were added to the stirred solution at room temperature. After 2 h, the products were concentrated under reduced pressure, and the residue was partitioned between chloroform (75 cm^3) and water (25 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was fractionated by short-column chromatography: the appropriate fractions, eluted with chloroform–ethanol (8:2 v/v), were combined, and evaporated under reduced pressure. Crystallization of the residue from ethyl acetate–light petroleum (60–80 °C) gave 2,3′-*anhydro*-5′-*O*-(tert-*butyldimethylsilyl*)-2′-*deoxy*-1-(β-D-threo-*pentofuranosyl*)*uracil* **8a** (0.33 g, 51%) (Found: C, 55.4; H, 7.6; N, 8.6. $C_{15}H_{24}N_2O_4Si$ requires C, 55.5; H, 7.5; N, 8.6%), m.p. 180 °C; R_f 0.39 (system A); $\delta_H[(CD_3)_2SO]$ 0.19 (6 H, s), 0.84 (9 H, s), 2.46 (1 H, m), 2.59 (1 H, d, *J* 12.9), 3.67 (1 H, dd, *J* 6.5 and 10.9), 3.73 (1 H, dd, *J* 6.3 and 10.9), 4.25 (1 H, m), 5.26 (1 H, m), 5.76 (1 H, d, *J* 7.4), 5.90 (1 H, d, *J* 3.7) and 7.67 (1 H, d, *J* 7.4); $\delta_C[(CD_3)_2SO]$ −5.54, −5.45, 17.99, 25.73, 32.63, 61.54, 77.07, 84.76, 86.89, 107.88, 140.80, 153.85 and 170.36.

The latter compound **8a** (0.324 g, 1.0 mmol) was dissolved in 1 mol dm^{-3} TEAF in acetonitrile (2 cm^3; 2 mmol) at room temperature. After 2 h, the products were concentrated under reduced pressure and the residue was partitioned between chloroform (10 cm^3) and water (25 cm^3). The aqueous solution was separated, washed with chloroform (2 × 10 cm^3), and then concentrated under reduced pressure. The residue was triturated with butan-1-ol to give *compound* **7a** as a solid (0.138 g, 65%) (Found, in material crystallized from ethanol–ethyl acetate: C, 51.5; H, 4.6; N, 13.4. $C_9H_{10}N_2O_4$ requires C, 51.4; H, 4.8; N, 13.3%), m.p. 198 °C; R_f 0.35 (system B); $\delta_H[(CD_3)_2SO]$ 2.47 (1 H, m), 2.59 (1 H, d, *J* 12.9), 3.51 (2 H, m), 4.21 (1 H, m), 5.08 (1 H, m), 5.28 (1 H, m), 5.77 (1 H, d, *J* 7.4), 5.89 (1 H, d, *J* 3.7) and 7.66 (1 H, d, *J* 7.4); $\delta_C[(CD_3)_2SO]$ 32.69, 59.59, 77.06, 85.29, 86.81, 107.83, 140.83, 153.98 and 170.41.

2,3′-*Anhydro*-2′-*deoxy*-5-*ethyl*-1-(β-D-threo-*pentofuranosyl*)-*uracil* **7c**.—A solution of 2′-deoxy-5-ethyluridine **4c** (0.512 g, 2.0 mmol), diphenyl sulfite (1.404 g, 6.0 mmol), 1-methylimidazole (0.31 cm^3, 0.4 mmol) in DMA (10 cm^3) was heated at 155 °C in an atmosphere of nitrogen for 25 min. The products were worked up as in the above preparation of compound **7a** and were then allowed to react with TBDMSCl (0.455 g, 3.0 mmol) and imidazole (0.408 g, 6.0 mmol) in acetonitrile (10 cm^3). Following work-up and chromatography of the products as above, 2,3′-*anhydro*-5′-O-(tert-*butyldimethylsilyl*)-2′-*deoxy*-5-*ethyl*-1-(β-D-threo-*pentofuranosyl*)*uracil* **8c** (0.355 g, 50%) (Found: C, 58.2; H, 8.15; N, 7.8. $C_{17}H_{28}N_2O_4Si$ requires C, 57.9; H, 8.0; N, 7.95%), m.p. 147 °C, was obtained as a crystalline solid [from ethyl acetate–light petroleum (boiling range 60–80 °C)]; R_f 0.38 (system A); $\delta_H[(CD_3)_2SO]$ 0.01 (6 H, s), 0.84 (9 H, s), 1.02 (3 H, t, *J* 7.4), 2.19 (2 H, m), 2.45 (1 H, m), 2.57

(1 H, m), 3.65 (1 H, dd, *J* 6.5 and 10.9), 3.71 (1 H, dd, *J* 6.3 and 10.9), 4.24 (1 H, m), 5.24 (1 H, m), 5.89 (1 H, d, *J* 3.7) and 7.52 (1 H, m); δ_C[$(CD_3)_2SO$] −5.55, −5.46, 12.24, 17.98, 20.19, 25.72, 32.64, 61.53, 76.85, 84.69, 86.75, 121.50, 135.93, 153.34 and 170.37.

