Enantiospecific Synthesis of 3′-Hetero-dideoxy Nucleoside Analogues as Potential Anti-HIV Agents[1]

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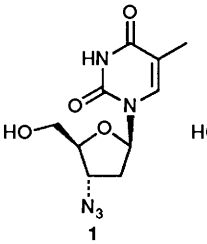
Two series of analogues of 2′,3′-dideoxy carbocyclic nucleosides, in which the 3′-carbon atom is replaced by either an oxygen or a sulfur atom, have been prepared enantiospecifically from diacetone-L-glucose and diacetone-D-glucose respectively. Within each series the guanosine, adenosine, uridine, cytidine and thymidine analogues were prepared, and their anti-HIV activity is discussed. X-Ray molecular structures of (2*R*,4*R*)-4-(6′-amino-9′*H*-purin-9′-yl)tetrahydrofuran-2-methanol and (3′*R*,5′*R*)-4-amino-1-{5′-[(benzyloxy)methyl]tetrahydro-3′-thienyl}pyrimidin-2(1*H*)-one have been determined.

A strategy for AIDS therapy is the reduction of viral replication by inhibition of HIV reverse transcriptase. 2′,3′-Dideoxy nucleoside analogues such as AZT **1** and ddC **2** inhibit this enzyme following intracellular phosphorylation of the 5′-hydroxy group by host cell kinases.

Limitation of clinical use of AZT owing to bone marrow toxicity, and peripheral neuropathy associated with use of ddC, are areas of concern which have spurred a continuing search for less toxic alternative agents.



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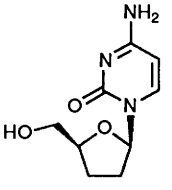

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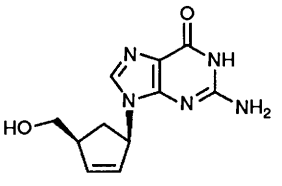

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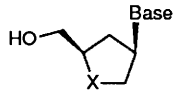
In attempts to prevent phosphorylase-mediated cleavage of the glycosidic linkage of nucleoside analogues,[2] various strategies have been adopted. These have included the use of *C*-nucleosides and carbocyclic analogues, and carbovir **3**[3,4] has emerged as a potent and selective anti-HIV agent. However, carbovir is an exception, and on the whole, carbocycles have proved disappointing as anti-HIV agents.[5] Inactivity of such analogues may well result from a lack of recognition by cellular kinases, possibly as a consequence of the differing electronic environment of the 5′-hydroxy group. We were interested in the possibility that an appropriate electronic environment could be restored by employing analogues of general structure **4**, isomeric with the prototype 2′,3′-dideoxy nucleosides.[1]

It is interesting to note that this type of analogue, where X is represented by NH, has been prepared,[6] but no member of the series exhibited significant anti-HIV activity *in vitro*.

We describe herein the synthesis of such analogues, where X is either oxygen or sulfur, and their evaluation *in vitro* for anti-HIV activity. In the case of carbovir **3**, it has been shown that the anti-HIV activity resides in the (−)-enantiomer (absolute configuration as shown).[4,7] It was therefore of interest to prepare 6′-methylene analogues of type **4** in *both* enantiomeric series, by routes which would be sufficiently flexible to allow incorporation of a range of naturally occurring nucleoside



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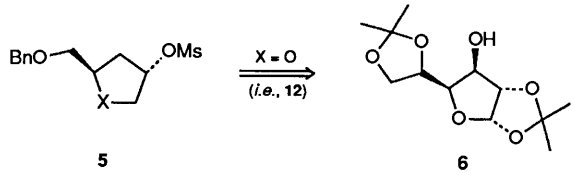
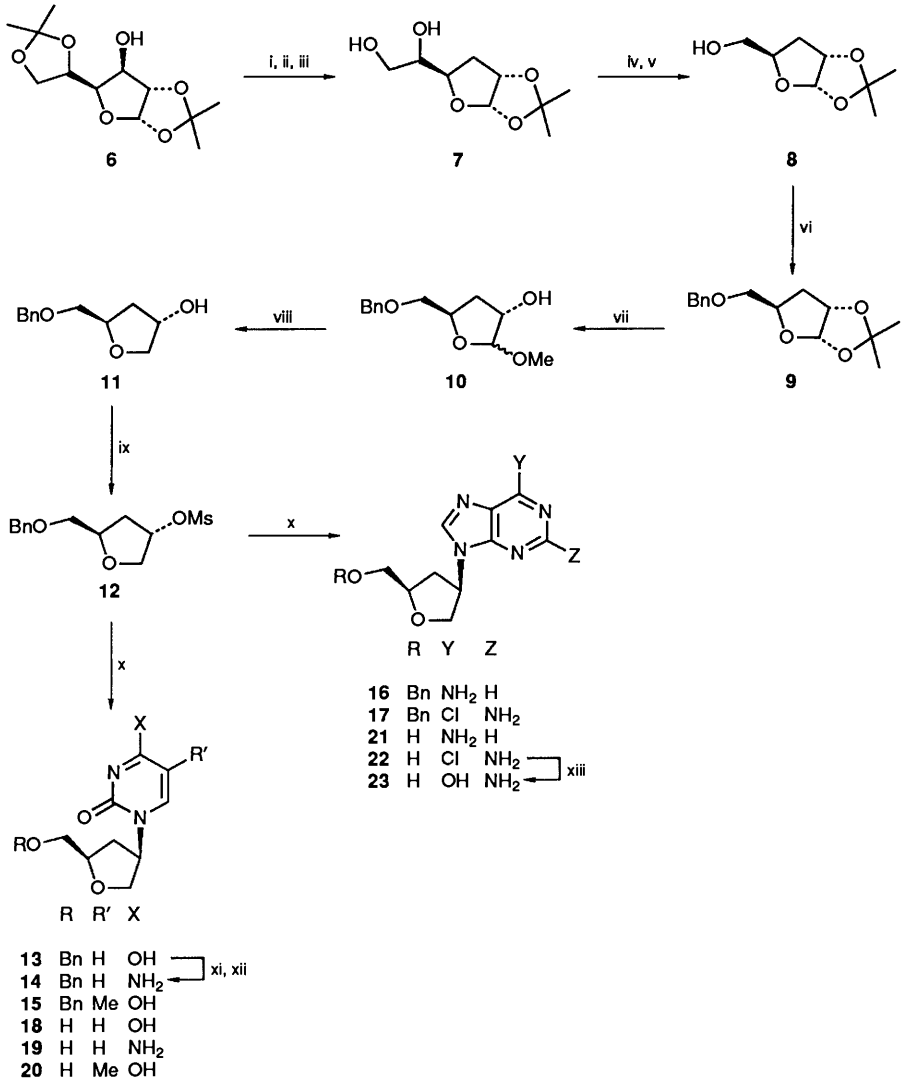


5 **6**

heterocyclic bases. Our synthetic strategy was based upon the preparation of generalised sugar analogues **5**, appropriate for S_N2-type mesyl ester displacement by such bases. Debenzylation would then furnish target compounds.

In the 3′-oxa series (X = O) (*i.e.*, compound **12**) we chose diacetone-L-glucose **6** as our starting material, thus, by deoxygenation at positions 1 and 3, and by cleavage of the 5,6-bond, the basic framework of target molecule **5** would be generated. In the forward direction, the early steps followed transformations well known in the carbohydrate literature (Scheme 1). Diacetone-L-glucose was readily converted into known diol **7**[8] in 58% overall yield following procedures described for the D-series by Gillard *et al.*[9] Cleavage of the 5,6-bond was accomplished by a periodate–borohydride sequence to deliver crystalline pentofuranose **8** in 76% yield, and benzylation proceeded cleanly to give compound **9** as an oil. Spectroscopic data were in agreement with those reported for the same compounds, prepared by a different route.[10] Methanolysis of the remaining acetonide group furnished the methyl glycosides **10** as a 4/1 β/α anomeric mixture. Subsequent exposure of this mixture to the conditions developed by Kraus[11] effected reductive cleavage of the acetal linkage to generate the tetrahydrofuran **11** in 82% yield over the two steps. Treatment of the derived methanesulfonate **12** with the appropriate nucleoside base under the conditions of Johnson and co-workers[12] gave the required products, the moderate yields being in accord with precedent. In this manner, the uracil **13**, thymine **15**, adenine **16** and 9-(2-amino-6-chloropurine) **17** variants were prepared. Conversion of the uracil **13** into the corresponding cytosine analogue **14** was readily achieved by the method of Reese.[13] Final deprotection by hydrogenolysis of the



Scheme 1 *Reagents and conditions*: i, NaH, CS_2, imidazole, MeI; ii, Bu_3SnH, PhMe, heat; iii, aq. MeOH, HCl; iv, $NaIO_4$, aq. MeOH; v, $NaBH_4$, MeOH; vi, NaH, BnBr, TBAI, THF, heat; vii, Dowex 50W-X8 (H), MeOH, heat; viii, Et_3SiH, BF_3·Et_2O, CH_2Cl_2; ix, MsCl, DMAP, CH_2Cl_2; x, nucleoside base, K_2CO_3, DMSO, heat; xi, 1,2,4-triazole, Et_3N, $POCl_3$, MeCN; xii, aq. NH_4 OH, 1,4-dioxane; xiii, aq. HCl, heat.
Note: For convenience sake, carbonyl groups of the nucleoside bases are shown as their enol tautomers.

