The Potential for Using Carbocyclic Nucleosides for the Treatment of AIDS. Part 1. Preparation of Some Analogues for Azidothymidine (AZT)

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The tricyclic compound **10** was converted into the fluoronorbornane **11** and the norbornanol **23** using fluoride ion and water respectively. The fluoro compound **11** was converted into the carbocyclic nucleosides **5** and **7** by a series of stereocontrolled reactions. Similarly the alcohol (**23**) furnished the nucleoside analogue **6**. Compound **5** showed weak anti-HIV (Human Immunodeficiency Virus) activity and the corresponding triphosphate **27** inhibited HIV-reverse transcriptase to a small degree. The relatively weak antiviral activity of compounds **5**–**7** compared to compounds **1** and **2** can be ascribed to the different preferred conformations of the two sets of compounds.

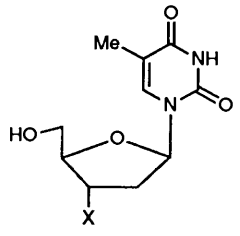
Acquired Immune Deficiency Syndrome (AIDS) is caused by a virus which was first isolated in 1982. This micro-organism, now called human immunodeficiency virus (HIV), belongs to the category of retroviruses so named because genetic information is transferred from RNA to DNA.

The invading virus binds to a target cell, primarily helper T-cells of the immune system. Subsequent fusion of viral and cell membranes leads to the injection of viral core proteins (including enzymes) and two strands of viral RNA into the cytosol. The proteins remain associated with the RNA as it is copied into a single strand of DNA by reverse transcriptase. A second virally coded enzyme, a polymerase, converts the single DNA strand into double stranded DNA.

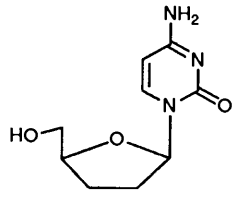
After cyclization the DNA migrates to the cell nucleus and becomes integrated into the host cell's chromosome with the aid of an integrase. Thus established, infection is permanent. The viral DNA is intimately involved in the second half of the viral life cycle, that is the production of new virus particles. This phase leads to lysis of the host cell and down-regulation of the immune system leading to the sufferer being liable, *inter alia*, to pathogenic infection by opportunistic bacteria or fungi.

The chemotherapy needed to restrict viral replication must be extremely selective. The viral life-cycle must be challenged without damage to the mammalian metabolism in general and, more specifically, without an untoward effect on uninfected cells. The reverse transcriptase enzyme that is a key feature of HIV has come under intense scrutiny since this protein is peculiar to the virus and is present only in virally infected cells. Hence inhibition of this enzyme offers a way of finding a selective antiviral agent.

The enzyme synthesizes DNA in the 5′ to 3′ direction using nucleoside triphosphates as building blocks. (Activation of the nucleoside by formation of the triphosphate is promoted by cellular kinases.) The reverse transcriptase of HIV-1 is the least accurate polymerase described to date.[1] This suggests that the polymerase will accept, as substrates, nucleoside analogues which would not be incorporated into DNA as readily by host-cell polymerases. This has proved to be the case. Nucleoside analogues devoid of an hydroxy group at the 3′-position are particularly useful analogues in this regard since DNA-synthesis is curtailed on admission of the surrogate nucleoside into the growing polymer. The best known reverse transcriptase inhibitor is azidothymidine (AZT) **1**;[2] the susceptibility of this substance (as its triphosphate) for incorporation into DNA is 100 fold greater for HIV-reverse transcriptase than for cellular DNA-polymerase-α.[3] Selective inhibition of viral replication is achieved. Another effective HIV inhibitor is 3′-fluoro-3′-deoxythymidine **2**.[4] Compounds **1** and **2** as well as dideoxycytidine **3** and dideoxydidehydrothymidine **4** have been examined in the clinic. All the compounds show good anti-HIV activity



1 X = N_3
2 X = F



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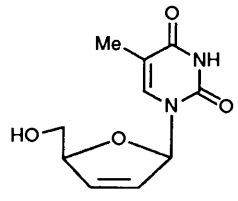

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but, unfortunately, the compounds display moderate to severe toxicity. Thus, treatment with AZT leads to suppression of bone-marrow formation leading to anaemia.[5] One problem is that AZT is rapidly metabolized. This necessitates frequent administration (every 4 h) of high doses (250 mg) of AZT to maintain a constant level of drug in the body.

In summary, it has been shown from other studies that inhibition of HIV-coded reverse transcriptase can be a very effective means of controlling viral replication and restricting the damage done by the AIDS virus. The drugs in use at the present time show gross side-effects, partly due to the rapid metabolism of the compounds. The search for a more stable nucleoside analogue displaying similar anti-viral activity to AZT represents a high priority issue for a number of research groups.

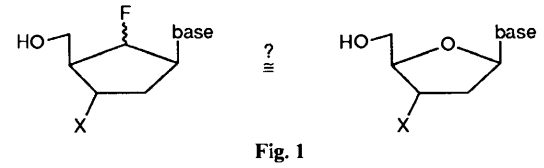


Fig. 1

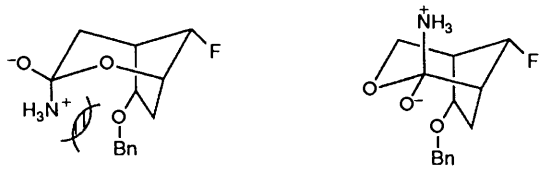
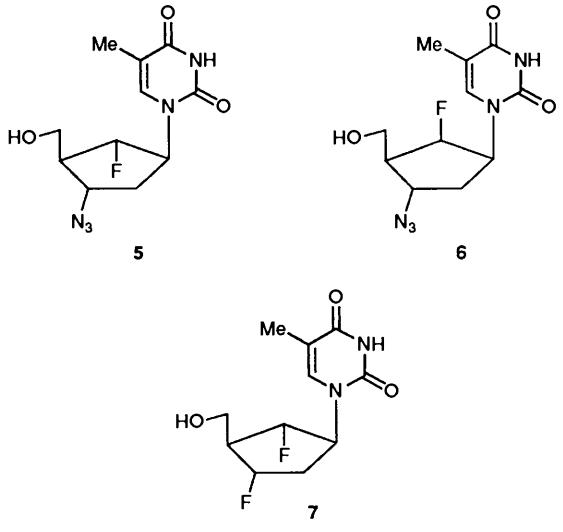


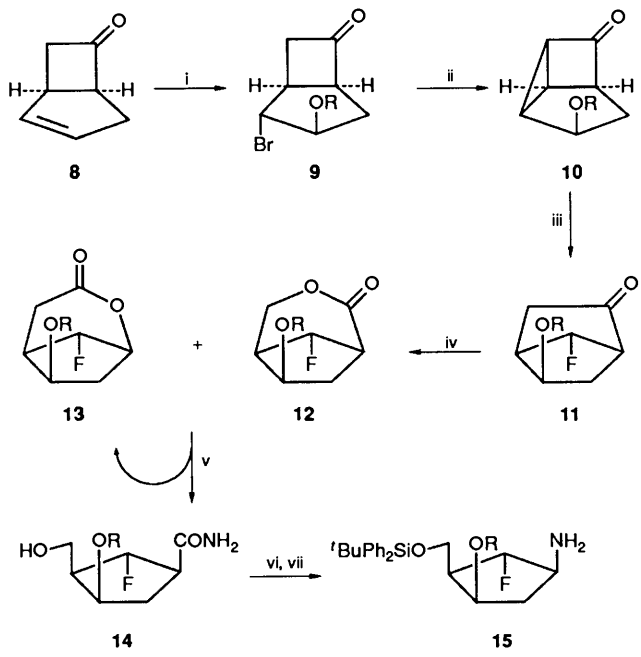
Fig. 2

Following the reasoning of Blackburn *et al.*[6] we sought to prepare stable surrogates of AZT by replacement of the deoxyribofuranose ring oxygen atom with a fluoromethylene unit (Fig. 1). The CHF moiety is essentially isosteric with an ether oxygen atom, and the inductive effect on neighbouring atoms is approximately the same. Being derivatives of cyclopentane the molecules were likely to be considerably more stable to metabolic breakdown (*e.g.* by phosphorylase enzymes) than the corresponding sugars. We describe herein the synthesis of close analogues of AZT **5**, **6** and an analogue **7** of the fluoro compound **2**.[7]



Synthesis of the Nucleoside Analogues **5**–**7**.—Cyclopentadiene was converted into bicyclo[3.2.0]hept-2-en-6-one **8** as previously described[8] (Scheme 1). Addition of *N*-bromoacetamide to the alkene unit in the presence of benzyl alcohol gave the ketone **9** (90%). This compound was treated with potassium *tert*-butoxide in ether at −60 °C for 0.5 h to give the strained tricyclic ketone **10** (100%).[9] Attempts at ring opening this ketone using alkali metal fluorides were unsuccessful but triethylamine–tris(hydrofluoride)[10] furnished the required norbornanone **11** in 57% yield on a multi-gram scale.