Compound **8c** (0.352 g, 1.0 mmol) was treated with TEAF in acetonitrile and worked up as above to give 2,3′-*anhydro*-2′-*deoxy*-5-*ethyl*-1-(β-D-threo-*pentofuranosyl*)*uracil* **7c** as a solid (0.152 g, 64%) (Found, in material crystallized from ethanol: C, 55.45; H, 5.9; N, 11.6. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.8%), m.p. 224 °C; R_f 0.37 (system B); δ_H[$(CD_3)_2SO$] 1.04 (3 H, t, *J* 7.4), 2.20 (2 H, quart, *J* 7.4), 2.46 (1 H, m), 2.58 (1 H, m), 3.50 (2 H, m), 4.21 (1 H, m), 5.07 (1 H, t, *J* 5.3), 5.26 (1 H, m), 5.89 (1 H, d, *J* 3.8) and 7.51 (1 H, m); δ_C[$(CD_3)_2SO$] 12.16, 20.17, 32.70, 59.66, 76.86, 85.28, 86.69, 121.45, 135.93, 153.45 and 170.43.

2,3′-*Anhydro*-2′-*deoxy*-5-*fluoro*-1-(β-D-threo-*pentofuranosyl*)-*uracil* **7d**.—A solution of 2′-deoxy-5-fluorouridine **4d** (0.492 g, 2.0 mmol), diphenyl sulfite (1.404 g, 6.0 mmol) and 1-methylimidazole (0.31 cm^3, 0.4 mmol) in DMA (10 cm^3) was heated at 155 °C in an atmosphere of nitrogen for 20 min. The products were worked up as in the above preparation of compound **7a** and were then allowed to react with TBDMSCl (0.455 g, 3.0 mmol) and imidazole (0.408 g, 6.0 mmol) in acetonitrile (5 cm^3). Following work-up and chromatography of the products as above, 2,3′-*anhydro*-5′-O-(tert-*butyldimethylsilyl*)-2′-*deoxy*-5-*fluoro*-1-(β-D-threo-*pentofuranosyl*)*uracil* **8d** (0.403 g, 59%) (Found: C, 52.2; H, 6.6; N, 7.9. $C_{15}H_{23}FN_2O_4Si$ requires C, 52.6; H, 6.8; N, 8.2%), m.p. 213 °C, was obtained as a crystalline solid (from ethyl acetate); R_f 0.33 (system A); δ_H[$(CD_3)_2SO$] 0.03 (6 H, s), 0.86 (9 H, s), 2.53 (1 H, m), 2.65 (1 H, m), 3.74 (2 H, m), 4.30 (1 H, m), 5.32 (1 H, m), 5.88 (1 H, d, *J* 3.7) and 8.14 (1 H, d, $J_{F,H}$ 5.3); δ_C[$(CD_3)_2SO$] −5.58, −5.49, 17.98, 25.70, 32.42, 61.32, 77.53, 84.91, 87.43, 125.54 (d, $J_{C,F}$ 39.5), 144.37 (d, $J_{C,F}$ 249.0), 151.61 and 162.95 (d, $J_{C,F}$ 16.2).

Compound **8d** (0.342 g, 1.0 mmol) was treated with TEAF in acetonitrile and worked up as above to give 2,3′-*anhydro*-2′-*deoxy*-5-*fluoro*-(β-D-threo-*pentofuranosyl*)*uracil* **7d** as a solid (0.152 g, 67%) (Found, in material crystallized from ethanol: C, 47.3; H, 3.85; N, 12.1. $C_9H_9FN_2O_4$ requires C, 47.4; H, 4.0; N, 12.3%), m.p. 193 °C (lit.,[4] 166–170 °C); R_f 0.34 (system B); δ_H[$(CD_3)_2SO$] 2.51 (1 H, m), 2.64 (1 H, m), 3.55 (2 H, m), 4.24 (1 H, m), 5.07 (1 H, t, *J* 5.0), 5.32 (1 H, m), 5.87 (1 H, d, *J* 3.0) and 8.10 (1 H, d, $J_{F,H}$ 5.0); δ_C[$(CD_3)_2SO$] 32.50, 59.36, 77.48, 85.41, 87.31, 125.51 (d, $J_{C,F}$ 36.7), 144.31 (d, $J_{C,F}$ 249.2), 151.70 and 163.02 (d, $J_{C,F}$ 16.5).