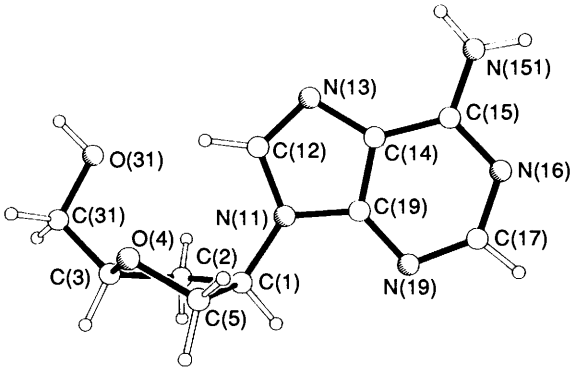


Fig. 1 X-ray molecular structure of compound **21**

5′-benzyl ether proved successful in all cases except compound **17**, and afforded target compounds **18**–**21** in good yields. In order to avoid by-products encountered upon attempted hydrogenolysis of compound **17**, recourse was made to boron tribromide-mediated debenzylation for the required deprotection to give compound **22**. Final conversion of the 2-amino-6-chloropurine base **22** into the corresponding guanine **23** was effected by 1 mol dm^{-3} hydrochloric acid to give target analogue **23**. In the case of 2′,3′-dideoxy adenosine analogue **21**, a single-crystal X-ray diffraction analysis (Fig. 1, Table 1) provided structural confirmation and supportive evidence for the structural assignments of the other analogues prepared. The

Table 1 Atomic co-ordinates (× 10^4) for compound **21**

	x	*y*	*z*
O(4)	13 762(3)	−1 388(3)	24(1)
O(31)	15 962(3)	−1 587(3)	809(1)
N(11)	12 362(3)	−84(3)	877(1)
N(13)	14 553(3)	2 412(3)	1 251(1)
N(16)	10 651(3)	3 108(3)	1 471(1)
N(18)	9 800(3)	365(3)	1 015(1)
N(151)	13 541(3)	5 070(3)	1 741(1(
C(1)	11 506(4)	−1 731(3)	571(1)
C(2)	12 083(4)	−3 102(4)	712(1)
C(3)	13 345(4)	−2 999(4)	295(1)
C(5)	12 146(5)	−1 298(5)	39(1)
C(12)	14 155(4)	927(4)	1 006(1)
C(14)	12 909(3)	2 373(3)	1 287(1)
C(15)	12 403(3)	3 549(3)	1 505(1)
C(17)	9 503(4)	1 595(4)	1 236(1)
C(19)	11 549(3)	835(3)	1 054(1)
C(31)	15 063(4)	−2 936(4)	446(1)

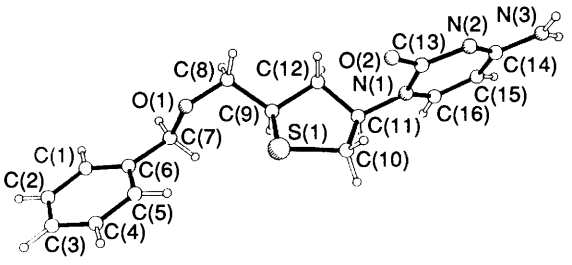
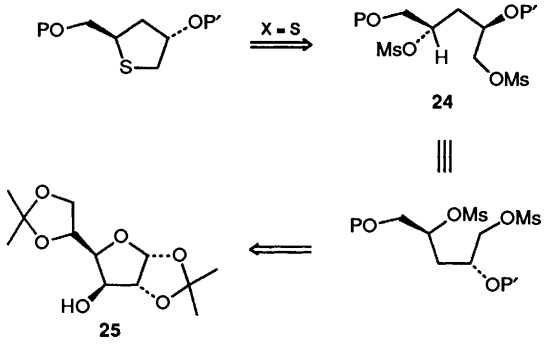


Fig. 2 X-ray molecular structure of compound **36**

enantiomers of this series of analogues were also prepared in the same manner from diacetone-D-glucose.

During the course of this work, a complementary route to the 3′-oxa series of compounds **18**–**21** and **23**, starting from D-glucose, was published by workers at Hoffmann-La Roche.[14]

For the synthesis of the 3′-thia series (**4**; X = S), we turned to diacetone-D-glucose **25** as a cheap chiral starting material. We reasoned that ring closure of a suitably protected bis-mesyl derivative **24** onto sulfide dianion would produce the required sugar analogue.



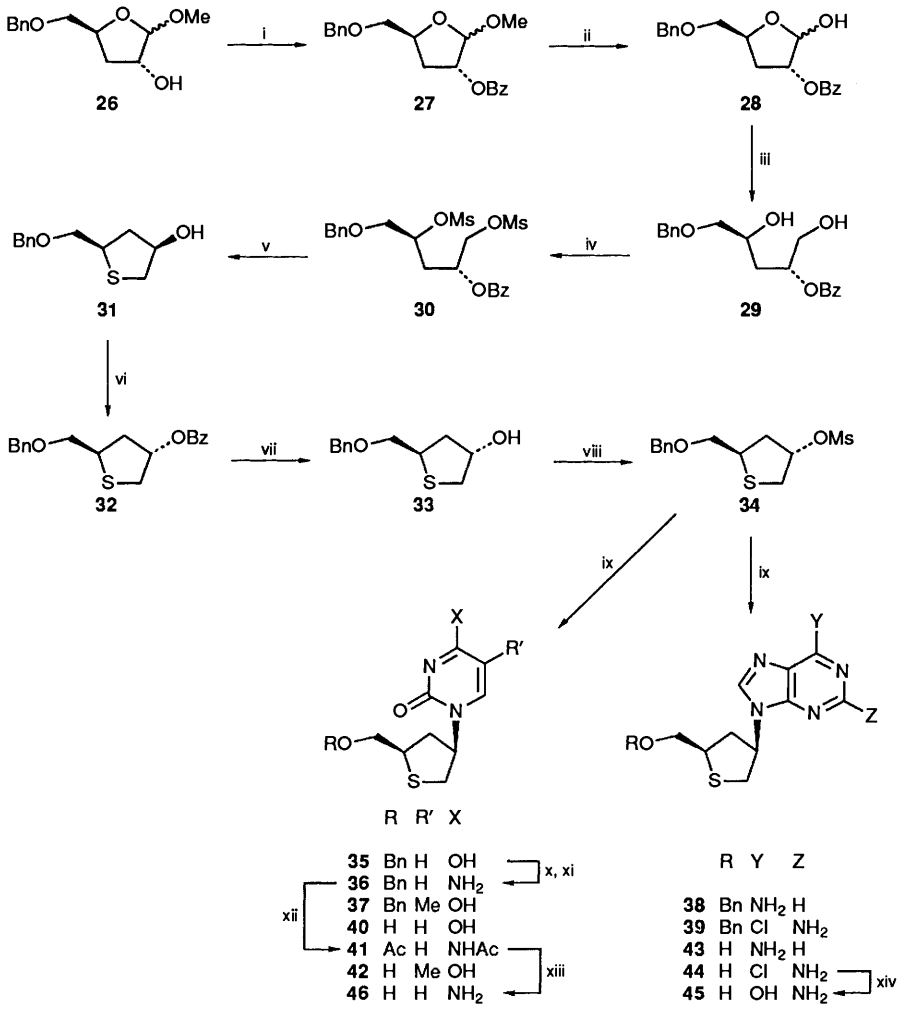
In its turn, we anticipated that compound **24** would be accessible *via* reductive ring opening of a suitable furanose. The early part of this route followed identically that described above in the L-series. Thus compound **26**, in the D-series, was prepared similarly to its enantiomer **10** (Scheme 2). Attempted epimerisation of the secondary hydroxy group at this stage was unsuccessful, using either caesium acetate displacement of the derived methanesulfonate or Mitsunobu-type esterification. This may well be due to an unfavourable steric interaction of the incoming nucleophile with the β-methyl acetal of the major anomer. In an attempt to circumvent this problem, we attempted to oxidise the methyl acetal to the corresponding lactone by application of conditions developed by Grieco,[15] employing boron trifluoride and *m*-chloroperbenzoic acid (MCPBA), but this too was unsuccessful. However, the route was sufficiently flexible to allow us to postpone this transformation until later in the synthesis. Reductive ring opening then called for orthogonal protection of the secondary hydroxy group and so the benzoate ester **27** was prepared. Hydrolysis to hemiacetal **28** proceeded upon exposure to aqueous trifluoroacetic acid (TFA), and ^{1}H NMR spectroscopy of the product showed only a single anomer to be present. Reductive opening to diol **29** was unreliable when using sodium borohydride as a reducing agent, but the milder sodium triacetoxyborohydride gave an excellent yield of the required product. Methanesulfonation of the diol, to give compound **30**, was effected in high yield with methanesulfonyl chloride in a dichloromethane–pyridine mixture. At this stage, we were concerned that ring closure onto sodium sulfide would prove difficult, owing to the β-effect of the oxygen substituents

Table 2 Atomic co-ordinates (× 10^4) for compound **36**

	x	*y*	*z*
S(1)	3 982(2)	4 911	1 992(2)
O(1)	4 001(5)	2 455(5)	2 749(4)
O(2)	5 069(4)	7 510(5)	3 933(4)
N(1)	2 787(5)	7 642(5)	3 281(4)
N(2)	4 086(5)	9 174(5)	4 281(4)
N(3)	3 049(6)	10 790(5)	4 670(5)
C(1)	3 275(9)	−86(7)	1 287(6)
C(2)	3 805(11)	−726(9)	658(7)
C(3)	4 558(10)	−198(9)	156(7)
C(4)	4 825(10)	975(9)	293(7)
C(5)	4 291(9)	1 636(8)	895(6)
C(6)	3 521(8)	1 109(7)	1 415(6)
C(7)	2 941(7)	1 869(7)	2 048(6)
C(8)	3 572(9)	3 300(7)	3 358(6)
C(9)	2 965(7)	4 398(6)	2 749(6)
C(10)	3 496(9)	6 448(7)	2 037(6)
C(11)	2 656(7)	6 509(6)	2 742(5)
C(12)	2 906(8)	5 449(6)	3 419(6)
C(13)	4 043(6)	8 091(6)	3 852(5)
C(14)	2 966(6)	9 731(6)	4 227(5)
C(15)	1 698(6)	9 253(6)	3 745(6)
C(16)	1 644(7)	8 227(7)	3 261(6)
S(1B)	817(2)	9 875(2)	7 864(2)
O(1B)	1 726(5)	12 319(5)	7 736(4)
O(2B)	−573(4)	6 911(4)	5 404(4)
N(1B)	1 635(5)	7 292(5)	6 195(4)
N(2B)	906(5)	5 418(5)	5 450(4)
N(3B)	2 423(5)	3 952(5)	5 534(5)
C(1B)	1 571(9)	15 181(7)	8 670(7)
C(2B)	873(11)	15 803(8)	9 196(8)
C(3B)	283(10)	15 253(8)	9 782(7)
C(4B)	377(10)	14 011(9)	9 905(7)
C(5B)	1 082(9)	13 425(7)	9 376(6)
C(6B)	1 689(7)	13 963(7)	8 755(6)
C(7B)	2 483(8)	13 310(7)	8 231(6)
C(8B)	2 494(8)	11 473(7)	7 434(6)
C(9B)	1 560(7)	10 488(6)	6 966(6)
C(10B)	907(11)	8 382(8)	7 453(8)
C(11B)	1 227(6)	8 449(6)	6 498(6)
C(12B)	2 239(8)	9 423(6)	6 647(6)
C(13B)	592(6)	6 554(6)	5 657(5)
C(14B)	2 173(6)	5 091(6)	5 729(5)
C(15B)	3 257(6)	5 819(6)	6 228(6)
C(16B)	2 913(6)	6 930(6)	6 442(6)