Baeyer–Villiger oxidation of the norbornanone **11** using *meta*-chloroperoxybenzoic acid (*m*CPBA) gave mainly the lactone **12** contaminated with the isomer **13** (total yield 94%, ratio **12**:**13** = 2:1).[11] The lactones were not separated but the mixture was treated with liquid ammonia at −33 °C. The lactone **12** reacted to form the required amide **14** (64%) while the 2-oxabicyclooctan-3-one **13** was recovered unchanged. This difference in reactivity was anticipated[12] and is due to the difference in energy levels of the two intermediates that lead to the monocyclic products. Thus as shown in Fig. 2, intermediate



Scheme 1 *Reagents and conditions:* i, *N*-Bromoacetamide, $PhCH_2OH$, room temp., 1 d; ii, KOBu^t, Et_2O, −60 °C, 0.5 h; iii, $Et_3N{\cdot}3HF$, CH_2Cl_2, room temp., 74 h; iv, *m*-$C_6H_4CO_3H$, $NaHCO_3$, CH_2Cl_2, 6 h; v, $NH_3(l)$, 1 h; vi, Bu^tPh_2SiCl, imidazole, DMF (dimethyl formamide), room temp., 15 h; vii, $PhI(OCOCF_3)_2$, MeCN, H_2O pyridine, room temp., 3 h

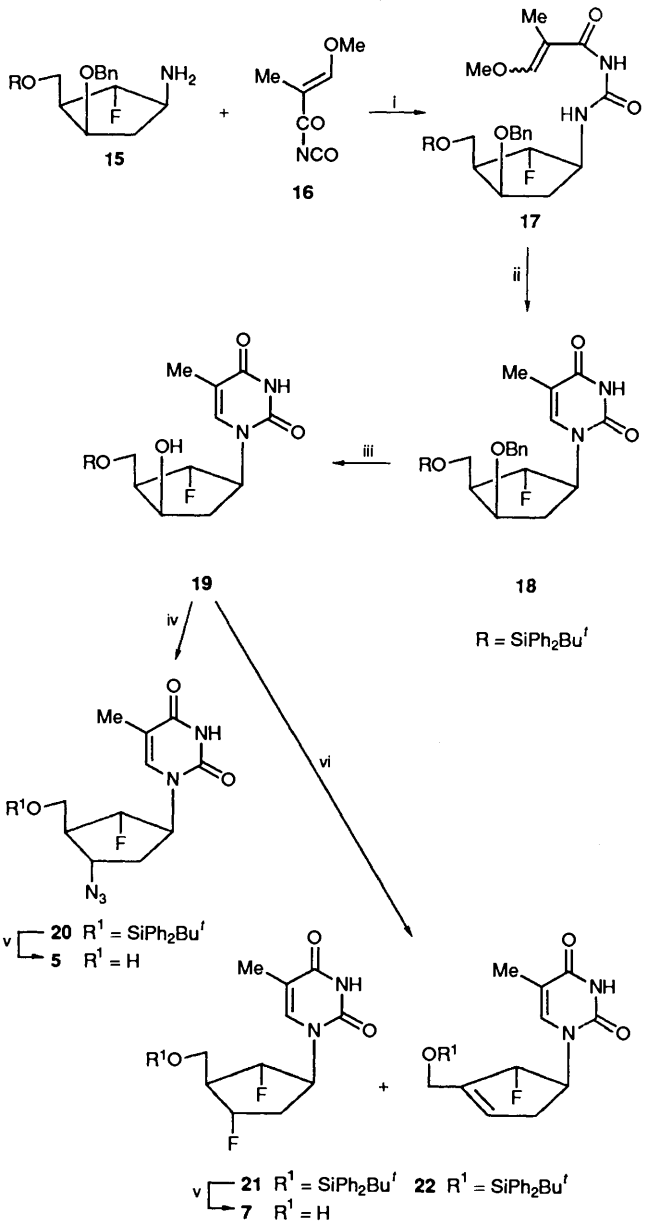
a is undoubtedly of higher energy than intermediate **b** due to presence of adverse transannular interactions.

The amide **14** was converted into the amine **15** in two steps (78% overall yield). This Hofmann reaction was best accomplished using [1,1-bis-(trifluoroacetoxy)]iodobenzene, a reagent which works under slightly acidic and very mild conditions.[13]

The amine **15** was coupled with the isocyanate **16** (available from α-methylacrylate[14]) to form the acryloylurea **17** (Scheme 2). Cyclization under basic conditions[15] was unsuccessful, but acidic conditions followed by reprotection of the primary hydroxy group furnished the required pyrimidinedione **18** (84% overall yield). Removal of the benzyl group was accomplished by hydrogenation over palladium(II) hydroxide to afford the alcohol **19** (75%). Mesylation (97% yield) and displacement of the mesyl group using azide ion (92% yield) gave the compound **20** which was deprotected to give the target molecule **5** (86%).

Treatment of the carbocyclic nucleoside analogue **19** with diethylaminosulphur trifluoride gave the difluoro compound **21** (61%) as well as a small amount of the alkene **22** (23%). Removal of the silyl protecting group furnished the required difluoro compound **7** (84%).

The preparation of the third target compound **6** utilized the tricyclic intermediate **10** as the starting material for a further sequence of reactions. Treatment of the ketone **10** with aqueous tetrahydrofuran (THF) gave the alcohol **23** (89%) (Scheme 3). Oxidation of the norbornanone **23** with *m*CPBA gave the ketones **24** and **25** in the ratio 62:38. This mixture was not separated. Treatment with diethylaminosulphur trifluoride (DAST) gave the required fluoro compound **26** (28% yield from **23**) and recovered lactone **24** (55% yield from **23**). The inductive effect of the hydroxy group is clearly not strong enough to channel the Baeyer–Villiger reaction in the desired direction. The unreactivity of the lactone **24** is probably due to the effect of the oxygen substituent in the β-position rendering nucleophilic attack on the activated species (*i.e.* R–OSF_2NEt_2) very slow. Certainly the activated species seemed to be remarkably stable: the polar compound formed on reaction



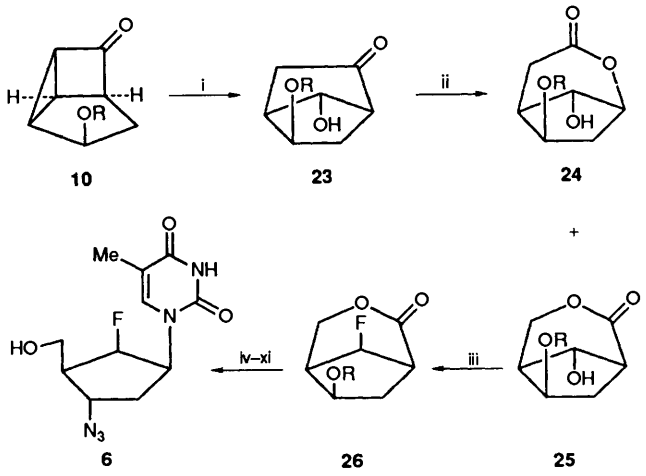
Scheme 2 *Reagents and conditions:* i, C_6H_6, DMF (dimethyl formamide), −20 °C to room temp. over 1 h then room temp., 15 h; ii, 2 mol dm^{-3} HCl, dioxane reflux 1.5 h then *tert*-butylchlorodiphenylsilane, imidazole DMF, room temp., 1 h; iii, H_2, $Pd(OH)_2/C$, $MeCO_2Et$, EtOH, room temp., 24 h; iv, MsCl, pyridine, room temp., 8 h, then NaN_3, DMSO (dimethyl sulphoxide), 55 °C, 1.5–7 h; v, $(Bu)_4NF$, THF (tetrahydrofuran), room temp., 4 h; vi, Et_2NSF_3, CH_2Cl_2, −30 °C, 0.5 h

of the lactone **24** with DAST was not affected by a saturated aqueous sodium hydrogen carbonate over a period of 2 min; stirring the mixture over 40 min gave a good yield of recovered **24**.