1-(2,3-*Dideoxy*-β-D-glycero-*pent*-2-*enofuranosyl*)*thymine* (*d4T*) **2**.—(*a*) Sodium hydride (60% dispersion in mineral oil; 3.8 g, 0.095 mol) was added to a stirred solution of 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)thymine **5b** (6.72 g, 30.0 mmol) in DMA (125 cm^3) in an atmosphere of nitrogen at room temperature. After 10 min, the reaction mixture was stirred *vigorously* and heated in an oil-bath at 100 °C. After a further period of 35–45 min, when TLC (system A) revealed that no substrate **5b** remained, the products were cooled, neutralized by the cautious addition of solid carbon dioxide, and then concentrated under reduced pressure (oil-pump; bath temperature <60 °C). The residue was dissolved in cold water (50 cm^3) and hydrochloric acid was added to the resulting solution until the pH dropped to ~7 (pH paper). The products were then concentrated to dryness under reduced pressure and evaporated with absolute ethanol (3 × 50 cm^3). The residue was extracted with acetone (3 × 100 cm^3). The combined extracts were evaporated under reduced pressure and the material obtained was purified by 'filtration' through a column of silica gel, with chloroform–ethanol (95:5 v/v) as the eluting solvent, to give 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine **2** (5.16 g, 76%) (Found, in material crystallized from methanol–benzene: C, 53.5; H, 5.25; N, 12.7. Calc. for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5%), m.p. 164 °C (lit.,[3c] 165–166 °C); R_f 0.34 (system A); δ_H[$(CD_3)_2SO$] 1.73 (3 H, d, *J* 0.5), 3.61 (2 H, m), 4.77 (1 H, m), 5.00 (1 H, m), 5.89 (1 H, m), 6.38 (1 H, m), 6.83 (1 H, m), 7.64 (1 H, m) and 11.26 (1 H, br s); δ_C[$(CD_3)_2SO$] 12.23, 62.32, 87.36, 88.95, 109.07, 126.01, 134.98, 136.83, 150.87 and 163.95.

(*b*) Sodium hydride (60% dispersion in mineral oil; 0.24 g, 6.0 mmol) was added to a stirred solution of compound **7b** (0.448 g, 2.0 mmol) in DMA (15 cm^3) in an atmosphere of nitrogen at room temperature. After 5 min, the reaction mixture was heated in an oil-bath at 100 °C. After a further period of 30 min, when TLC (system A) revealed that no starting material **7b** remained, the products were worked up and purified as in (*a*) above, taking account of the smaller scale of the experiment. 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine **2** (0.365 g, 81%) was obtained with identical properties [m.p., TLC (system A), ^1H NMR] with those of the product described in (*a*) above.

1-(2,3-*Dideoxy*-β-D-glycero-*pent*-2-*enofuranosyl*)*uracil* **6a**.—(*a*) Sodium hydride (60% dispersion in mineral oil; 0.12 g, 3.0 mmol) was added to a stirred solution of 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)uracil **5a** (0.21 g, 1.0 mmol) in DMA (10 cm^3) in an atmosphere of nitrogen at room temperature. After 5 min, the reaction mixture was heated in an oil-bath at 100 °C. After a further period of 35 min, when TLC (system A) revealed that no starting material **5a** remained, the products were worked up and purified as in the above conversion of compound **5b** into d4T **2**, taking into account the scale of the experiment, to give 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil **6a** (0.143 g, 68%) (Found, in material crystallized from methanol–benzene: C, 51.2; H, 4.7; N, 13.3. Calc. for $C_9H_{10}N_2O_4$: C, 51.4; H, 4.8; N, 13.3%), m.p. 151 °C (lit.,[3c] 153–154 °C); R_f 0.32 (system A); δ_H[$(CD_3)_2SO$] 3.60 (2 H, m), 4.79 (1 H, m), 4.98 (1 H, br), 5.59 (1 H, d, *J* 8.0), 5.91 (1 H, m), 6.40 (1 H, m), 6.82 (1 H, m), 7.76 (1 H, d, *J* 8.0) and 11.28 (1 H, br); δ_C[$(CD_3)_2SO$] 62.23, 87.39, 89.07, 101.53, 125.73, 135.04, 141.04, 150.78 and 163.20.

(*b*) Sodium hydride (60% dispersion in mineral oil; 0.12 g, 3.0 mmol) was added to a stirred solution of compound **7a** (0.21 g, 1.0 mmol) in DMA (10 cm^3) in an atmosphere of nitrogen at room temperature. After 5 min, the reaction mixture was heated in an oil-bath at 100 °C. After a further period of 30 min, when TLC (system A) revealed that no starting material **7a** remained, the products were worked up and purified as in the above conversion of substrate **5b** into d4T **2**, taking into account the scale of the experiment. 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil **6a** (0.149 g, 71%) was obtained with identical properties [m.p., TLC (system A), ^1H NMR] with those of the product described in (*a*) above.