adjacent to both centres undergoing S_N2 displacement.[16] In the event, however, heating of the bis-methanesulfonate with powdered anhydrous sodium sulfide in dimethylformamide (DMF)[17] effected ring closure, concomitant with removal of the benzoate group, to afford the tetrahydrothiophene **31** in good yield. Epimerisation of the secondary alcohol was now easily accomplished using Mitsunobu esterification[18] with benzoic acid, followed by deprotection. Methanesulfonate **34** was obtained in good yield, and S_N2 displacement with a range of nucleoside bases was undertaken using similar conditions to those employed in the 3′-oxa series. A single-crystal X-ray diffraction analysis (Fig. 2, Table 2) of the cytidine analogue **36**, derived as before from the corresponding uridine analogue **35**, provided structural confirmation.

Owing to the inapplicability of hydrogenolysis of benzyl groups in the 3′-thia series, final deprotection was carried out in most cases by low-temperature exposure to boron tribromide, and acid-mediated hydrolysis of compound **44** to give the guanosine analogue **45**, was carried out as in the 3′-oxa series. Owing to its insolubility in dichloromethane, an alternative two-step protocol was adopted for cytidine analogue **36**. Thus, acetolysis with boron trifluoride–diethyl ether in acetic anhydride gave, as the major product, diacetyl derivative **41**, and subsequent ammonolysis furnished the fully deprotected analogue **46**.



Scheme 2 *Reagents and conditions*: i, BzCl, DMAP, CH_2Cl_2; ii, TFA, water, THF; iii, $NaBH(OAc)_3$, PhMe; iv, MsCl, pyridine, CH_2Cl_2; v, Na_2S, DMF, heat; vi, BzOH, DEAD, Ph_3P, THF; vii, K_2CO_3, MeOH; viii, MsCl, DMAP, CH_2Cl_2; ix, nucleoside base, K_2CO_3, DMSO, heat; x, 1,2,4-triazole, Et_3N, $POCl_3$, MeCN; xi, NH_3, aq. 1,4-dioxane; xii, $BF_3{\cdot}Et_2O$, Ac_2O; xiii, NH_3, MeOH; xiv, aq. HCl, heat.

Biological Activity.—The target compounds were evaluated for anti-viral activity against HIV-1 (RF strain) *in vitro* in whole cell assay (MT4 cells).* Activity was noted in only two target compounds, **21** and **23**, with IC_{50}-values (*i.e.*, the concentration required to reduce viral replication by 50%) of 10 μg cm^{-3} and 4.8 μg cm^{-3}, respectively. These figures are in agreement with those reported by the Hoffmann-La Roche workers.[14] None of the other compounds tested displayed activity at concentrations below 100 μg cm^{-3}. Direct comparison between results of the two enantiomeric series of the 3′-oxa analogues gives further evidence of specific chiral recognition by the enzymes involved. Furthermore, the inactivity of all the corresponding 3′-thia analogues, even though in the 'natural' enantiomeric series, may well be the result of a lack of recognition by the cellular kinases responsible for activation to the corresponding triphosphates.

Experimental

All reactions were routinely carried out under nitrogen. Organic extracts were dried over $MgSO_4$ unless otherwise stated, and evaporated using a rotary evaporator. Light petroleum refers to the fraction boiling between 40 and 60 °C. Tetrahydrofuran (THF) was dried by passage through a column of activated alumina, and CH_2Cl_2 and DMF were stored over activated 4 Å sieves. ^1H NMR spectra were recorded for solutes in the solvent indicated at 250 MHz on a Bruker AC250 spectrometer. Chemical shifts are reported in δ-values relative to Me_4Si as internal standard, and *J*-values are given in Hz. IR spectra were recorded on a Nicolet 5 SXC FT instrument, UV spectra were recorded on a Perkin-Elmer Lambda 5 instrument, and optical rotations (units for $[\alpha]_D$ are 10^{-1} deg cm^2 g^{-1}) were determined using either a Perkin-Elmer 241 or an Optical Activity automatic polarimeter. Mass spectra were recorded on a Finnigan MAT 8400 double-focussing spectrometer, and accurate mass determinations were made by Reading Scientific Services Ltd. using a VG Analytical 7070E instrument in EI mode and by the University of Manchester Mass Spectroscopy Service using a Kratos Concept 1S instrument in CI mode on compounds estimated to be >95% pure by ^1H NMR spectroscopy and TLC.

General Procedure A: Hydrogenolytic Debenzylation.—To a solution of a benzyl ether (~1% w/v) in methanol were added conc. hydrochloric acid (5 drops) and 10% palladium-on-carbon catalyst (a weight-equivalent to the substrate). The mixture was stirred vigorously under hydrogen until the reaction was complete (TLC). The catalyst was filtered off

* We thank J. M. Cameron, J. A. V. Coates, C. Penn, N. Cammack and H. Jenkinson of the Virology Department of Glaxo Group Research for the presentation of these data.

through a pad of Kieselguhr and the filtrate was evaporated to give a residue, which was purified by column chromatography and, if possible, crystallisation.

General Procedure B: Debenzylation by Boron Tribromide.—To a chilled (solid CO_2–acetone bath) and stirred solution of a benzyl ether (~2% w/v) in dichloromethane was added dropwise a 1 mol dm^{-3} solution of boron tribromide in dichloromethane (4 mol equiv.). The mixture was stirred until the reaction was complete (TLC) (generally <2 h), whereupon an equal volume of 2 mol dm^{-3} aq. ammonia was added. The cooling-bath was removed, and stirring was continued for 30–45 min. Evaporation of the mixture gave a residue from which the product was isolated by column chromatography and, if possible, crystallisation.

3-*Deoxy*-1,2-O-*isopropylidene*-α-L-erythro-*pentofuranose* **8**.—A solution of sodium periodate (7.15 g, 33.4 mmol) in water (50 cm^3) was added to a stirred solution of 3-deoxy-1,2-*O*-isopropylidene-α-L-glucose **7** (6.21 g, 30.4 mmol) in a mixture of methanol (100 cm^3) and water (50 cm^3). After 15 min, the mixture was diluted with brine and extracted repeatedly with chloroform. The combined extracts were dried, filtered, and evaporated to give a solid (7.07 g), which was taken up in methanol (450 cm^3). To this stirred solution was added sodium borohydride (1.26 g, 33.4 mmol) portionwise and the mixture was stirred for 25 min, before addition of hydrochloric acid (2 mol dm^{-3}; 15 cm^3). After evaporation of most of the solvent, brine (250 cm^3) was added, and the mixture was extracted with chloroform (3 × 200 cm^3). The extracts were dried, filtered, and evaporated to give the *title compound* **8** as a solid (4.05 g, 76%).* An analytical sample was recrystallised from diethyl ether, m.p. 78–79 °C; $[\alpha]_D^{23}$ +14 (*c* 1.3, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 3585br, 1453, 1382 and 1373; $\delta_H(CDCl_3)$ 5.82 (1 H, d, *J* 4, 1-H), 4.76 (1 H, t, *J* 4, 2-H), 4.35 (1 H, m, 4-H), 3.90 (1 H, ddd, *J* 12, 5 and 2.5, 5-H^a), 3.57 (1 H, m, 5-H^b), 2.01 (1 H, dd, *J* 13 and 5, 3-H^a), 1.82 (2 H, m, 3-H^b and OH), 1.51 (3 H, s, Me) and 1.32 (3 H, s, Me) (Found: C, 55.0; H, 8.3. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10%).

5-O-*Benzyl*-3-*deoxy*-1,2-O-*isopropylidene*-α-L-erythro-*pentofuranose* **9**.—A solution of compound **8** (3.99 g, 22.9 mmol) in THF (130 cm^3) was added to a stirred suspension of sodium hydride (606 mg, 25.2 mmol) in THF (130 cm^3). The mixture was stirred for 20 min, then benzyl bromide (2.99 cm^3, 25.2 mmol) and tetrabutylammonium iodide (TBAI) (50 mg) were added, and the mixture was stirred for 1.5 h at 50 °C. After the mixture had cooled, methanol (10 cm^3) was added, and the mixture was evaporated to give a residue, which was subjected to column chromatography [$CHCl_3$–MeOH (20:1)] giving the *title compound* **9** as an oil (5.45 g, 90%), $[\alpha]_D^{23}$ +13 (*c* 1.5, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1452, 1382 and 1373; $\delta_H(CDCl_3)$ 7.32 (5 H, m, Ph), 5.85 (1 H, d, *J* 4, 1-H), 4.73 (1 H, t, *J* 4, 2-H), 4.58 (2 H, s, PhCH_2), 4.40 (1 H, m, 4-H), 3.66 (1 H, dd, *J* 10 and 3, 5-H^a), 3.55 (1 H, dd, *J* 10 and 4, 5-H^b), 2.06 (1 H, dd, *J* 13 and 5, 3-H^a), 1.78 (1 H, ddd, *J* 13, 10 and 5, 3-H^b), 1.51 (3 H, s, Me) and 1.32 (3 H, s, Me); *m/z* (EI) 264 (M^+), 181, 143, 105 and 91; (+ve CI, NH_3) 282 (MNH_4^+), 264 (M^+) and 224 (Found: M^+, 264.1345. Calc. for $C_{15}H_{20}O_4$: M, 264.1362).