The fluoro compound **26** was converted into the azide **6** in 10 steps (13% overall yield) using conditions closely similar to those described for the transformation of the isomer **12** into the azide **5**.

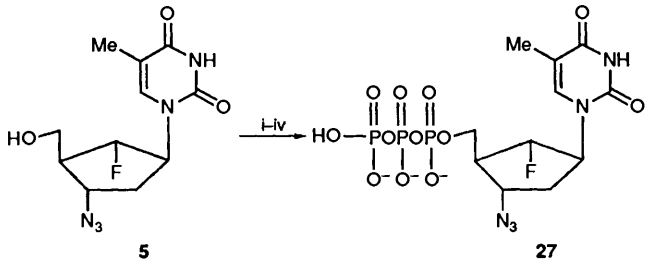
Biological Data.—The nucleoside analogues **5**–**7** were tested for antiviral activity on HIV (RF strain) infected MT4 cells. Only compound **5** showed weak activity (IC_{50} *ca.* 100 μg/cm^3).

The ability of nucleoside analogues to be effective anti-HIV agents is strongly dependent on their intracellular phosphorylation to the corresponding triphosphates. This activation is provided by thymidine kinase(s) and/or thymidylate kinase(s).



Scheme 3 *Reagents and conditions:* i, H_2O, THF (tetrahydrofuran), room temp., 39 h; ii, *m*-chloroperoxybenzoic acid, $NaHCO_3$, CH_2Cl_2, 1–6 h; iii, DAST (diethylaminosulphur trifluoride), CH_2Cl_2, room temp., 12 h; iv, $NH_3(l)$, −33 °C, 16 h (83%); v, *tert*-butylchlorodiphenylsilane, imidazole, DMF (dimethylformamide), room temp., 4 h (97%); vi, $PhI(OCOCF_3)_2$, CH_3CN, H_2O, pyridine, room temp., 6 h (75%); vii, $MeOCH{=}C(CH_3)CONCO$, benzene DMF, −20 °C to room temp. over 1 h then room temp., 15 h (75%); viii, 2 mol dm^{-3} aqueous HCl, dioxane reflux then *tert*-butylchlorodiphenylsilane, imidazole, DMF, room temp., 1 h (70%); ix, H_2, $Pd(OH)_2/C$, CH_3CO_2Et, EtOH, room temp., 24 h then MsCl, pyridine, room temp., 8 h (78%); x, NaN_3, DMSO (dimethylsulphoxide), 55 °C, 7 h (54%); xi, Bu_4NF, THF, room temp., 4 h (100%)

In order to rule out the possibility that the required phosphorylation did not take place in HIV-infected cells, the azide **5** was converted into the triphosphate **27** using the procedure outlined in Scheme 4. The triphosphate **27** showed



Scheme 4 *Reagents and conditions:* i, $(tert\text{-}BuO)_2PNEt_2$, 1*H*-tetrazole, THF (tetrahydrofuran), room temp., 15 min then *m*-chloroperoxybenzoic acid −40 °C, CH_2Cl_2; ii, CF_3CO_2H, CH_2Cl_2, room temp., 1 h then aqueous NH_3; iii, 1,1′-carbonyldiimidazole, DMF (dimethyl formamide), 6.5 h; iv, $P_2O_7H_4{\cdot}NBu_3$, DMF, room temp., 24 h

activity as an inhibitor of HIV-coded reverse transcriptase but at a level (IC_{50} = 1.1 μ mol dm^{-3}) *ca.* two orders of magnitude higher than AZT-triphosphate (IC_{50} = 0.02 μ mol dm^{-3} in the same test system [16]).

The disappointing biological activity of the nucleoside analogues **5**–**7** may be due to the fact that they are all unable to take up a shape that can interact strongly with the target enzyme. X-Ray data on azidothymidine **1** [17] and the difluoro compound **7** (Fig. 3) are available and some comparisons can be made. It has been argued that the C(4′)*endo*, C(3′)*exo* conformation exhibited by the 'B' form of AZT in the crystalline state, reflecting a higher than usual (*ca.* 8 kJ mol^{-1}) energy state, may represent the form in which AZT interacts with enzymes.[18] The preferred shape of the difluoro compound **5** in the crystalline form is distinctly different. The observed $_1E$ conformation results in the base unit and the 5′-hydroxy group being distant [C(6)–N(1′) distance, *i.e.* the C(21)–N(6) distance using the numbering system described in Fig. 3, = 4.90 Å; the

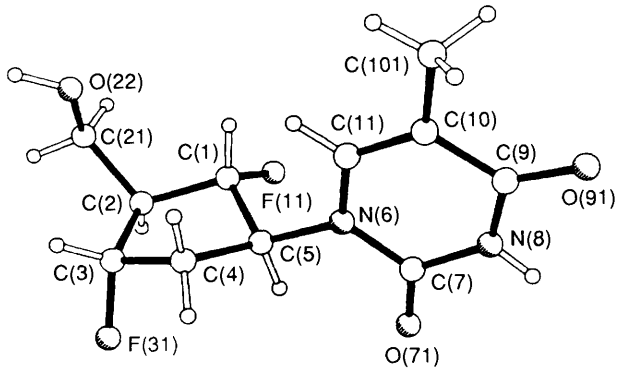


Fig. 3

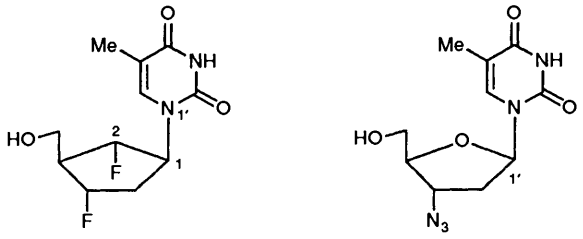


Fig. 4

corresponding distance in AZT (B) is *ca.* 3.5 Å]. Obviously the preferred conformation of the carbocyclic nucleoside may be different in solution. However the $^3J_{1,2}$ coupling (6.5 Hz) corresponds to a dihedral angle of at least 150° (Karplus equation), comparable to the value (157°) found in the solid state.[19] The $^3J_{1,2}$ coupling constant for the AZT-analogue **5** was found to be 7.0 Hz.

While the orientation of the base is *anti-* in both cases, the different non-bonded interactions that are set up in changing the ring-oxygen atom to a CHF moiety seem to have a profound affect on the conformation of the five-membered ring (Fig. 4) adversely affecting the antiviral activity. More detailed discussions on the conformation–biological activity question will be reserved for a later paper.

In conclusion, the carbocyclic nucleosides **5–7** were synthesized and tested for anti-HIV activity. Compound **5** showed marginal activity in the assay involving infected cells; compounds **6** and **7** were inactive. The triphosphate **27** acted as an inhibitor of HIV-coded reverse transcriptase but the level of activity was *ca.* 1% of that shown by AZT-triphosphate. The disappointing biological activity of the fluoro compounds **5–7** can be attributed to the difficulty in the attainment of the required conformation for the compounds to have the requisite interaction with the reverse transcriptase enzyme.