1-(2,3-*Dideoxy*-β-D-glycero-*pent*-2-*enofuranosyl*)-5-*ethyluracil* **6c**.—(*a*) Sodium hydride (60% dispersion in mineral oil; 0.12 g, 3.0 mmol) was added to a stirred solution of 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-5-ethyluracil **5c** (0.238 g, 1.0 mmol) in DMA (10 cm^3) in an atmosphere of nitrogen at room temperature. After 5 min, the reaction mixture was heated in an oil-bath at 100 °C. After a further period of 35 min, when TLC (system A) revealed that no starting material **5c** remained, the products were worked up and purified as in the above conversion of compound **5b** into d4T **2**, taking into account the scale of the experiment, to give 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-ethyluracil **6c** (0.164 g, 69%) (Found, in material crystallized from ethyl acetate–benzene: C, 55.9; H, 6.0; N, 11.4. Calc. for $C_{11}H_{14}N_2O_4$: C, 55.5; H, 5.9; N, 11.8%), m.p. 112 °C (lit.,[21] 118–119 °C); R_f 0.28 (system A); δ_H[$(CD_3)_2SO$] 0.99 (3 H, t, *J* 7.4), 2.16 (2 H, m), 3.62 (2 H, m), 4.78 (1 H, m), 5.04

(1 H, br), 5.92 (1 H, m), 6.40 (1 H, m), 6.85 (1 H, m), 7.63 (1 H, m) and 11.30 (1 H, br); $\delta_C[(CD_3)_2SO]$ 12.45, 19.45, 62.00, 87.21, 88.80, 114.61, 125.92, 134.94, 136.07, 150.61 and 163.40.

(*b*) Sodium hydride (60% dispersion in mineral oil; 0.12 g, 3.0 mmol) was added to a stirred solution of compound **7c** (0.238 g, 1.0 mmol) in DMA (10 cm^3) in an atmosphere of nitrogen at room temperature. After 5 min, the reaction mixture was heated in an oil-bath at 100 °C. After a further period of 30 min, when TLC (system A) revealed that no starting material **7c** remained, the products were worked up and purified as in the conversion of compound **5b** into **2**, taking into account the scale of the experiment. 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-ethyluracil **6c** (0.165 g, 69%) was obtained with identical properties [m.p., TLC (system A), ^1H NMR] as those of the product described in (*a*) above.

1-(2,3-*Dideoxy*-β-D-glycero-*pent*-2-*enofuranosyl*)-5-*fluorouracil* **6d**.—(*a*) Sodium hydride (60% dispersion in mineral oil; 0.18 g, 4.5 mmol) was added to a stirred solution of 1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-5-fluorouracil **5d** (0.342 g, 1.5 mmol) in DMA (10 cm^3) in an atmosphere of nitrogen at room temperature. After 5 min, the reaction mixture was heated in an oil-bath at 100 °C. After a further period of 35 min when TLC (system A) revealed that no starting material **5d** remained, the products were worked up and purified as in the above conversion of **5b** into **2**, taking into account the scale of the experiment, to give 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-fluorouracil **6d** (0.254 g, 74%) (Found, in material crystallized from methanol–benzene: C, 47.5; H, 3.7; N, 11.9. Calc. for $C_9H_9FN_2O_4$: C, 47.4; H, 4.0; N, 12.3%), m.p. 135 °C (lit.,[4] 138–139 °C); R_f 0.29 (system A); $\delta_H[(CD_3)_2SO]$ 3.66 (2 H, m), 4.81 (1 H, m), 5.12 (1 H, m), 5.90 (1 H, m), 6.39 (1 H, m), 6.82 (1 H, m), 8.18 (1 H, d, $J_{F,H}$ 7.1) and 11.83 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 61.74, 87.47, 89.38, 125.28 (d, $J_{C,F}$ 34.4), 125.69, 135.22, 139.60 (d, $J_{C,F}$ 230.2), 149.32 and 157.11 (d, $J_{C,F}$ 26.3).

(*b*) Sodium hydride (60% dispersion in mineral oil; 0.18 g, 4.5 mmol) was added to a stirred solution of compound **7d** (0.342 g, 1.5 mmol) in DMA (10 cm^3) in an atmosphere of nitrogen at room temperature. After 5 min, the reaction mixture was heated in an oil-bath at 100 °C. After a further period of 30 min, when TLC (system A) revealed that no starting material **7d** remained, the products were worked up and purified as in the above conversion of compound **5b** into d4T **2**, taking into account the scale of the experiment. 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-fluorouracil **6d** (0.254 g, 74%) was obtained with identical properties [m.p., TLC (system A), ^1H NMR] with those of the product described in (*a*) above.