Methyl 5-O-*Benzyl*-3-*deoxy*-α-L-erythro-*pentofuranoside and Methyl* 5-O-*Benzyl*-3-*deoxy*-β-L-erythro-*pentofuranoside* **10**.—A stirred mixture of compound **9** (5.37 g, 20.3 mmol) and Dowex 50W-X8(H) resin (10.74 g) in methanol (260 cm^3) was heated at reflux for 18 h. The mixture was cooled, filtered, and evaporated, and the residue was purified by column chromatography [$CHCl_3$–MeOH (20:1)] to give the *title compounds* **10** as an oil (4.57 g, 94%), shown by NMR spectroscopy to be a ~4:1 mixture of methyl β and α glycosides. A small sample of the mixture was separated by column chromatography [$CHCl_3$–MeOH (20:1)] give the methyl β-glycoside as an oil, $\delta_H(CDCl_3)$ 7.30 (5 H, m, Ph), 4.80 (1 H, s, 1-H), 4.55 (3 H, m, PhCH_2 and 4-H), 4.19 (1 H, m, 2-H), 3.46 (2 H, m, 5-H_2), 3.28 (3 H, s, OMe), 2.52 (1 H, br s, OH) and 1.90 (2 H, m, 3-H_2); *m/z* (+ve CI, methane) 239 (MH^+), 221, 207 and 91.

3S,5R-5-[(*Benzyloxy*)*methyl*]*tetrahydrofuran*-3-*ol* **11**.—Triethylsilane (11.03 cm^3, 69.3 mmol) and boron trifluoride–diethyl ether (6.02 cm^3, 49.5 mmol) were added to a stirred, ice-cooled solution of the epimeric mixture **10** (4.69 g, 19.8 mmol) in dichloromethane (100 cm^3), and the solution was stirred at room temperature for 20 h. Further boron trifluoride–diethyl ether (2.41 cm^3, 19.8 mmol) was added and the mixture was stirred for 24 h before being partitioned between saturated aq. sodium hydrogencarbonate (100 cm^3) and chloroform (2 × 100 cm^3). The combined extracts were washed with brine (75 cm^3), dried, filtered and evaporated to give a residue, which was purified by column chromatography [light petroleum–ethyl acetate (1:2)] to give the *title compound* **11** as a gum (3.60 g, 87%), $[\alpha]_D^{23}$ +7.75 (*c* 1.29, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 3595 and 3423 br; $\delta_H(CDCl_3)$ 7.32 (5 H, m, Ph), 4.58 (2 H, s, PhCH_2), 4.52 (1 H, m, 3-H), 4.39 (1 H, m, 5-H), 4.00 (1 H, dd, *J* 10 and 4, 2-H^a), 3.76 (1 H, d, *J* 10, 2-H^b), 3.58 (1 H, dd, *J* 11 and 3, BnOCH^a), 3.50 (1 H, dd, *J* 11 and 5, BnOC*H*^{b}), 1.92 (2 H, m, 4-H_2); *m/z* (EI) 208, 180, 105, 91 and 87; (+ve CI, NH_3), 226 (MNH_4^+) and 209 (MH^+) (Found: MH^+, 209.1179. $C_{12}H_{16}O_3$ requires MH, 209.1178).

(2R,4S)-2-[(*Benzyloxy*)*methyl*]-4-[(*methylsulfonyl*)*oxy*]-*tetrahydrofuran* **12**.—Methanesulfonyl chloride (0.71 cm^3, 9.18 mmol) was added dropwise to a stirred, ice-cooled solution of the alcohol **11** (1.47 g, 7.06 mmol) and 4-(dimethylamino)pyridine (DMAP) (1.74 g, 14.12 mmol) in dichloromethane (115 cm^3), and the solution was stirred for 30 min. The mixture was then diluted with chloroform (50 cm^3), washed successively with saturated aq. sodium hydrogencarbonate (150 cm^3) and brine (50 cm^3), dried, filtered, and evaporated. The residue was purified by column chromatography [light petroleum–ethyl acetate (2:1)] to give the *title compound* **12** as an oil (1.92 g, 95%), $\nu_{max}(CHBr_3)/cm^{-1}$ 1452, 1359 and 1335; $\delta_H(CDCl_3)$ 7.30 (5 H, m, Ph), 5.33 (1 H, m, 4-H), 4.60 (2 H, s, PhCH_2), 4.35 (1 H, m, 2-H), 4.14 (1 H, dd, *J* 11 and 6, 5-H^a), 4.02 (1 H, d, *J* 11, 5-H^b), 3.61 (1 H, dd, *J* 10 and 4, BnOC*H*^{a}), 3.50 (1 H, dd, *J* 10 and 6, BnOC*H*^{b}), 3.02 (3 H, s, SO_2Me), 2.30 (1 H, dd, *J* 15 and 6, 3-H^a) and 2.11 (1 H, m, 3-H^b); *m/z* (+ve EI) 286 (M^+), 107 and 91.

(3′R,5′R)-9-{5′-[(*Benzyloxy*)*methyl*]*tetrahydrofuran*-3′-*yl*}-9H-*purin*-6-*amine* **16**.—Adenine (0.89 g, 6.56 mmol) and potassium carbonate (1.21 g, 8.74 mmol) were added to a stirred solution of methanesulfonate **12** (1.25 g, 4.37 mmol) in dry dimethyl sulfoxide (DMSO) (20 cm^3) and the mixture was heated at 85 °C for 18 h. After evaporation, the residue was partitioned between chloroform (400 cm^3) and brine (150 cm^3). The combined organic extracts were dried, filtered, and evaporated, and the residue was subjected to column chromatography [$CHCl_3$–MeOH (18:1)]. The major product was recrystallised from chloroform–diethyl ether (5:3), to give the *title compound* **16** (0.66 g, 46%) as a crystalline solid, m.p. 159–160 °C; $[\alpha]_D^{22}$ +42.2 (*c* 0.83, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1651, 1597 and 1576; λ_{max}(EtOH)/nm 260 (ε 14 400); $\delta_H(CDCl_3)$ 8.36 (1 H, s, 2-H), 8.20 (1 H, s, 8-H), 7.32 (5 H, m, Ph), 5.61 (2 H, br s, NH_2), 5.32 (1 H, m, 3′-H), 4.61 (2 H, m, PhCH_2), 4.20 (2 H,

* The enantiomer of compound **8** has been reported {m.p. 79–80 °C; $[\alpha]_D^{20}$ −10 [*c* 0.80, (CH_2Cl_2)]} (ref. 19).

m, 5′-H and 2′-H^a), 4.06 (1 H, dd, *J* 10 and 6, 2′-H^b), 3.77 (1 H, dd, *J* 11 and 3, BnOC*H*^{a}), 3.63 (1 H, dd, *J* 11 and 5, BnOC*H*^{b}), 2.70 (1 H, dt, *J* 14, 8 and 8, 4′-H^a) and 2.14 (1 H, m, 4′-H^b) (Found: C, 62.8; H, 5.8; N, 21.4. $C_{17}H_{19}N_5O_2$ requires C, 62.76; H, 5.89; N, 21.52%).

The following compounds were prepared in a similar manner:

(3′,R,5′R)-9-{5′-[(*Benzyloxy*)*methyl*]*tetrahydrofuran*-3′-*yl*-6-*chloro*-9H-*purin*-2-*amine* **17**, a gum purified by column chromatography [$CHCl_3$–MeOH (30:1)] (52% yield), $[\alpha]_D^{23}$ +3 (*c* 1.6, $CHCl_3$); ν_{max}(DMSO)/cm^{-1} 1641, 1609 and 1556; λ_{max}(MeOH)/nm 223 (ε 27 400), 247 (5700) and 310 (7600); δ_H([$^2H_6$]DMSO) 8.16 (1 H, s, 8-H), 7.32 (5 H, m, Ph), 6.91 (2 H, br s, NH_2), 5.02 (1 H, m, 3′-H), 4.52 (2 H, s, PhCH_2), 4.11 (2 H, m, 5′-H and 2′-H^a) 3.94 (1 H, dd, *J* 9 and 6, 2′-H^b), 3.61 (2 H, m, BnOCH_2), 2.60 (1 H, dt, *J* 14, 8 and 8, 4′-H^a) and 2.02 (1 H, m, 4′-H^b); *m*/*z* (+ve EI) 359 (M$^+$), 268, 253, 170 and 91; (+ve CI, NH_3) 362 and 360 (MH$^+$) (Found: MH$^+$, 360.1212. $C_{17}H_{18}{}^{35}ClN_5O_2$ requires MH, 360.1227).

(3′,R,5′R)-1-{5′-[(*Benzyloxy*)*methyl*]*tetrahydrofuran*-3′-*yl*}-*pyrimidine*-2,4(1H,3H)-*dione* **13**, a gum purified by column chromatography [EtOAc–MeOH (4:1)] (55% yield), δ_H-($CDCl_3$) 9.40 (1 H, s, NH), 7.73 (1 H, d, *J* 7, 6-H), 7.35 (5 H, m, Ph), 5.41 (1 H, d, *J* 7, 5-H), 5.37 (1 H, m, 3′-H), 4.59 (2 H, m, PhCH_2), 4.08 (1 H, m, 5′-H), 3.80–4.02 (3 H, m, BnOCH^a and 2′-H_2), 3.63 (1 H, dd, *J* 10 and 4, BnOCH^b), 2.57 (1 H, dt, *J* 14, 8 and 8, 4′-H^a) and 1.96 (1 H, m, 4′-H^b) (Found: M$^+$, 302.1264. $C_{16}H_{18}N_2O_4$ requires M, 302.1266).