Experimental

THF (tetrahydrofuran) and Et_2O were dried and distilled over sodium metal and benzophenone. DMF (dimethylformamide), CH_2Cl_2, NEt_3 and pyridine were dried and distilled over CaH_2 and stored over molecular sieves (4 Å). Ethyl acetate and light petroleum (fraction of b.p. 40–60 °C) were distilled.

TLC was performed on pre-coated glass plates (Merck silica gel 60F 254). The plate was visualized using UV light (λ 254 nm) or phosphomolybdic acid or *p*-anisaldehyde if not stated otherwise.

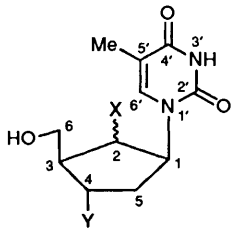
Flash chromatography was performed over silica (Merck silica 60, 40–63 μm). Gravity chromatography was performed over silica (Merck silica 60, 63–200 μm).

Sephadex chromatography was performed on a column (25 × 1000 mm) containing Sephadex LH-20 (90 g). The column was connected with a UV detector (λ 254 nm, LKB 238 Uvicord SII) and a fraction collector. The column was run with a flow rate of 24 $cm^3\ h^{-1}$; 4 cm^3 fractions were collected.

Ion exchange Sephadex chromatography was performed on a column (15 × 400 mm) containing Sephadex DEAE A-25 gel (8 g). The column was connected with a UV detector (λ 254 nm) and a fraction collector. The column was run with a flow rate of 90 $cm^3\ h^{-1}$; 9 cm^3 fractions were collected.

UV spectroscopy was carried out using a Beckmann Acta MIV. IR spectroscopy utilized a Perkin-Elmer 357 grating spectrophotometer while NMR spectroscopic studies employed a Bruker AM250 or a Hitachi Perkin-Elmer R-24B machine. *J* values are given in Hz. Mass spectroscopy was carried out using a VG 12-253 machine or VG ZAB-F apparatus (the latter studies at high resolution were carried out at the SERC-Mass Spectroscopy Service Unit at Swansea).

The carbocyclic nucleosides are numbered in the following way:



5endo-*Benzyloxy*-7anti-*fluorobicyclo*[2.2.1]*heptan*-2-*one* **11**.—To a stirred solution of the tricycle **10** (17.2 mmol) in methylene dichloride (50 cm^3) was added triethylamine tris(hydrofluoride) (Fluka) (3.7 cm^3) at room temp. After 74 h the pale yellow solution was washed with water (50 cm^3), the aqueous phase was back extracted with methylene dichloride (50 cm^3) and the combined organic fractions were dried and evaporated. The residue was chromatographed over silica [eluent light petroleum–ethyl acetate (15:1)] to give the *title compound* (57%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1755; $\delta(CDCl_3)$ 7.54–7.36 (5 H, m, ArH), 5.04 (1 H, dddd, *J* 56, 2, 2 and 2, 7-H), 4.53 and 4.47 (2 H, 2 × d, *J* 12, CH_2O), 4.46 (1 H, m, 5-H), 2.97 (1 H, m, 1-H), 2.80 (1 H, dd, *J* 19, 6.5, 3*endo*-H), 2.77 (1 H, m, 4-H), 2.55 (1 H, m, 6*exo*-H), 2.00 (1 H, dd, *J* 19, 4.5, 3*exo*-H) and 1.62 (1 H, dm, *J* 13.5, 6*endo*-H) (Found: C, 72.0; H, 6.7. $C_{14}H_{15}FO_2$ requires C, 71.8; H, 6.45%).

5endo-*Benzyloxy*-7anti-*hydroxybicyclo*[2.2.1]*heptan*-2-*one* **23**.—To a stirred solution of the tricycle **10** (10 mmol) in THF (25 cm^3) at room temp. was added water (25 cm^3). Stirring was continued for 39 h after which the emulsion was evaporated and dried. The residue was chromatographed over silica [eluent light petroleum–ethyl acetate 2:1] to give the *title compound* **23** (89%), m.p. 48–51 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3390 and 1745. $\delta_H(CDCl_3)$ 7.58–7.29 (5 H, m, ArH), 4.52 and 4.46 (2 H, 2 × d, *J* 12, CH_2O), 4.50 (1 H, m, 5-H), 4.30 (1 H, m, 7-H), 2.77 (1 H, m, 1-H), 2.69 (1 H, d, *J* 18.5, 3*endo*-H), 2.59 (1 H, m, 6*exo*-H), 2.55 (1 H, m, 4-H), 2.29 (1 H, br s, OH), 1.96 (1 H, dd, *J* 18.5 and 4.5, 3*exo*-H) and 1.53 (1 H, ddm, *J* 13 and 1, 6*endo*-H) (Found: C, 72.2; H, 7.1. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9%).

Baeyer–Villiger Oxidation of Ketones **11** *and* **23**.—A suspension of the ketone (1 mmol), 85% *meta*-chloroperoxybenzoic acid (*m*CPBA) (1.6 mmol) and sodium hydrogen carbonate (300 mg) in methylene dichloride (4 cm^3) was stirred at room temp. for 1–6 h. The suspension was washed with 10%

aqueous sodium sulphite (5 cm^3) and saturated aqueous sodium hydrogen carbonate (5 cm^3) and each aqueous layer was back extracted with methylene dichloride (3 × 5 cm^3). The combined organic layers were dried and evaporated and the residue was chromatographed over silica using light petroleum–ethyl acetate (ratio 5:1 and 5:4, respectively) as eluent.

From the ketone **11** was obtained an inseparable mixture of the *lactones* **12** and **13** in the ratio 67:33 (94%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; $\delta_H(CDCl_3)$ (for lactone **12**) 4.67 (1 H, ddd, *J* 11, 7.5 and 1.0, 4*endo* -H), 4.62 and 4.50 (2 H, 2 × d, *J* 12, OCH_2) 4.12 (1 H, ddd, *J* 11, 3.5 and 1, 4*exo*-H), 3.13 (1 H, br t, *J* 7.5, 1-H), 1.93 (1 H, dd, *J* 14.5, 3.5, 7*endo*-H). (For lactone **13**) 4.65 (1 H, m, 1-H), 4.57 and 4.49 (2 H, 2 × d, *J* 12, CH_2O), 3.17 (1 H, ddd, *J* 18.5, 6.5 and 2.0, 4*endo*-H) and 2.10 (1 H, *J* 16, 0.4, 7*endo*-H). Overlapping signals for lactones **12** and **13** 7.43–7.24 (5 H, m, Ar-H), 5.17 (1 H, dm, *J* 52, 8-H), 4.42 (1 H, m, 6-H), 2.85 (1 H, m, 5-H), 2.66–2.48 (1 H, m, 7*exo*-H) (Found: C, 67.4; H, 6.3. $C_{14}H_{15}FO_3$ requires C, 67.2; H, 6.0%).

From the ketone **23** was obtained an inseparable mixture of the *lactones* **24** and **25** in the ratio 62:38 (100%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3400 and 1735; $\delta(CDCl_3)$ (for lactone **24**) 3.10 (1 H, dd, *J* 20, 3.5, 4*endo*-H), 2.00 (1 H, dm, *J* 16, 7*endo*-H) (For lactone **25**) 4.65 (1 H, dd, *J* 11, 1, 4*endo*-H), 4.12 (1 H, *J* 11, 3.5, 4*exo*-H), 2.85 (1 H, d, *J* 7.5, 1-H) and 1.83 (1 H, dd, *J* 14.5, 3.0, 7*endo*-H). Overlapping signals for lactones **24** and **25** δ_H 7.42–7.24 (5 H, m, ArH), 4.61–3.39 (5 H, CH_2O, 6-H and 8-H, 1 H of **24**), 2.69–2.50 (2 H, m, 5-H and 7*exo*-H) and 2.13 (1 H, br s, OH) (Found: $(M + NH_4)^+$ 266.1392. $C_{14}H_{16}O_4$ requires M + NH_4, 266.1392).