5′-O-(tert-*Butyldimethylsilyl*)-2′-*deoxy*-5-(*trifluoromethyl*)-*uridine* **9e**.—TBDMSCl (0.78 g, 5.18 mmol) was added to a stirred solution of 2′-deoxy-5-(trifluoromethyl)uridine **4e** (1.48 g, 5.0 mmol) in dry pyridine (20 cm^3) at room temperature. After 12 h, the products were concentrated under reduced pressure and the thick residual syrup obtained was triturated several times with cold water and then filtered. The residue was further washed with cold water and crystallized from ethyl acetate–light petroleum (60–80 °C) to give the *title compound* **9e** (1.82 g, 88%) (Found: C, 46.8; H, 6.1; N, 6.7. $C_{16}H_{25}F_3N_2O_5Si$ requires C, 46.8; H, 6.1; N, 6.8%), m.p. 189 °C; R_f 0.50 (system A); $\delta_H[(CD_3)_2SO]$ 0.02 (6 H, s), 0.82 (9 H, s), 2.08 (1 H, m), 2.24 (1 H, m), 3.70 (1 H, dd, *J* 3.7 and 11.7), 3.80 (1 H, dd, *J* 2.7 and 11.6), 3.92 (1 H, m), 4.15 (1 H, m), 5.29 (1 H, br), 6.01 (1 H, t, *J* 6.6), 8.11 (1 H, s) and 11.91 (1 H, br); $\delta_C(CDCl_3)$ −6.13, −6.21, 17.81, 25.35, 41.48, 63.02, 71.23, 86.04, 87.91, 103.75 (quart, $J_{C,F}$ 32.8), 121.78 (quart, $J_{C,F}$ 269.7), 140.15 (quart, $J_{C,F}$ 5.9), 149.13 and 158.89.

5′-O-(tert-*Butyldimethylsilyl*)-2′-*deoxy*-5-*iodouridine* **9f**.—TBDMSCl (0.825 g, 5.47 mmol) was added to a stirred solution of 2′-deoxy-5-iodouridine **4f** (1.85 g, 5.22 mmol) in dry pyridine (20 cm^3) at room temperature. After 12 h, the products were concentrated under reduced pressure and the thick residual syrup thus obtained was triturated with cold water (40 cm^3) and then filtered. The residue was further washed with cold water and crystallized from ethyl acetate to give the *title compound* **9f** (1.87 g, 76%) (Found: C, 38.4; H, 5.2; N, 6.1. $C_{15}H_{25}IN_2O_5Si$ requires C, 38.5; H, 5.4; N, 6.0%), m.p. 196 °C; R_f 0.55 (system A); $\delta_H[(CD_3)_2SO]$ 0.11 (3 H, s), 0.12 (3 H, s), 0.90 (9 H, s), 1.98–2.17 (2 H, m), 3.73 (1 H, dd, *J* 3.4 and 11.5), 3.81 (1 H, dd, *J* 2.7 and 11.5), 3.86 (1 H, m), 4.17 (1 H, m), 5.29 (1 H, d, *J* 4.1), 6.09 (1 H, dd, *J* 5.9 and 7.8), 8.00 (1 H, s) and 11.72 (1 H, br s); $\delta_C[(CD_3)_2SO]$ −5.28, −5.24, 18.11, 25.99, 40.23, 63.23, 69.72, 70.59, 84.88, 87.25, 143.98, 150.01 and 160.45.

2,3′-*Anhydro*-5′-O-(tert-*butyldimethylsilyl*)-2′-*deoxy*-5-(*trifluoromethyl*)-1-(β-D-threo-*pentofuranosyl*)*uracil* **8e**.—Methanesulfonyl chloride (0.59 cm^3, 7.6 mmol) was added dropwise to a stirred solution of 5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-(trifluoromethyl)uridine **9e** (2.051 g, 5.0 mmol) and triethylamine (3.03 cm^3, 21.7 mmol) in dichloromethane (20 cm^3) at 0 °C (ice–water-bath), and the reaction mixture was allowed to warm up to room temperature. After 1 h, saturated aq. sodium hydrogen carbonate (5 cm^3) was added and the products were extracted with chloroform (50 cm^3). The dried ($MgSO_4$) chloroform layer was evaporated under reduced pressure and the residue was redissolved in a solution of diisopropylethylamine (3.48 cm^3, 20 mmol) in propan-1-ol (10 cm^3). The reaction solution was heated, under reflux, for 1 h and the products were concentrated under reduced pressure. The residue was fractionated by short-column chromatography: the appropriate fractions, eluted with chloroform–ethanol (8:2 v/v), were combined, and evaporated under reduced pressure to give the *title compound* **8e** (1.44 g, 73%) [Found, in material crystallized from ethyl acetate–light petroleum (60–80 °C): C, 49.0; H, 5.8; N, 7.0. $C_{16}H_{23}F_3N_2O_4Si$ requires: C, 49.0; H, 5.9; N, 7.1%], m.p. 167–170 °C; R_f 0.38 (system A); $\delta_H[(CD_3)_2SO]$ 0.01 (6 H, s), 0.84 (9 H, s), 2.52 (1 H, m), 2.68 (1 H, m), 3.76 (2 H, m), 4.29 (1 H, m), 5.35 (1 H, m), 6.06 (1 H, d, *J* 3.7) and 8.47 (1 H, m); $\delta_C[(CD_3)_2SO]$ −5.68, −5.58, 17.97, 25.66, 32.53, 61.02, 78.02, 84.64, 87.65, 108.31 (quart, $J_{C,F}$ 30.6), 122.72 (quart, $J_{C,F}$ 270.3), 142.49 (quart, $J_{C,F}$ 5.9), 154.34 and 165.11.