(3′*R*,5′*R*)-1-{5′-[(Benzyloxy)methyl]tetrahydrofuran-3′-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione **15**, a gum purified by column chromatography [$CHCl_3$–MeOH (30:1)] (20% yield), ν_{max}($CHBr_3$)/cm^{-1} 3373 and 1676; λ_{max}(EtOH)/nm 270 (ε 8500); δ_H($CDCl_3$) 8.26 (1 H, br s, NH), 7.53 (1 H, s, 6-H), 7.33 (5 H, m, Ph), 5.35 (1 H, m, 3′-H), 4.60 (2 H, m, PhCH_2), 4.08 (1 H, m, 5′-H), 4.08–3.82 (3 H, m, BnOCH^a and 2′-H_2), 3.62 (1 H, dd, *J* 10 and 4, BnOCH^b), 2.57 (1 H, dt, *J* 14, 8 and 8, 4′-H^a), 1.94 (1 H, m, 4′-H^b) and 1.65 (3 H, s, Me); *m*/*z* (EI) 317 (MH$^+$), 209, 181 and 127.

(3′R,5′R)-4-*Amino*-1-{5′-[(*benzyloxy*)*methyl*]*tetrahydrofuran*-3′-*yl*}*pyrimidin*-2(1H)-*one* **14**.—Phosphoryl trichloride (0.176 cm^3, 1.88 mmol) was added dropwise to a stirred, ice-cooled suspension of 1,2,4-triazole (584 mg, 8.45 mmol) in acetonitrile 5.0 cm^3). Triethylamine (1.14 cm^3, 8.17 mmol) was added dropwise to the resulting mixture. After 20 min, a solution of dione **13** (284 mg, 0.94 mmol) in acetonitrile (5.0 cm^3) was slowly added. The mixture was stirred at room temperature for 18 h, whereupon further phosphoryl trichloride (0.088 cm^3) was added. After a further 22 h, the solvents were removed and the residue was subjected to column chromatography [EtOAc–MeOH (8:1)], to afford the major product as a yellow gum (414 mg). This was suspended in 1,4-dioxane (6 cm^3) and treated, with stirring, with aq. ammonia (*d* 0.880; 0.9 cm^3). After 19 h, the mixture was evaporated and the residue was partitioned between water (10 cm^3) and ethyl acetate (3 × 25 cm^3). The combined organic extracts were washed with brine, dried, filtered, and evaporated to give a residue, which was purified by column chromatography [EtOAc–EtOH 4:1)] to furnish the title compound **14** as a gum (52 mg, 15%), δ_H($CDCl_3$) 7.70 (1 H, d, *J* 7, 6-H), 7.33 (5 H, m, Ph), 5.58 (1 H, d, *J* 7, 5-H), 5.45 (1 H, m, 3′-H), 4.58 (2 H, m, PhCH_2), 4.08 (1 H, m, 5′-H), 4.00–3.75 (3 H, m, BnOCH^a and 2′-H_2), 3.59 (1 H, dd, *J* 10 and 4, BnOCH^b), 2.56 (1 H, dt, *J* 14, 8 and 8, 4-H^a) and 1.84 (1 H, m, 4-H^b).

The following compounds were prepared by debenzylation according to General Procedure A.

(3′R,5′R)-1-[5′-(*Hydroxymethyl*)*tetrahydrofuran*-3′-*yl*]-*pyrimidine*-2,4(1H,3H)-*dione* **18**, a gum purified by column chromatography [$CHCl_3$–MeOH (9:1)] (55% yield), ν_{max}-(DMSO)/cm^{-1} 3360br, 1685 and 1460; λ_{max}(EtOH)/nm 266 (ε 9000); δ_H([$^2H_6$]DMSO) 11.24 (1 H, br s, NH), 7.73 (1 H, d, *J* 7, 6-H), 5.60 (1 H, d, *J* 7, 5-H), 5.11 (1 H, m, 3′-H), 4.92 (1 H, t, OH), 3.95–3.70 (3 H, m, 5′-H and 2′-H_2), 3.62 (1 H, m, HOCH^a), 3.50 (1 H, m, HOCH^b), 2.42 (1 H, dt, *J*, 14, 8 and 8, 4′-H^a) and 1.74 (1 H, m, 4′-H^b); *m*/*z* (EI) 212 (M$^+$) and 112 (Found: M$^+$, 212.0814. $C_9H_{12}N_2O_4$ requires M, 212.0797).

(3′R,5′R)-4-*Amino*-1-[5′-(*hydroxymethyl*)*tetrahydrofuran*-3′-*yl*]*pyrimidin*-2(1H)-*one* **19**, a gum purified by column chromatography [$CHCl_3$–MeOH (9:1)] (67% yield), $[\alpha]_D^{23}$ −6 (*c* 0.5, DMSO); ν_{max}(Nujol)/cm^{-1} 3394, 3317, 3118, 1717, 1677 and 1538; λ_{max} (pH 6 buffer)/nm 284 (ε 3000); δ_H([$^2H_6$]DMSO) 9.68 (1 H, br s, NH), 8.59 (1 H, br s, NH), 8.10 (1 H, d, *J* 7, 6-H), 6.12 (1 H, d, *J* 7, 5-H), 5.10 (1 H, m, 3′-H), 4.00 (1 H, br d, *J* 10, 2′-H^a), 3.88 (1 H, m, 5′-H), 3.79 (1 H, dd, *J* 10 and 5, 2′-H^b), 3.65 (1 H, dd, *J* 12 and 3, HOCH^a), 3.50 (1 H, dd, *J* 12 and 3, HOCH^b), 2.47 (1 H, m, 4′-H^a) and 1.81 (1 H, m, 4′-H^b); *m*/*z* (+ve CI, CH_4), 212 (MH$^+$) and 112 (Found: M$^+$, 211.0954. $C_9H_{13}N_3O_3$ requires M, 211.0957).

(3′R,5′R)-1-[5′-(*Hydroxymethyl*)*tetrahydrofuran*-3′-*yl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* **20**, a gum purified by column chromatography [$CHCl_3$–EtOH (9:1)] (54% yield), $[\alpha]_D^{23}$ +15 (*c* 1.90, DMSO); ν_{max}(DMSO)/cm^{-1} 3412br, 1695, 1680 and 1469; λ_{max}(MeOH)/nm 271 (ε 14 200); δ_H-([$^2H_6$]DMSO) 11.23 (1 H, br s, NH), 7.62 (1 H, s, 6-H), 5.11 (1 H, m, 3′-H), 4.97 (1 H, t, OH), 3.90–3.48 (5 H, m, 5′-H and 2′-H_2 and HOCH_2), 2.39 (1 H, dt, *J* 14, 8 and 8, 4′-H^a) and 1.75 (4 H, m, 4′-H^b and Me); *m*/*z* (EI) 226 (M$^+$) and 126 (Found: M$^+$, 226.0952. $C_{10}H_{14}N_2O_4$ requires M, 226.0953).

(2R,4R)-4-(6′-*Amino*-9′H-*purin*-9′-*yl*)*tetrahydrofuran*-2-*methanol* **21**, as crystals (from EtOH) (73% yield), m.p. 184–185 °C; $[\alpha]_D^{22}$ +31.9 (c 1.05, MeOH); ν_{max}(Nujol)/cm^{-1} 3600–3200br, 1678, 1607 and 1572; λ_{max}(MeOH)/nm 260 (ε 13 300); δ_H([$^2H_6$]DMSO) 8.23 (1 H, s, 2′-H), 8.13 (1 H, s, 8′-H), 7.18 (2 H, br s, NH_2), 5.17 (1 H, m, 4-H), 4.90 (1 H, t, *J* 5.5, OH), 3.99 (3 H, m, 2-H and 5-H_2), 3.61 (1 H, ddd, *J* 2, 4 and 5.5, HOCH^a), 3.54 (1 H, ddd, *J* 12, 5 and 5.5, HOCH^b), 2.57 (1 H, dt, *J* 13, 8 and 8, 3-H^a) and 1.90 (1 H, ddd, *J* 13, 8 and 5, 3-H^b) (Found: C, 51.05; H, 5.5; N, 29.7. Calc. for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77%).

X-Ray Experimental Data for Compound **21**.—*Crystal data.* $C_{10}H_{13}N_5O_2$, M = 235.24. Trigonal, $a = b = 8.529(1)$, $c = 27.109(6)$ Å, $V = 1708(1)$ Å^3 (by least-squares refinement on diffractometer angles for 18 automatically centred reflections, $\lambda = 1.541\,84$ Å). Space group $P3_2\,2\,1$ (No. 154), $Z = 6$, $D_c = 1.37$ g cm^{-3}. $F(000) = 744$, μ(Cu-Kα) = 8.0 cm^{-1}. Compound crystallised from ethanol as hexagonal plates, data crystal approximately 0.23 × 0.23 × 0.025 mm.

Data collection and processing. Three-dimensional, room temperature (295 K) X-ray data were collected on a Nicolet R3m/V diffractometer with monochromatised Cu-Kα X-radiation; $2\theta/\omega$ mode with scan range (ω) 1.36 degrees plus Kα separation and a variable scan speed (1.95–14.65 deg min^{-1}). 4136 Reflections were measured ($0 < 2\theta < 115°$, min *hkl* − 10,0,0; max *hkl* 10,10,30) with 1558 unique reflections [$R(\sigma) = 0.044$, Friedel opposites merged]. 1405 Reflections had $I > 3.0\sigma(I)$. No absorption correction was applied. Control reflections (3) were monitored every 97 reflections and showed no appreciable decay during exposure (59.3 h) 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 with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined in the riding mode. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.000\,28|F_o|^2]^{-1}$, and refinement converged at *R* 0.033, R_w 0.035; goodness-of-fit 1.50.

Maximum and mean shift/error in final cycle of refinement

was 0.025 and 0.001, respectively. It was not possible to confirm the absolute configuration unambiguously using Rogers's η refinement [η 0.74(89)], owing to the absence of a strong anomalous scattering atom in the molecule.