Reaction of the Lactone **25** *with DAST* (*Diethylaminosulphur Trifluoride*).—To a stirred solution of a mixture of the lactones **24** and **25** (ratio 62:38) (1.36 g) in methylene dichloride (150 cm^3) at room temp. was added DAST (4.0 cm^3) over 5 min, under an atmosphere of nitrogen. The solution was stirred over 12 h and cooled to 10 °C. Saturated aqueous sodium hydrogen carbonate (100 cm^3) was added dropwise over 20 min. After the mixture had been vigorously stirred for 40 min the layers were separated and the aqueous layer was extracted with methylene dichloride (2 × 50 cm^3). The combined organic layers were dried and evaporated. The residue was chromatographed over silica using ethyl acetate–light petroleum (1:5 then 1:1) as eluent to give, in the first fractions, 6endo-*benzyloxy*-8syn-*fluoro*-3-*oxabicyclo*[3.2.1]*octan*-2-*one* **26** (384 mg) m.p. 117–118 °C (ether); ν_{max}/cm^{-1} 1745; $\delta_H(CDCl_3)$ 7.45–7.28 (5 H, m, ArH), 5.04 (1 H, dt, *J* 53, 5, 8-H), 4.73 (1 H, dd, *J* 11, 2.5, 4*endo*-H), 4.57 and 4.48 (2 H, 2 × d, *J* 12, OCH_2), 4.47 (1 H, dd, *J* 11, 3.5, 4*exo*-H), 4.09 (1 H, m, 6-H), 3.08 (1 H, br t, *J* 6, 1-H), 2.71 (1 H, m, 5-H), 2.33 (1 H, dm, *J* 15, 7*exo*-H) and 1.95 (1 H, ddd, *J* 15, 5.5 and 4, 7*endo*-H) (Found: C, 67.3; H, 6.0. $C_{14}H_{15}FO_3$ requires C, 67.2; H, 6.0%). Later fractions contained unchanged lactone **24** (752 mg).

Treatment of the Lactones **12** *and* **13** *with Liquid Ammonia*.—A solution of the lactones **12** and **13** (4.04 g, ratio 64:36) in liquid ammonia (10 cm^3) was stirred at reflux for 1 h. The ammonia was evaporated and the residue was chromatographed over silica using ethyl acetate–light petroleum (1:3) and then ethyl acetate as eluent. The first fractions contained unchanged **13** as a colourless gum (1.45 g) (Found: C, 67.6; H, 6.2. $C_{14}H_{15}FO_3$ requires C, 67.2; H, 6.0%). Later fractions contained the *amide* **14** (2.76 g), m.p. 67–68.5 °C (ether); ν_{max}/cm^{-1} 3525, 3500, 3410, 3360, 3195, 1690 and 1600; $\delta_H(CDCl_3)$ 7.43–7.24 (5 H, m, ArH), 5.89 and 5.74 (2 H, 2 × br s, NH_2), 5.31 (1 H, dt, *J* 55, 7.5, 2-H), 4.65 and 4.38 (2 H, 2 × d, *J* 12, OCH_2), 4.20 (1 H, m, 4-H), 3.93 and 3.86 (2 H, 2 × dd, *J* 11.5, 3.5 and *J* 11.5, 5.5, CH_2), 2.87 (1 H, dm, *J* 23, 1-H) and 2.55–2.16 (4 H, m, 3-H, 2 × 5-H and OH) (Found: C, 63.05; H, 7.0. $C_{14}H_{18}FNO_3$ requires C, 62.9; H, 6.8%).

Conversion of the Amide **14** *into the Amine* **15**.—To a stirred solution of the amide **14** (405 mg, 1.515 mmol) and imidazole (3.03 mmol) in DMF (5 cm^3) was added *tert*-butylchlorodiphenylsilane (1.82 mmol) dropwise with stirring at room temp. After 15 h the DMF was evaporated and the residue diluted with methylene dichloride. The solution was filtered, the filtrate evaporated to dryness and the product chromatographed over silica using ethyl acetate–light petroleum (2:3) as eluent to give the silyl-protected compound (94% yield) as a colourless gum. To a stirred solution of this compound (1.00 g, 1.98 mmol) in acetonitrile (4 cm^3) was added [1,1-bis(trifluoroacetoxy)]-iodobenzene (3.96 mmol), distilled water (1.6 cm^3) and pyridine (0.36 cm^3) under nitrogen. After being stirred for 3 h at room temp. in the dark the solution was evaporated under reduced pressure and the residue was chromatographed over silica (63–200 μm) using methanol–ethyl acetate (1:25) as eluent to give the trifluoroacetate salt of the amine **15** (1.00 g, 85%) as a yellow oil. The salt was dissolved in methylene dichloride (20 cm^3) and the solution was vigorously shaken with 5% aqueous ammonia (40 cm^3). The aqueous phase was separated and extracted with methylene dichloride (2 × 20 cm^3) and the combined organic fractions were dried and evaporated to give the amine **15** (0.78 g) (83%) as a yellow oil; ν_{max}/cm^{-1} 3300; $\delta_H(CDCl_3)$ 7.75–7.19 (15 H, m, Ar-H), 4.59 (1 H, ddd, *J* 54.5, 7 and 4.5, 2-H), 4.56 and 4.42 (2 H, 2 × d, *J* 12, CH_2O), 4.14 (1 H, m, 4-H), 4.08 and 3.88 (2 H, 2 × dd, *J* 10, 9 and *J* 10, 6, CH_2), 3.38 (1 H, dm, *J* 21, 1-H), 2.51–1.73 (3 H, m, 3-H and 2 × 5-H), 1.60 (2 H, br s, NH_2), 1.07 [9 H, s, $(CH_3)_3C$] [Found: $(M + H)^+$, 478.2585. $C_{29}H_{36}FNO_2Si$ requires (M + H), 478.2578].

Preparation of the Pyrimidine Derivative **18**.—To a stirred solution of the amine **15** (209 mg, 0.437 mmol) in dry DMF (2.5 cm^3) was added β-methoxy-α-methylacryloyl isocyanate **16** (0.44 mol dm^{-3} solution in benzene; 2.3 cm^3) dropwise under an atmosphere of nitrogen at −15 to −20 °C. The solution was warmed to room temp. over 1 h. After the mixture had been stirred for 15 h, the DMF was evaporated and the residue was chromatographed over silica using ethyl acetate–light petroleum (1:4) as eluent to give the *acryloylurea* **17** (98%) [Found: $(M + H)^+$, 619.3014. $C_{35}H_{43}FN_2O_5Si$ requires (M + H) 619.3004]. An emulsion of the acryloylurea **17** (182.5 mg, 0.295 mmol), 1,4-dioxane (3 cm^3) and 4 mol dm^{-3} aqueous hydrochloric acid (3 cm^3) was heated under reflux for 1.5 h. The solvent was evaporated. Ethyl acetate (5 cm^3) was added and removed by distillation. More ethyl acetate (5 cm^3) was added and the process was repeated. The residue was dried and dissolved in DMF (3 cm^3). Imidazole (0.9 mmol) and *tert*-butyldiphenylsilyl chloride (0.9 mmol) were added and the solution was stirred at room temp. under an atmosphere of nitrogen for 1 h. The DMF was evaporated and the residue chromatographed over silica using ethyl acetate–light petroleum (ratio 1:2) as eluent to give the *pyrimidinedione* **18** (145 mg, 84%) as white crystals, m.p. 166–167 °C; λ_{max}/nm 269; ν_{max}/cm^{-1} 3390 and 1690; $\delta_H(CDCl_3)$ 8.67 (1 H, br s, NH), 7.75–7.21 (16 H, m, ArH and 6′-H), 5.41 (1 H, dm, *J* 23, 1-H), 4.86 (1 H, ddd, *J* 55, 10 and 6, 2-H), 4.56 (2 H, br s, CH_2O), 4.25 (1 H, br t, *J* 4.5, 4-H), 4.12 and 3.95 (2 H, t and dd, *J* 10 and *J* 10, 5, CH_2), 2.69–1.83 (3 H, m, 3-H and 2 × 5-H), 1.63 (3 H, d, *J* 1, 5′-CH_3) and 1.11 [9 H, s, $(CH_3)_3C$] (Found: C, 70.2; H, 6.6. $C_{34}H_{39}FN_2O_4Si$ requires C, 69.6; H, 6.7%).