2,3′-*Anhydro*-5′-O-(tert-*butyldimethylsilyl*)-2′-*deoxy*-5-*iodo*-1-(β-D-threo-*pentofuranosyl*)*uracil* **8f**.—Methanesulfonyl chloride (0.39 cm^3, 5.0 mmol) was added dropwise to a stirred solution of 5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-iodouridine **9f** (1.404 g, 3.0 mmol) and triethylamine (3.03 cm^3, 21.7 mmol) in dichloromethane (20 cm^3) at 0 °C (ice–water-bath). The reaction was then allowed to proceed and the products were worked up as above in the preparation of compound **8e**. The residue obtained was redissolved in a solution of diisopropylethylamine (2.07 cm^3, 12.0 mmol) in propan-1-ol (10 cm^3), and the resulting solution was heated under reflux for 1 h. The products were then worked up and fractionated as above in the preparation of compound **8e** to give the *title compound* **8f** (0.91 g, 68%) (Found, in material crystallized from ethyl acetate: C, 39.8; H, 4.9; N, 6.2. $C_{15}H_{23}IN_2O_4Si$ requires C, 40.0; H, 5.15; N, 6.2%), m.p. 188 °C; R_f 0.36 (system A); $\delta_H[(CD_3)_2SO]$ 0.01 (6 H, s), 0.84 (9 H, s), 2.46 (1 H, m), 2.61 (1 H, m), 3.71 (2 H, m), 4.26 (1 H, m), 5.28 (1 H, m), 5.91 (1 H, d, *J* 3.7) and 8.30 (1 H, s); $\delta_C[(CD_3)_2SO]$ −5.58, −5.48, 17.99, 25.71, 32.39, 61.23, 77.40, 80.65, 84.74, 87.06, 145.25, 154.13 and 166.81.

1-(2,3-*Dideoxy*-β-D-glycero-*pent*-2-*enofuranosyl*)-5-(*trifluoromethyl*)*uracil* **6e**.—Freshly cut sodium metal (0.161 g, 7.0 mmol) was added to a solution of diphenyl diselenide (1.248 g, 4.0 mmol) in THF (5 cm^3)–HMPA (5 cm^3). The stirred mixture

was heated at 80 °C for 12 h and was then cooled to room temperature. 2,3′-Anhydro-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-(trifluoromethyl)-1-(β-D-*threo*-pentofuranosyl)uracil **8e** (0.784 g, 2.0 mmol) was added and the stirred reaction mixture was heated at 50 °C for 2 h. Air was bubbled through the cooled products for 30 min. The resulting yellow-coloured solution was concentrated under reduced pressure (bath temperature < 25 °C) and was then partitioned between ethyl acetate (50 cm^3) and water (10 cm^3). The organic layer was separated, further washed with water (3 × 10 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was freed from other selenium-containing materials by chromatography on silica gel: the appropriate fractions, eluted with chloroform, were evaporated and the residue was dissolved in 1 mol dm^{-3} TEAF in acetonitrile (6 cm^3; 6 mmol). After 1 h, the solution was evaporated under reduced pressure and the products were fractionated by short-column chromatography: the appropriate fractions, eluted with chloroform–ethanol (95:5 v/v), were combined, and evaporated under reduced pressure to give selenide **10e** as a solid (0.584 g); R_f 0.52 (system A); $\delta_H[(CD_3)_2SO]$ 2.37 (1 H, m), 2.66 (1 H, m), 3.65–3.9 (3 H, m), 3.96 (1 H, m), 5.44 (1 H, t, *J* 4.3), 5.89 (1 H, dd, *J* 1.8 and 6.7), 7.35 (3 H, m), 7.58 (2 H, m), 8.93 (1 H, s) and 11.80 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 34.29, 40.39, 58.38, 85.37, 86.68, 102.02 (quart, $J_{C,F}$ 31.8), 122.83 ($J_{C,F}$ 269.2), 126.97, 127.93, 129.29, 134.29, 142.19 (quart, $J_{C,F}$ 5.7), 149.52 and 159.15.