The final electron-density-difference synthesis showed no peaks >0.14 or <-0.24 e Å^{-3}. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[20]

The following compound was prepared according to General Procedure B.

(2R,4R)-4-(2′-*Amino*-6′-*chloro*-9′H-*purin*-9′-*yl*)*tetrahydrofuran*-2-*methanol* **22**, a solid, was purified by column chromatography [$CHCl_3$–MeOH (9:1)] (35% yield), m.p. 195–196 °C; $[\alpha]_D^{23}$ +14 (*c* 0.7, DMSO); ν_{max}(Nujol)/cm^{-1} 3400–3000br, 1618 and 1564; λ_{max}(EtOH)/nm 224 (ε 29 500), 248 (6000) and 310 (8100); δ_H([$^2H_6$]DMSO) 8.26 (1 H, s, 8′-H), 6.91 (2 H, br s, NH_2), 5.03 (1 H, m, 4-H), 4.94 (1 H, t, OH), 4.10–3.90 (3 H, m, 5-H_2 and 2-H), 3.58 (2 H, m, HOCH_2), 2.57 (1 H, m, 3-H^a) and 2.03 (1 H, m, 3-H^b); *m*/*z* (+ve) CI, NH_3), 272 and 270 (MH^+) (Found: MH^+, 270.0762. $C_{10}H_{12}{}^{35}ClN_5O_2$ requires MH, 270.0758).

(3′R,5′R)-2-*Amino*-1,9-*dihydro*-9-[5′-(*hydroxymethyl*)*tetrahydrofuran*-3′-*yl*]-6H-*purin*-6-*one* **23**.—A stirred solution of compound **22** (247 mg, 0.93 mmol) in 1 mol dm^{-3} aq. hydrochloric acid (12 cm^3) was heated at 80 °C for 100 min and then evaporated to give a residue, which was dissolved in water (2 cm^3). 2 Mol dm^{-3} aq. sodium hydroxide (0.8 cm^3) was added to the solution to bring the pH to 8, whereupon a precipitate formed. This was filtered off and recrystallised from water to give the *title compound* **23** as a hygroscopic solid (81 mg, 35%), m.p. 302–306 °C; $[\alpha]_D^{22}$ +16.1 (*c* 0.59, MeOH); ν_{max}(Nujol)/cm^{-1} 3700–3000br, 1726, 1669 and 1627; λ_{max} (pH 6 buffer)/nm 253 (ε 12 200); δ_H([$^2H_6$]DMSO) 10.58 (1 H, br s, NH), 7.81 (1 H, s, 8-H), 6.45 (2 H, br s, NH_2), 4.91 (2 H, m, OH, 3′-H), 3.92 (3 H, m, 5′-H and 2′-H_2), 3.56 (2 H, m, HOCH_2), 2.50 (1 H, m, 4′-H^a) and 1.97 (1 H, m, 4′-H^b); *m*/*z* (+ve thermospray) 252 (MH^+) and 274 (MNa^+) (Found: C, 45.8; H, 6.0; N, 26.8. $C_{10}H_{13}N_5O_3$·0.7H_2O requires C, 45.52; H, 5.46; N, 26.55%). Indicated purity by HPLC 99.3% (t_R 3.06 min; eluent 5% acetonitrile in 0.05 mol dm^{-3} phosphate buffer, pH 1.6; column S5-ODS-2, 150 × 4.6 mm; flow 1.0 cm^3 min; detection at 250 nm).

Methyl 2-O-*Benzoyl*-5-O-*benzyl*-3-*deoxy*-α-*and*-β-D-erythro-*pentofuranoside* **27**.—Benzoyl chloride (26.05 cm^3, 224.4 mmol) was added dropwise to a stirred solution of compound **26** (44.50 g, 187 mmol) and DMAP (45.7 g, 374 mmol) in dry dichloromethane (1 dm^3) at 0 °C. After 1 h, the solution was washed with saturated aq. sodium hydrogencarbonate (600 cm^3). The aqueous layer was washed with chloroform (2 × 150 cm^3) and the combined organic extracts were washed with brine (300 cm^3), dried, filtered, and then evaporated to give a residue, which was purified by column chromatography [light petroleum–ethyl acetate (4:1)] to give the *title compounds* **27** (59.73 g, 93%) as a yellow oil, shown by NMR spectroscopy to be a 4:1 mixture of β and α anomers. A small sample of pure β anomer was isolated by column chromatography for characterisation purposes; ν_{max}($CHBr_3$)/cm^{-1} 1716; δ_H($CDCl_3$) 8.03 (2 H, m, *o*-PhCO_2), 7.56 (1 H, m, *p*-PhCO_2), 7.42 (2 H, m, *m*-PhCO_2), 7.34 (5 H, m, *Ph*CH_2), 5.34 (1 H, d, *J* 4, 2-H), 5.04 (1 H, s, 1-H), 4.61 (3 H, m, 4-H and PhCH_2), 3.57 (2 H, m, 5-H_2), 3.38 (3 H, s, OMe) and 2.18 (2 H, m, 3-H_2); *m*/*z* (+ve CI, NH_3) 360 (MNH_4^+), 343 (MH^+) and 311 (Found: MNH_4^+, 360.1824. $C_{20}H_{22}O_5$ requires MNH_4, 360.1811).

2-O-*Benzoyl*-5-O-*benzyl*-3-*deoxy*-D-erythro-*pentofuranose* **28**.—TFA (250 cm^3) was added to a stirred mixture of the methyl glycoside **27** (44.49 g, 130 mmol) in a mixture of water (125 cm^3) and THF (10 cm^3). After 5 h, aq. sodium carbonate (1.7 mol dm^{-3}; 1 dm^3) was added very slowly. Considerable effervescence occurred. The mixture was extracted with $CHCl_3$ (3 × 350 cm^3) and the combined organic extracts were washed with brine (200 cm^3), dried, filtered and evaporated to give a yellow oil, which was purified by column chromatography [light petroleum–ethyl acetate (2:1)] to give the *title compound* **28** (38.42 g, 90%) as a light yellow oil; ν_{max}($CHBr_3$)/cm^{-1} 3585 and 1717; δ_H($CDCl_3$) 8.02 (2 H, m, *o*-PhCO_2), 7.58 (1 H, m, *p*-PhCO_2), 7.43 (2 H, m, *m*-PhCO_2), 7.35 (5 H, m, *Ph*CH_2), 5.41 (1 H, d, *J* 8, 1-H), 5.33 (1 H, d, *J* 5, 2-H), 4.66 (3 H, m, PhCH_2 and 4-H), 3.93 (1 H, d, *J* 8, OH), 3.72 (1 H, dd, *J* 10 and 3, 5-H^a), 3.51 (1 H, dd, *J* 10 and 3, 5-H^b), 2.49 (1 H, ddd, *J* 13, 8 and 5, 3-H^a) and 2.16 (1 H, dd, *J* 13 and 8, 3-H^b); *m*/*z* (+ve CI, NH_3), 346 (MNH_4^+), 328 and 311 (Found: MNH_4^+, 346.1644. $C_{19}H_{20}O_5$ requires MNH_4, 346.1654).

(2R,4S)-2-*Benzoyloxy*-5-(*benzyloxy*)*pentane*-1,4-*diol* **29**.—Sodium triacetoxyborohydride (30.27 g, 142.8 mmol) was added to a stirred solution of compound **28** (44.81 g, 136 mmol) in toluene (800 cm^3). The mixture was heated at 80 °C for 45 min and then evaporated, and the residue was purified by column chromatography [$CHCl_3$–MeOH (25:1)] to give the *title compound* **29** (37.22 g, 83%) as a clear gum; $[\alpha]_D^{23}$ +12 (*c* 1.4, MeOH); ν_{max}($CHBr_3$)/cm^{-1} 3220br and 1713; δ_H([$^2H_6$]DMSO) 7.96 (2 H, d, *o*-PhCO_2), 7.65 (1 H, m, *p*-PhCO_2), 7.51 (2 H, m, *m*-PhCO_2), 7.30 (5 H, m, *Ph*CH_2), 5.20 (1 H, m, 2-H), 4.90 (1 H, t, *J* 6, 1-OH), 4.84 (1 H, d, *J* 5, 4-OH), 4.44 (2 H, s, PhCH_2), 3.78 (1 H, m, 4-H), 3.62 (2 H, m, 5-H_2), 3.35 (2 H, obscured by H_2O signal, 1-H_2), 1.92 (1 H, m, 3-H^a) and 1.71 (1 H, dt, *J* 13, 6 and 6, 3-H^b); *m*/*z* (EI) 225, 122, 105 and 91; (+ve CI, NH_3) 348 (MNH_4^+), 331 (MH^+) and 208 (Found: MH^+, 331.1559. $C_{19}H_{22}O_5$ requires MH, 331.1545).

(2R,4S)-2-*Benzoyloxy*-5-*benzyloxy*-1,4-*bis*[(*methylsulfonyl*)*oxy*]*pentane* **30**.—Methanesulphonyl chloride (18.16 cm^3, 235.5 mmol) was added to a stirred solution of diol **29** (5.18 g, 15.7 mmol) in a mixture of dichloromethane (100 cm^3) and pyridine (100 cm^3) at 0 °C. After being stirred at 4 °C for 18 h, the mixture was partitioned between chloroform (500 cm^3) and saturated aq. sodium hydrogencarbonate (2 cm^3). The aqueous layer was washed with chloroform (3 × 150 cm^3) and the combined organic extracts were dried, filtered and evaporated. The residue was purified by column chromatography [light petroleum–ethyl acetate (1:2)] to give the *title compound* **30** (6.87 g, 90%) as a light yellow oil; ν_{max}($CHBr_3$)/cm^{-1} 1719 and 1360; δ_H($CDCl_3$) 8.04 (2 H, d, *o*-PhCO_2), 7.60 (1 H, m, *p*-PhCO_2), 7.54 (2 H, m, *m*-PhCO_2), 7.30 (5 H, m, *Ph*CH_2), 5.48 (1 H, m, 2-H), 5.00 (1 H, m, 4-H), 4.51 (4 H, m, 1-H_2 and PhCH_2), 3.69 (2 H, d, *J* 6, 5-H_2), 3.00 (6 H, s, 2 × $MeSO_2$), 2.28 (2 H, t, *J* 7, 3-H_2); *m*/*z* (EI) 486 (M^+), 381 ([M − PhCO]$^+$), 105 ([PhCO]$^+$) and 91.