Preparation of the Carbocyclic Nucleoside **5**.—A suspension of the benzyl ether **18** (118 mg, 0.20 mmol) and $Pd(OH)_2$ (20%)/C (250 mg) in ethyl acetate (1.4 cm^3) and ethanol (1.4 cm^3) was stirred under an atmosphere of hydrogen at room

temp. for 24 h. The catalyst was removed by filtration through Kieselguhr and the filtrate was evaporated. Chromatography over silica using ethyl acetate–light petroleum (ratio 2:3) as eluent gave the *alcohol* **19** (75%) as a colourless gum [Found: $(M + H)^+$ 497.2244. $C_{27}H_{33}FN_2O_4Si$ requires (M + H) 497.2272]. To a stirred solution of the alcohol **19** (45.6 mg, 0.092 mmol) in pyridine (0.3 cm^3) was added methanesulphonyl chloride (0.4 mmol) at room temp. After 8 h the solvent was evaporated and the residue was chromatographed over silica using ethyl acetate–light petroleum (ratio 2:3) as eluent to give the mesylate of the *alcohol* **19** (97%) [Found: $(M + H)^+$, 575.2056. $C_{28}H_{35}FN_2O_2SiS$ requires (M + H), 575.2047]. The mesylate (0.1 mmol) and sodium azide (0.5 mmol) in dimethyl sulphoxide (DMSO) (0.55 cm^3) was stirred at 55 °C for 1.5 h. The crude material was dissolved in methylene dichloride (10 cm^3) and washed with water (10 cm^3). The aqueous layer was separated and extracted with methylene dichloride. The combined organic layers were evaporated to give the *azide* **20** (92%) as a white solid, m.p. 184–188 °C. A portion of this material was recrystallized from methylene dichloride to give white needles, m.p. 192–193 °C (Found: C, 61.9; H, 6.2. $C_{27}H_{32}FN_5O_3Si$ requires C, 62.2; H, 6.2%). The silylated compound **20** (39.6 mg, 0.076 mmol) in THF (0.27 cm^3) was stirred with a 1 mol dm^{-3} solution of tetrabutylammonium fluoride in THF (0.115 mmol) for 4 h at room temp. The mixture was applied to the top of a silica column (5 g) and eluted with light petroleum–ethyl acetate (ratio 1:2) to give the *fluoro-azide* **5** (18.5 mg, 86%) as white crystals, m.p. 178–179 °C; λ_{max}(MeOH)/nm 268; ν_{max}(MeCN)/cm^{-1} 3490, 3250, 2100 and 1690; δ_H($CDCl_3$) 7.45 (1 H, q, *J* 1, 6′-H), 5.19 (1 H, dt, *J* 55, 7, 2-H), 4.80 (1 H, m, 1-H), 4.13 (1 H, m, 4-H), 3.78 and 3.73 (2 H, 2 × dd, *J* 10.5 and 4.5 and *J* 10.5 and 5, CH_2), 2.48–2.11 (3 H, m, 3-H and 2 × 5 H) and 1.87 (3 H, d, *J* 1, 5′-CH_3) [Found: $(M + H)^+$ 284.1155. $C_{11}H_{14}FN_5O_3$ requires (M + H) 284.1159].

Preparation of the Difluoro Compound **7**.—To a solution of the alcohol **19** (50 mg, 0.1 mmol) in methylene dichloride (1.4 cm^3) was added DAST (0.15 mmol) at −25 to −30 °C under an atmosphere of nitrogen, with stirring. After 30 min the solution was warmed to 0 °C and treated with saturated aqueous sodium hydrogen carbonate (4 cm^3). The separated aqueous phase was extracted with methylene dichloride (3 × 5 cm^3). The combined organic extracts were dried and evaporated and the residue was chromatographed over silica using ethyl acetate–light petroleum (ratio 1:4) as eluent to give, in the first fractions, the *difluoro compound* **21** (30.5 mg, 61%) m.p. 158–163 °C [Found: $(M + H)^+$ 499.2212. $C_{27}H_{32}F_2N_2O_3Si$ requires (M + H), 499.2229]. Later fractions contained 1-[(1β,2α)-[3-(tert-*butyldiphenylsilyloxymethyl*)-2-*fluoro*]*cyclopent*-3-*enyl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* **22** (11.3 mg, 23%) as a colourless gum; λ_{max}/nm 269; ν_{max}/cm^{-1} 3390 and 1690; δ_H($CDCl_3$) 8.58 (1 H, br s, NH), 7.74–7.33 (10 H, Ar-H), 6.85 (1 H, q, *J* 1, 6′-H), 6.05 (1 H, m, 4-H), 5.71 (1 H, dm, *J* 56, 2-H), 4.92 (1 H, dddd, *J* 26, 9, 5 and 3.5, 1-H), 4.35 (2 H, m, CH_2), 2.96 and 2.58 (2 × H, 2 × m, 2 × 5-H), 1.92 (3 H, d, *J* 1, 5′-CH_3) and 1.10 [9 H, s, $(CH_3)_3C$] [Found: $(M + H)^+$ 479.2159. $C_{27}H_{31}FN_2O_3Si$ requires (M + H), 479.2167].

The silyl ether **21** (25.0 mg, 0.05 mmol) in THF (0.18 cm^3) was treated with a 1 mol dm^{-3} solution of tetrabutylammonium fluoride in THF (0.075 mmol). After being stirred for 4 h, the solution was applied to the top of a silica column (3 g). Ethyl acetate was used as eluent to afford the *carbocyclic nucleoside* **7** (84%), m.p. 199–201 °C (ethanol); λ_{max}/nm 269; ν_{max}(CH_3CN)/cm^{-1} 3520, 3250 and 1690; δ_H(CD_3OD) 7.44 (1 H, q, *J* 1, 6′-H), 5.21 (1 H, dt, *J* 55 and 6.5, 2-H), 5.18–4.91 (2 H, m, 1-H and 4-H), 3.81 and 3.77 (2 H, dd and dd, *J* 10.5 and 5 and 10.5 and 6, CH_2), 2.65–2.29 (3 H, m, 3-H and 2 × 5-H) and 1.91 (3 H, d, *J* 1, 5′-CH_3) [Found: $(M + H)^+$ 261.1058. $C_{11}H_{14}F_2N_2O_3$ requires (M + H) 261.1050].