Hydrogen peroxide (30%; 2.0 cm^3, ~20 mmol) was added to a stirred solution of the above product (0.217 g, ~0.5 mmol) in THF (5 cm^3) at 0 °C (ice–water-bath) and the reactants were allowed to warm up to room temperature. After 2.5 h, the products were concentrated under reduced pressure and the residue was fractionated by short-column chromatography: the appropriate fractions, eluted with chloroform–ethanol (95:5 v/v), were combined, and evaporated under reduced pressure to give the *title compound* **6e** (0.109 g, 52% overall yield based on **8e**) [Found, in material crystallized from ethyl acetate–light petroleum (60–80 °C): C, 42.6; H, 3.1; N, 9.8. $C_{10}H_9F_3N_2O_4 \cdot 0.2H_2O$ requires C, 42.6; H, 3.4; N, 9.9%], m.p. 110 °C; R_f 0.36 (system A); $\delta_H[(CD_3)_2SO]$ 3.65 (2 H, m), 4.87 (1 H, m), 5.14 (1 H, m), 5.95 (1 H, m), 6.43 (1 H, m), 6.85 (1 H, m), 8.64 (1 H, s) and 11.87 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 61.26, 87.80, 89.55, 102.84 (quart, $J_{C,F}$ 31.9), 122.54 (quart, $J_{C,F}$ 269.2), 125.54, 135.64, 143.22 (quart, $J_{C,F}$ 5.6), 149.91 and 158.91.

1-(2,3-*Dideoxy*-β-D-glycero-*pent*-2-*enofuranosyl*)-5-*iodouracil* **6f**.—2,3′-Anhydro-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-iodo-1-(β-D-*threo*-pentofuranosyl)uracil **8f** (0.90 g, 2.0 mmol) was added to a solution of sodium phenyl selenide,[18] prepared from diphenyl diselenide (1.248 g, 4.0 mmol) and sodium metal (0.161 g, 7.0 mmol) and the reaction mixture was heated at 50 °C for 2 h as in the above preparation of compound **6e**. Air was bubbled through the cooled products which, after 30 min, were worked up, treated with TEAF, and then purified as above to give compound **10f** as a solid (0.643 g), R_f 0.44 (system A); $\delta_H[(CD_3)_2SO]$ 2.34 (1 H, m), 2.58 (1 H, m), 3.63 (1 H, m), 3.79 (2 H, m), 3.94 (1 H, m), 5.38 (1 H, t, *J* 4.3), 5.91 (1 H, dd, *J* 3.1 and 6.8), 7.36 (3 H, m), 7.58 (2 H, m), 8.57 (1 H, s) and 11.64 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 35.28, 39.70, 59.15, 68.54, 84.61, 86.25, 127.40, 127.83, 129.31, 133.99, 144.94, 149.95 and 160.50.

Hydrogen peroxide (30%; 2.0 cm^3, ~20 mmol) was added to a stirred solution of the above product (0.246 g, ~0.5 mmol) in THF (5 cm^3) at 0 °C (ice–water-bath), and the reactants were allowed to warm up to room temperature. After 3 h, the products were worked up and purified as in the above preparation of compound **6e** to give the *title compound* **6f** (0.127 g, 49% overall yield based on **8f**) [Found, in material crystallized from ethyl acetate–light petroleum (60–80 °C): C, 32.05; H, 2.5; N, 8.0. $C_9H_9IN_2O_4$ requires C, 32.2; H, 2.7; N, 8.3%], m.p. 145 °C; R_f 0.35 (system A); $\delta_H[(CD_3)_2SO]$ 3.62 (2 H, m), 4.83 (1 H, m), 5.12 (1 H, m), 5.93 (1 H, m), 6.41 (1 H, m), 6.78 (1 H, m), 8.34 (1 H, s) and 11.68 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 61.49, 68.99, 87.54, 89.14, 125.87, 135.37, 145.96, 150.44 and 160.51.