(3R,5R)-5-[(*Benzyloxy*)*methyl*]*tetrahydrothiophen*-3-*ol* **31**.—Powdered anhydrous sodium sulphide (4.23 g, 54.2 mmol) was added to a stirred mixture bis-methanesulfonate **30** (2.64 g, 5.42 mmol) in dry DMF (120 cm^3) and the mixture was heated at 100 °C. After 3 h the mixture was evaporated, then the residue was partitioned between chloroform (200 cm^3) and saturated aq. sodium hydrogencarbonate (200 cm^3). The aqueous layer was washed with chloroform (100 cm^3) and the combined organic extracts were washed with brine (100 cm^3), dried, filtered, then evaporated. The residue was purified by column chromatography [light petroleum–ethyl acetate (3:1)] to give the *title compound* **31** (0.89 g, 73%) as a light yellow oil; $[\alpha]_D^{23}$ −43 (*c* 1.5, $CHCl_3$); ν_{max}($CHBr_3$)/cm^{-1} 3395; δ_H($CDCl_3$) 7.35 (5 H, m, *Ph*CH_2), 4.67 (1 H, d, *J* 12, PhCH^a), 4.58 (1 H, d, *J* 12,

PhC*H*^{b}), 4.49 (1 H, m, 3-H), 3.94 (1 H, d, *J* 9, OH), 3.70 (1 H, m, 5-H), 3.58 (2 H, m, BnOCH_2), 3.06 (1 H, dd, *J* 12 and 4, 2-H^a), 2.91 (1 H, br d, *J* 12, 2-H^b), 2.18 (1 H, ddd, *J* 13, 4 and 9, 4-H^a) and 2.00 (1 H, br d, *J* 13, 4-H^b); *m/z* (EI) 224 (M^+), 206 ([M − H_2O]$^+$), 117, 103 and 91 (Found: M^+, 224.0858. $C_{12}H_{16}O_2S$ requires M, 224.0871).

(2R,4S)-4-*Benzoyloxy*-2-[(*benzyloxy*)*methyl*]*tetrahydrothiophene* **32**.—A solution of diethyl azodicarboxylate (DEAD) (1.11 cm^3, 7 mmol) in THF (10 cm^3) was added dropwise to a stirred solution of the alcohol **31** (0.82 g, 3.65 mmol), triphenylphosphine (1.84 g, 7.0 mmol) and benzoic acid (0.86 g, 7.0 mmol) in THF (30 cm^3) at room temperature. After 50 min the mixture was partitioned between chloroform (200 cm^3) and saturated aq. sodium hydrogencarbonate (200 cm^3). The aqueous layer was further extracted with chloroform (100 cm^3) and the combined organic extracts were dried, filtered, and evaporated to give a yellow oil. This was purified by column chromatography [light petroleum–ethyl acetate (6:1)] to give the *title compound* **32** (0.98 g, 82%) as a clear oil; $[\alpha]_D^{23}$ −85 (*c* 1.5, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1714; $\delta_H(CDCl_3)$ 8.04 (2 H, m, *o*-PhCO_2), 7.53 (1 H, m, *p*-PhCO_2), 7.44 (2 H, m, *m*-PhCO_2), 7.34 (5 H, m, *Ph*CH_2), 5.76 (1 H, m, 4-H), 4.58 (2 H, br s, PhCH_2), 3.91 (1 H, m, 2-H), 3.66 (1 H, dd, *J* 9 and 6, BnOC*H*^{a}), 3.59 (1 H, dd, *J* 9 and 7, BnOC*H*^{b}), 3.32 (1 H, dd, *J* 12 and 5, 5-H^a), 3.07 (1 H, br d, *J* 12, 5-H^b), 2.50 (1 H, m, 3-H^a) and 1.91 (1 H, ddd, *J* 13, 9 and 4, 3-H^b); *m/z* (EI) 328, 206, 122, 105, 91 and 85; (+ve CI, NH_3) 346 (MNH_4^+), 329 (MH^+), 221 and 207 (Found: M^+, 328.1180. $C_{19}H_{20}O_3S$ requires M, 328.1133).

(3S,5R)-5-[(*Benzyloxy*)*methyl*]*tetrahydrothiophen*-3-*ol* **33**.—Potassium carbonate (1.21 g, 8.79 mmol) was added to a stirred solution of benzoate **32** (0.96 g, 2.93 mmol) in methanol (50 cm^3). After 30 min the mixture was evaporated, then the residue was partitioned between chloroform (50 cm^3) and water (50 cm^3). The aqueous layer was further washed with chloroform (2 × 50 cm^3) and the combined organic extracts were dried, filtered, and evaporated to give a residue, which was purified by column chromatography [light petroleum–ethyl acetate (1:1)] to give the *title compound* **33** (0.53 g, 81%) as a clear oil; $[\alpha]_D^{23}$ −62 (*c* 1.3, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 3594; $\delta_H(CDCl_3)$ 7.33 (5 H, m, *Ph*CH_2), 4.63 (1 H, m, 3-H), 4.57 (2 H, br s, PhCH_2), 3.79 (1 H, m, 5-H), 3.60 (1 H, dd, *J* 9 and 7, BnOC*H*^{a}), 3.52 (1 H, dd, *J* 9 and 7, BnOC*H*^{b}), 3.09 (1 H, dd, *J* 12 and 4, 2-H^a), 2.84 (1 H, br d, *J* 12, 2-H^b), 2.25 (1 H, m, 4-H^a), 2.00 (1 H, d, *J* 7, OH) and 1.70 (1 H, ddd, *J* 13, 9 and 4, 4-H^b); *m/z* (EI) 224 (M^+), 206, 117 and 91; (+ve CI, NH_3) 242 (MNH_4^+), 225 (MH^+) and 117 (Found: M^+, 224.0858. $C_{12}H_{16}O_2S$ requires M, 224.0871).

(2R,4S)-2-[(*Benzyloxy*)*methyl*]-4-[(*methylsulfonyl*)*oxy*]*tetrahydrothiophene* **34**.—Methanesulfonyl chloride (0.22 cm^3, 2.78 mmol) was added to a stirred solution of the alcohol **33** (0.48 g, 2.14 mmol) and DMAP (0.52 g, 4.28 mmol) in dichloromethane (60 cm^3) at 0 °C. After 1 h, the mixture was partitioned between chloroform (100 cm^3) and aq. sodium hydrogencarbonate (50 cm^3). The aqueous layer was washed with chloroform (50 cm^3) and the combined organic extracts were dried, filtered, and evaporated to give an oil, which was purified by column chromatography [light petroleum–ethyl acetate (1:1)] to give the *title compound* **34** (0.61 g, 94%), a light yellow oil. An analytical sample was prepared by crystallisation from diethyl ether; m.p. 63–64 °C; $[\alpha]_D^{22}$ −66.6 (*c* 1.08, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1361 and 1333; $\delta_H(CDCl_3)$ 7.32 (5 H, m, *Ph*CH_2), 5.45 (1 H, m, 4-H), 4.56 (2 H, s, PhCH_2), 3.82 (1 H, m, 2-H), 3.60 (1 H, dd, *J* 9 and 7, BnOC*H*^{a}), 3.55 (1 H, dd, *J* 9 and 7, BnOC*H*^{b}), 3.25 (1 H, dd, *J* 12 and 5, 5-H^a), 3.12 (1 H, dd, *J* 12 and 3, 5-H^b), 3.05 (3 H, s, $MeSO_2$), 2.50 (1 H, m, 3-H^a) and 1.94 (1 H, ddd, *J* 13, 9 and 4, 3-H^b) (Found: C, 51.4; H, 6.0; S, 21.1. $C_{13}H_{18}O_4S_2$ requires C, 51.63; H, 6.00; S, 21.20%).

(3′R,5′R)-1-{5′-[(*Benzyloxy*)*methyl*]*tetrahydro*-3′-*thienyl*}*pyrimidine*-2,4-(1H,3H)-*dione* **35**.—Uracil (1.44 g, 12.84 mmol) and potassium carbonate (2.36 g, 17.12 mmol) were added to a stirred solution of methanesulfonate **34** (2.59 g, 8.56 mmol) in dry DMSO (20 cm^3) and the mixture was heated at 85 °C. After 24 h, the mixture was evaporated and the residue was then purified by chromatography [$CHCl_3$–MeOH (10:1)] to give crude product **35** (2.04 g). A sample of crude compound **35** (231 mg) was further purified by column chromatography [light petroleum–ethyl acetate (1:1)] to afford a small sample (46 mg) as a gum, which was triturated with diethyl ether to give a *solid* for characterisation purposes; m.p. 117–119 °C; $[\alpha]_D^{22}$ −17.2 (*c* 1.04, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1704 and 1687; λ_{max}(EtOH)/nm 265 (ε 11 200); $\delta_H(CDCl_3)$ 9.25 (1 H, br s, NH), 7.35 (6 H, m, *Ph*CH_2 and 6-H), 5.69 (1 H, d, *J* 7, 5-H), 5.20 (1 H, m, 3′-H), 4.55 (2 H, br s, PhCH_2), 3.60 (3 H, m, BnOCH_2 and 5′-H), 3.13 (1 H, dd, *J* 10 and 7, 2′-H^a), 2.91 (1 H, m, 2′-H^b), 2.56 (1 H, m, 4′-H^a) and 1.92 (1 H, m, 4′-H^b); *m/z* (EI) 319 (MH^+), 207 and 91 (Found: MH^+, 319.1109. $C_{16}H_{18}N_2O_3S$ requires MH, 319.1116) (Found: C, 58.5; H, 5.5; N, 8.6; S, 10.0. $C_{16}H_{18}N_2O_3S{\cdot}0.6H_2O$ requires C, 58.37; H, 5.88; N, 8.51; S, 9.74%).