Preparation of 1-[(1β,2β,3β,4α-[4-*Azido*-2-*fluoro*-3-(*hydroxymethyl*)]-*cyclopentyl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* **6**.—The lactone **26** (731 mg, 2.92 mmol) in liquid ammonia (10 cm^3) was stirred at reflux for 16 h. The ammonia was evaporated and the residue crystallized from methanol at −20 °C to give [(1β,2β,3β,4β)-4-*benzyloxy*-2-*fluoro*-3-(*hydroxymethylcyclopentyl*)]*amide* (645 mg, 83%) as white needles, m.p. 150–151 °C (Found: C, 63.1; H, 6.8. $C_{14}H_{18}FNO_3$ requires C, 62.9; H, 6.8%). To the fluoroamide (210 mg, 0.785 mmol) and imidazole (1.57 mmol) in DMF (2.5 cm^3) was added *tert*-butylchlorodiphenylsilane (0.94 mmol) with stirring. After 4 h the DMF was evaporated. Dichloromethane (10 cm^3) was added and the suspension was filtered. The filtrate was evaporated and the residue chromatographed over silica using ethyl acetate–light petroleum (ratio 2:3) as eluent to give [(1β,2β,3β,4β)-4-*benzyloxy*-3-(tert-*butyldiphenylsilyloxymethyl*)-2-*fluorocyclopentyl*)]*amide* (386 mg, 97%) which solidified on addition of chloroform, m.p. 80–84 °C [Found: (M + H), 506.2528. $C_{30}H_{36}FNO_3Si$ requires (M + H), 506.2526]. To a stirred solution of the silyloxyamide (376 mg, 0.744 mmol) in acetonitrile (1.5 cm^3) was added [1,1-bis(trifluoroacetoxy)]iodobenzene (1.48 mmol) followed by distilled water (0.60 cm^3) and pyridine (134 mm^3) under an atmosphere of nitrogen. The pale yellow solution was stirred at room temp. for 6 h. The solvents were evaporated and the residue was chromatographed over silica (63–200 μm) using ethyl acetate–methanol as eluent (ratio 25:1) to give a trifluoroacetate salt. This salt was dissolved in dichloromethane (20 cm^3) and the solution was vigorously shaken with 5% aqueous ammonia (40 cm^3). The two phases were separated and the aqueous phase was washed with dichloromethane (2 × 20 cm^3). The combined organic fractions were dried and evaporated to give [(1β,2β,3β,4β)-4-*benzyloxy*-3-(tert-*butyldiphenylsilyloxymethyl*)-2-(*fluorocyclopentyl*)]*amine* (265 mg, 75%) as a yellow gum (Found: [M + H], 478.2584. $C_{29}H_{36}FNO_2Si$ requires [M + H], 478.2578). To the amine (132 mg, 0.277 mmol) in dry DMF (1.2 cm^3) was added dropwise over 5 min at −15 to −20 °C a 0.44 mol dm^{-3} solution of β-methoxy-α-methylacryloyl isocyanate (0.55 mmol) in benzene under an atmosphere of nitrogen. The solution was warmed to room temp. over 1 h and stirring was continued for 15 h. After evaporation of the solvents the residue was chromatographed over silica using ethyl acetate–light petroleum (ratio 1:4) as eluent to give 3-*methoxy*-2-*methyl*-N-[(1β,2β,3β,-4β)-4-*benzyloxy*-3-(tert-*butyldiphenylsilyloxymethyl*)-2-*fluorocyclopentylaminocarbonyl*]*prop*-2-*enamide* (128 mg, 75%) as a white solid, m.p. 134–135 °C (ethanol–chloroform) (Found: C, 68.1; H, 7.05. $C_{35}H_{43}FN_2O_5Si$ requires C, 67.9; H, 7.0%). A solution of the propenamide (122 mg, 0.197 mmol) and 1,4-dioxane (2 cm^3) and 4 mol dm^{-3} aqueous hydrochloric acid (2 cm^3) was heated at reflux for 1.5 h. The emulsion was evaporated and the residue was azeotroped using ethyl acetate (2 × 5 cm^3) and dried. The residue was dissolved in DMF (2 cm^3). Imidazole (0.6 mmol) and *tert*-butyldiphenylsilyl chloride (0.6 mmol) were added and the solution was stirred at room temp. for 1 h under an atmosphere of nitrogen. The DMF was evaporated and the residue was chromatographed over silica using ethyl acetate–light petroleum (ratio 1:2) as eluent to give 1-[(1β,2β,3β,4β)-4-*benzyloxy*-3-(tert-*butyldiphenylsilyloxymethyl*)-2-*fluorocyclopentyl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* (81 mg, 70%) as a white solid, m.p. 182–183 °C (ethanol–dichloromethane) [Found: (M + H) 587.2738. $C_{34}H_{39}FN_2O_4Si$ requires (M + H), 587.2742]. A suspension of the pyrimidine dione (78 mg, 0.133 mmol) and 20%

$Pd(OH)_2/C$ (170 mg) in ethyl acetate (1.0 cm^3) and ethanol (1.0 cm^3) was stirred under an atmosphere of hydrogen at room temp. for 24 h. The catalyst was removed by filtration through Kieselguhr and the filtrate was evaporated to give 1-[(1β,2β,3β,4β)-3-(tert-*butyldiphenylsiloxymethyl*)-2-*fluoro*-4-*hydroxycyclopentyl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* (69 mg) [Found: (M + H) 497.2266. $C_{27}H_{33}FN_2O_4Si$ requires (M + H) 497.2272]. To a solution of the crude alcohol (33.4 mg, 0.067 mmol) in pyridine (0.2 cm^3) was added methanesulphonyl chloride (0.276 mmol). After 8 h the solvent was evaporated and the residue was chromatographed over silica to give 1-[(1β,2β,3β,-4β)-3-(tert-*butyldiphenylsilyloxymethyl*)-2-*fluoro*-4-(*methylsulphonyloxy*)*cyclopentyl*]-5-*methylpyrimidine*-2,4-(1H,3H)-*dione* (28.8 mg), m.p. 181–183 °C [Found: (M + H) 575.2087. $C_{28}H_{35}FN_2O_6SSi$ requires (M + H) 575.2047]. A suspension of the mesylate (23.4 mg, 0.041 mmol) and sodium azide (0.205 mmol) in DMSO (0.23 cm^3) was stirred at 55 °C for 7 h. The solvent was evaporated and the residue was chromatographed over silica using ethyl acetate–light petroleum [ratio (1:5)] as eluent to give 1-[(1β,2β,3β,4α)-4-*azido*-3-(tert-*butyldiphenylsilyloxymethyl*)-2-*fluorocyclopentyl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* (11.5 mg) [Found: (M + H) 522.2346. $C_{27}H_{32}FN_5O_3Si$ requires (M + H) 522.2337]. The azide (11.0 mg, 0.021 mmol) in THF (0.07 cm^3) was treated with a solution of 1 mol dm^{-3} tetrabutylammonium fluoride (0.03 mmol) in THF. After 4 h the mixture was applied to the top of a silica column (4 g) and eluted with light petroleum in ethyl acetate (ratio 2:3) to give the *title compound* **6** (6 mg), m.p. 176–177 °C (MeOH); λ_{max}/nm 269; ν_{max}(MeCN)/cm^{-1} 3500, 3250, 2100 and 1690; $\delta_H(CD_3OD)$ 7.46 (1 H, br s, 6′-H), 5.11 (1 H, dt, *J* 55, 3.5, 2-H), 5.10 (1 H, m, 1-H), 4.09 (1 H, m, 4-H), 3.83 and 3.70 (2 H, dd and ddd *J* 11, 8, and 11, 7 and 1.5, 2 × 3-H), 2.64 and 2.14 (2 H, 2 × m, 2 × H-5), 2.31 (1 H, dm, *J* 32.5, 3-H) and 1.88 (3 H, d, *J* 1, 5′-CH_3) [Found: (M + H) 284.1159. $C_{11}H_{14}FN_5O_3$ requires (M + H) 284.1159].