2′,3′-*Dideoxy*-5-(*trifluoromethyl*)*uridine* **11b**.—2,3′-Anhydro-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-(trifluoromethyl)-1-(β-D-*threo*-pentofuranosyl)uracil **8e** (0.392 g, 1.0 mmol), thiophenol (0.55 g, 5.0 mmol), tripropylamine (1.9 cm^3, 10.0 mmol) and DMA (5 cm^3) were stirred and heated together at 120 °C for 6 h. The products were then evaporated under reduced pressure and the residue thus obtained was triturated with light petroleum (60–80 °C; 3 × 25 cm^3) and then dissolved in 1 mol dm^{-3} TEAF in acetonitrile (4 cm^3, 4 mmol). After 1 h, the products were concentrated under reduced pressure and fractionated by short-column chromatography: the appropriate fractions, eluted with chloroform–ethanol (9:1 v/v), were evaporated to give a glass (0.277 g), R_f 0.52 (system A); $\delta_H[(CD_3)_2SO]$ 2.35 (1 H, m), 2.71 (1 H, m), 3.61 (1 H, m), 3.80–3.95 (3 H, m), 5.47 (1 H, m), 5.97 (1 H, dd, *J* 2.5 and 6.7), 7.25–7.50 (5 H, m), 8.90 (1 H, s) and 11.79 (1 H, br); $\delta_C[(CD_3)_2SO]$ 39.72, 40.94, 58.89, 85.40, 85.91, 102.08 (quart, $J_{C,F}$ 31.9), 122.83 (quart, $J_{C,F}$ 269.1), 127.02, 129.15, 130.67, 133.33, 142.22 (quart, $J_{C,F}$ 5.6), 149.52 and 159.15.

The above product (0.194 g) and Raney nickel (1.0 g) were heated together in ethanol (10 cm^3), under reflux, for 2 h. The products were filtered and the residue was washed several times with hot ethanol. The combined filtrate and washings were concentrated under reduced pressure and the residue was fractionated by short-column chromatography: the appropriate fractions, eluted with chloroform–ethanol (84:16 v/v), were evaporated under reduced pressure to give 2′,3′-dideoxy-5-(trifluoromethyl)uridine **11b** (0.096 g, 49% overall yield based on **8e**) [Found, in material crystallized from ethyl acetate–light petroleum (60–80 °C): C, 41.1; H, 3.85; N, 9.3. $C_{10}H_{11}F_3N_2O_4 \cdot 0.6H_2O$ requires C, 41.3; H, 4.2; N, 9.6%], m.p. 159 °C; R_f 0.41 (system A); $\delta_H[(CD_3)_2SO]$ 1.75–1.95 (2 H, m), 2.13 (1 H, m), 2.32 (1 H, m), 3.81 (1 H, m), 4.11 (1 H, m), 5.28 (1 H, m), 5.90 (1 H, d, *J* 5.1), 8.95 (1 H, s) and 11.80 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 23.18, 32.94, 60.48, 82.87, 86.55, 101.85 (quart, $J_{C,F}$ 31.9), 122.94 (quart, $J_{C,F}$ 268.6), 142.45, 149.61 and 159.23.

3′-*Azido*-2′,3′-*dideoxy*-5-(*trifluoromethyl*)*uridine* **11c**.—A stirred solution of 2,3′-anhydro-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-(trifluoromethyl)-1-(β-D-*threo*-pentofuranosyl)-uracil **8e** (0.392 g, 1.0 mmol) and lithium azide (0.15 g, 3.06 mmol) in DMA (5 cm^3) was heated at 120 °C for 2 h. The products were then concentrated under reduced pressure and the residue was partitioned between chloroform (50 cm^3) and water (10 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was redissolved in acetonitrile (5 cm^3). 1 mol dm^{-3} TEAF in acetonitrile (3 cm^3, 3 mmol) was then added. After 1 h, the products were concentrated under reduced pressure and fractionated by short-column chromatography: the appropriate fractions, eluted with chloroform–ethanol (9:1 v/v), were evaporated under reduced pressure to give 3′-azido-2′,3′-dideoxy-5-(trifluoromethyl)uridine **11c** (0.212 g, 66%) (Found, in material crystallized from aq. ethanol: C, 37.7; H, 3.1; N, 21.9. Calc. for $C_{10}H_{10}F_3N_5O_4$: C, 37.4; H, 3.1; N, 21.8%), m.p. 113 °C (lit.,[20] 116–117 °C); R_f 0.52 (system A); $\delta_H[(CD_3)_2SO]$ 2.38 (1 H, m), 3.53 (1 H, m), 3.63 (1 H, m), 3.76 (1 H, m), 3.89 (1 H, m), 4.36 (1 H, m), 5.44 (1 H, t, *J* 4.4), 6.02 (1 H, dd, *J* 4.2 and 6.5), 8.74 (1 H, s) and 11.87 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 37.53, 58.24, 59.49, 84.72, 85.16, 102.59 (quart, $J_{C,F}$ 31.8), 122.65 (quart, $J_{C,F}$ 269.3), 142.06 (quart, $J_{C,F}$ 5.6), 149.44 and 158.98.

Acknowledgements

This work has been generously supported by a project grant from the MRC AIDS Directed Programme. We also thank Roche Products Ltd (Welwyn Garden City) and Pfizer Central Research (Sandwich) for generous gifts of nucleoside starting materials.

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Paper 2/01730J
Received 1*st April* 1992
Accepted 11*th June* 1992