Preparation of the Triphosphate **27**.—To the alcohol **5** (18.4 mg, 0.065 mmol) and di-*tert*-butyl *N*,*N*-diethylphosphoramidite[20] (0.098 mmol) in dry THF (0.16 cm^3) was added 1*H*-tetrazole (0.195 mmol) with stirring at room temp. After 15 min the solution was cooled to −40 °C and treated rapidly with *meta*-chloroperoxybenzoic acid (0.13 mmol) in dry dichloromethane (0.15 cm^3). The solution was warmed to room temp. and treated with 10% aqueous sodium sulphite (1 cm^3) and stirred. After 10 min the aqueous phase was separated and extracted with dichloromethane (3 × 2 cm^3). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate and the aqueous layer was back extracted with dichloromethane. The combined fractions of dichloromethane were dried and evaporated. The residue was chromatographed over silica using light petroleum–ethyl acetate (ratio 1:2) as eluent to give 1-[(1β,2α,3β,4α)-4-azido-3-(di-*tert*-butylphosphoryloxymethyl)-2-fluorocyclopentyl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (25.0 mg, 81%). A solution of the ester (21.1 mg, 0.044 mmol) in dichloromethane (0.1 cm^3) and trifluoroacetic acid (0.03 cm^3) was stirred at room temp. for 1 h. The colourless solution was evaporated and ethanol (1 cm^3) was added. The solvent was evaporated. More ethanol (1 cm^3) was added and removed under reduced pressure. The residue was dissolved in concentrated aqueous ammonia (2 drops) and the solution was diluted with ethanol (0.5 cm^3). After 2 h at 4 °C the suspension was filtered and the white solid was washed with cold ethanol and dried to give the ammonium salt of 1-[(1β,2α,3β,4α)-4-azido-2-fluoro-3-phosphoryloxymethylcyclopentyl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (15.8 mg, 94%), m.p. 150 °C (decomp.). To the anhydrous phosphate (12.6 mg, 0.033 mmol) and DMF (0.3 cm^3) was added a solution of 1,1′-carbonyldiimidazole (0.165 mmol) in DMF (0.3 cm^3) at room temp. under an atmosphere of nitrogen. After 6.5 h, methanol (11 mm^3) was added and, after 30 min, tributylammonium pyrophosphate in DMF (1.7 cm^3, 0.165 mmol) was added. After 24 h, imidazolium pyrophosphate was filtered off and washed with DMF (3 × 1 cm^3). The filtrate was diluted with methanol (10 cm^3) and evaporated. The residue was dissolved in water (1 cm^3) and applied to a DEAE-A-25 Sephadex column and eluted with a linear gradient of triethylammonium carbonate (0–0.4 mol dm^{-3}, 250 cm^3 each, then 0.4 mol dm^{-3}, pH 7.5). Fractions were evaporated and the residue was azeotroped with methanol (2 × 5 cm^3) to give the tris(triethylammonium) salt of 1-[(1β,2α,3β,4α)-4-*azido*-2-*fluoro*-3-(*diphosphorylphosphoryloxymethylcyclopentyl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* **27** (18.4 mg, 67%) as a colourless gum; λ_{max}/nm 268; ν_{max}(MeCN)/cm^{-1} 3250, 2100, 1690 and 1245; $\delta_H(CD_3OD)$ 7.67 (1 H, q, *J* 1, 6′-H), 5.26 (1 H, dt, *J* 54, 7, 2-H), 5.11 (1 H, m, 1-H), 4.32–4.21 (3 H, m, 2 × 3-H and 4-H), 3.18 (18 H, q, *J* 7, 9 × NCH_2), 2.48–2.06 (3 H, m, 3-H and 2 × 5-H), 1.92 (3 H, d, *J* 1, 5′-CH_3) and 1.31 (27 H, t, *J* 7, 9 × NCH_2CH_3); $[M - H]^+$ [-ve FAB] 522.

Table 1 Atomic coordinates (× 10^4) for $C_{11}H_{14}N_2O_3F_2$

Atom	*x*	*y*	*z*
C(1)	3456(3)	2448(3)	3489(2)
C(2)	3591(3)	2471(4)	4256(2)
C(3)	4254(3)	3787(4)	4398(2)
C(4)	4375(3)	4525(4)	3731(2)
C(5)	4387(3)	3341(3)	3223(2)
N(6)	4280(2)	3754(3)	2508(1)
C(7)	5101(3)	3354(4)	2057(1)
N(8)	4911(3)	3766(3)	1402(1)
C(9)	4075(3)	4619(3)	1167(2)
C(10)	3274(3)	5029(3)	1669(2)
C(11)	3409(3)	4581(4)	2303(2)
F(11)	3537(2)	1090(2)	3231(1)
C(21)	2500(3)	2402(4)	4641(2)
O(22)	1841(2)	3591(3)	4486(1)
F(31)	5325(2)	3428(3)	4627(1)
O(71)	5913(2)	2679(3)	2221(1)
O(91)	4056(2)	4947(3)	570(1)
C(101)	2354(4)	6002(6)	1465(2)

Crystal Data for $C_{11}H_{14}N_2O_3F_2$.—$C_{11}H_{14}N_2O_3F_2$, M = 260.24. Orthorhombic, a = 11.999(1), b = 9.653(2), c = 19.769(4) Å, V = 2289.9(5) $Å^3$ (by least-squares refinement on diffractometer angles for 15 automatically centred reflections, λ = 1.541 84 Å), space group *Pbca* (No. 61), Z = 8, D_c = 1.51 g cm^{-3}. Dimensions of data crystal 0.35 × 0.10 × 0.02 mm, cut from a clear colourless plate. F(000) = 1088, μ(Cu-Kα) = 1.10 mm^{-1}.

Data Collection and Processing.—Three-dimensional, room temperature (295 K) X-ray data collected on a Nicolet R3m/V diffractometer with monochromatized Cu-Kα X-radiation. 2θ/ω mode with scan range (ω) of 1.04 degrees plus Kα separation and variable scan speed (1.72–11.72° min^{-1}); 1885 reflections measured (1.0 < 2θ < 115°, min. *hkl* 0 0 0, max. *hkl* 14 11 22) of which 1558 were unique [R(sigma) = 0.045, Friedel opposites merged] giving 1207 with $I > 1.5\sigma(I)$. No absorption correction. 3 control reflections monitored every 97 reflections showed no appreciable decay during 25.6 h of exposure of the crystal to X-rays.

Structure Analysis and Refinement.—Direct methods resulted in the location of all the non-hydrogen atoms. Full matrix least-squares refinement was used with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogens bonded to N(8) and O(22) and the methyl hydrogens were freely refined,

Table 2 Selected bond lengths (Å) with estimated standard deviations in parentheses and selected bond angles (°) with estimated standard deviations in parentheses for $C_{11}H_{14}N_2O_3F_2$

Bond	Length (Å)	Bond	Length (Å)
C(1)–C(2)	1.527(4)	C(1)–C(5)	1.506(4)
C(2)–C(3)	1.525(5)	C(3)–C(4)	1.506(5)
C(4)–C(5)	1.522(5)	C(5)–N(6)	1.473(4)
N(6)–C(7)	1.384(4)	N(6)–C(11)	1.377(4)
C(7)–N(8)	1.374(4)	N(8)–C(9)	1.379(4)
C(9)–C(10)	1.436(5)	C(10)–C(11)	1.337(4)

Bond	Angle (°)	Bond	Angle (°)
C(5)–C(1)–C(2)	105.0(3)	C(3)–C(2)–C(1)	104.5(3)
C(4)–C(3)–C(2)	106.4(3)	C(5)–C(4)–C(3)	102.9(3)
C(4)–C(5)–C(1)	101.1(3)	N(6)–C(5)–C(1)	115.2(3)
N(6)–C(5)–C(4)	115.4(3)	C(7)–N(6)–C(5)	118.7(3)
C(11)–N(6)–C(5)	120.3(3)	C(11)–N(6)–C(7)	120.9(3)
N(8)–C(7)–N(6)	114.1(3)	C(9)–N(8)–C(7)	127.7(3)
C(10)–C(9)–N(8)	114.8(3)	C(11)–C(10)–C(9)	118.5(3)
C(10)–C(11)–N(6)	123.8(3)		

the remaining hydrogen atoms were refined in the riding mode with individual isotropic thermal parameters. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.00024|F_o|^2]^{-1}$ refinement converged at R 0.050, R_w 0.046, goodness-of-fit = 1.42. The final electron density difference synthesis showed no peaks > 0.24 or < −0.20 e Å^{-3}. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[21] A full list of bond lengths and angles and thermal parameters are available from the CCDC.*

* For details of the crystallographic deposition system see Instructions for Authors (1991), *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.

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