The following compounds were prepared in a similar manner:

(3′*R*,5′*R*)-1-{5′-[(*Benzyloxy*)*methyl*]*tetrahydro*-3′-*thienyl*}-5-*methylpyrimidine*-2,4(1*H*,3*H*)-*dione* **37**, a gum purified by column chromatography (EtOAc) (11% yield), $\nu_{max}(CHBr_3)/cm^{-1}$ 3380 and 1683; λ_{max}(EtOH)/nm 270 (ε 8600); $\delta_H(CDCl_3)$ 9.50 (1 H, s, NH), 7.35 (5 H, m, *Ph*CH_2), 7.13 (1 H, s, 6-H), 5.18 (1 H, m, 3′-H), 4.56 (2 H, s, PhCH_2), 3.60 (3 H, m, BnOCH_2 and 5′-H), 3.09 (1 H, m, 2′-H^a), 2.90 (1 H, m, 2′-H^b), 2.50 (1 H, m, 4′-H^a) and 1.91 (4 H, m, 4′-H^b and Me); *m/z* (EI) 332 (M^+) and 206.

(3′R,5′R)-9-{5′-[(*Benzyloxy*)*methyl*]*tetrahydro*-3′-*thienyl*}-9H-*purin*-6-*amine* **38**, as crystals (from EtOH) (26% yield), m.p. 177–178 °C; $[\alpha]_D^{23}$ −10.0 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 3402, 1627 and 1584; λ_{max}(MeOH)/nm 261 (ε 8600); $\delta_H(CDCl_3)$ 8.36 (1 H, s, 2-H), 7.92 (1 H, s, 8-H), 7.35 (5 H, m, *Ph*CH_2), 5.70 (2 H, br s, NH_2), 5.14 (1 H, m, 3′-H), 4.56 (2 H, s, PhCH_2), 3.80 (1 H, m, 5′-H), 3.60 (2 H, m, BnOCH_2), 3.33 (2 H, m, 2′-H_2), 2.74 (1 H, m, 4′-H^a) and 2.36 (1 H, m, 4′-H^b) (Found: C, 59.65; H, 5.6; N, 20.4. $C_{17}H_{19}N_5OS$ requires C, 59.80; H, 5.61; N, 20.52%).

(3′R,5′R)-9-{5′-[(*Benzyloxy*)*methyl*]*tetrahydro*-3′-*thienyl*}-6-*chloro*-9H-*purin*-2-*amine* **39**, a gum purified by column chromatography [$CHCl_3$–MeOH (15:1)] (26% yield), $[\alpha]_D^{23}$ −22 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 3411, 1608 and 1565; λ_{max}(MeOH)/nm 311; $\delta_H(CDCl_3)$ 7.88 (1 H, s, 8-H), 7.35 (5 H, m, *Ph*CH_2), 5.41 (2 H, br s, NH_2), 4.98 (1 H, m, 3′-H), 4.57 (2 H, m, PhCH_2), 3.77 (1 H, m, 5′-H), 3.58 (2 H, m, BnOCH_2), 3.28 (2 H, d, 2′-H_2), 2.69 (1 H, m, 4′-H^a) and 2.30 (1 H, m, 4′-H^b); *m/z* (EI) 378, 377, 376, 375, 170 and 91; (+ve CI, NH_3) 378 and 376 (MH^+), 340, 170 and 91 [Found: (M^+ + 1), 376.0974. $C_{17}H_{19}ClN_5OS$ requires MH, 376.0999].

(3′R,5′R)-4-*Amino*-1-{5′-[(*benzyloxy*)*methyl*]*tetrahydro*-3′-*thienyl*}*pyrimidin*-2(1H)-*one* **36**.—Phosphoryl trichloride (3.13 cm^3, 33.73 mmol) was added dropwise to a stirred suspension of 1,2,4-triazole (10.69 g, 154.8 mmol) in acetonitrile (100 cm^3) at 0 °C. Triethylamine (20.44 cm^3, 146.55 mmol) was added dropwise during 5 min to the resulting mixture. After 20 min, a solution of crude dione **35** (1.76 g, 5.53 mmol) in acetonitrile (100 cm^3) was added dropwise to the stirred mixture. After 30 min, the reaction mixture was allowed to warm to room temperature, and after 19 h the mixture was cooled to 0 °C and triethylamine (27 cm^3) and then water (18 cm^3) were added. The

mixture was evaporated and the residue was then partitioned between chloroform (100 cm^3) and saturated aq. sodium hydrogen carbonate (150 cm^3). The aqueous layer was further extracted with chloroform (2 × 100 cm^3) and the combined organic extracts were washed with brine (80 cm^3), dried over sodium sulfate, filtered, and evaporated to give a yellow residue. To this stirred residue were added 1,4-dioxane (56 cm^3) and aq. ammonia (*d* 0.88; 11.4 cm^3). After 17 h the solution was evaporated and the residue was purified by column chromatography [$CHCl_3$–MeOH (10:1)] to give the *title compound* **36** (0.27 g, 11%) as an off-white solid. Recrystallisation from ethanol provided a sample for X-ray analysis and characterisation, m.p. 188–190 °C; $[\alpha]_D^{23}$ −7 (*c* 0.9, DMSO); ν_{max}(Nujol)/cm^{-1} 1643 and 1465; λ_{max}(EtOH)/nm 276 (ε 7900); δ_H([$^2H_6$]DMSO) 7.70 (1 H, d, *J* 7, 6-H), 7.35 (5 H, m, *Ph*CH_2), 7.05 (2 H, br s, NH_2), 5.67 (1 H, d, *J* 7, 5-H), 4.97 (1 H, m, 3′-H), 4.52 (2 H, s, PhCH_2), 3.63 (2 H, m) and 3.45 (1 H, m, BnOCH_2 and 5′-H), 2.90 (2 H, m, 2′-H_2), 2.27 (1 H, m, 4-H^a) and 1.90 (1 H, m, 4-H^b) (Found: C, 60.5; H, 6.1; N, 13.4. $C_{16}H_{19}N_3O_2S$ requires C, 60.55; H, 6.03; N, 13.24%).

X-ray Experimental data for **36**.—*Crystal data.* $C_{16}H_{19}N_3O_2S$, M = 317.41. Monoclinic, *a* = 10.445(7), *b* = 11.392(8), *c* = 14.107(8) Å, β = 107.94(5)°, *V* = 1597(3) $Å^3$ (by least-squares refinement on diffractometer angles for 15 automatically centred reflections, λ = 1.541 84 Å). Space group $P2_1$ (No. 4), *Z* = 4, D_c = 1.32 g cm^{-3}. *F*(000) = 672, μ(Cu-Kα) = 18.5 cm^{-1}. The compound was crystallised from ethanol as plates, data crystal approximately 0.40 × 0.22 × 0.07 mm.

Data collection and processing. Three-dimensional, room temperature (295 K) X-ray data collected on a Nicolet R3m/V diffractometer with monochromatised Cu-Kα X-radiation. 2θ/ω mode with scan range (ω) 1.14 degrees plus Kα separation and a variable scan speed (1.95–14.65 deg min^{-1}). 4334 Reflections measured (0 < 2θ < 115°, min *hkl* −11, −12, 0, max *hkl* 10,12,15); 4143 unique reflections [*R*(σ) 0.044, Friedel opposites merged]. 2830 Reflections with $I > 3.0\sigma(I)$. No absorption correction. 2 Control reflections monitored every 98 reflections showed no appreciable decay during 68.9 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 (for two crystallographically independent molecules). Full-matrix least-squares refinement with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined in riding mode. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.003|F_o|^2]^{-1}$, and refinement converged at *R* 0.065, R_w 0.068, goodness-of-fit 1.26. Maximum and mean shift/error in final cycle of refinement were 0.687 and −0.008, respectively. The absolute configuration was determined using Rogers's η refinement [η 0.98(9)]. The final electron-density-difference synthesis showed no peaks >0.53 or <−0.61 e $Å^{-3}$. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[20]

(3′R,5′R)-N-{1-[(5′-*Acetoxymethyl*)*tetrahydro*-3′-*thienyl*]-2-*oxo*-1,2-*dihydropyrimidin*-4-*yl*}*acetamide* **41**.—Boron trifluoride–diethyl ether (0.27 cm^3, 2.22 mmol) was added to a stirred suspension of compound **36** (234 mg, 0.74 mmol) in acetic anhydride (9 cm^3) at 0 °C. After 2 h, TLC indicated an incomplete reaction and further boron trifluoride–diethyl ether (91 mm^3, 0.72 mmol) was added. After 30 min, the mixture was partitioned between chloroform (50 cm^3) and saturated aq. sodium hydrogencarbonate (100 cm^3). Potassium chloride (5 g) was dissolved in the aqueous layer, which was then washed with chloroform (2 × 50 cm^3). The combined organic extracts were dried, filtered, and evaporated to give an oil, which was azeotroped with toluene (20 cm^3) under reduced pressure to remove residual acetic anhydride. The residue was purified by column chromatography [$CHCl_3$–MeOH (20:1)] to give the title compound **41** (115 mg, 50%) as a clear oil; ν_{max}($CHBr_3$)/cm^{-1} 1732, 1691, 1627, 1554 and 1483; λ_{max}(MeOH)/nm 246 and 299; δ_H($CDCl_3$) 9.82 (1 H, br, s, NH), 7.80 (1 H, d, *J* 7, 6-H), 7.47 (1 H, d, *J* 7, 5-H), 5.28 (1 H, m, 3′-H), 4.23 (1 H, dd, *J* 11 and 6, AcOC*H*^{a}), 4.15 (1 H, dd, *J* 11 and 7, AcOC*H*^{b}), 3.72 (1 H, m, 5′-H), 3.23 (1 H, dd, *J* 10 and 7, 2′-H^a), 3.01 (1 H, t, *J* 10, 2′-H^b), 2.57 (1 H, m, 4′-H^a), 2.30 (3 H, s, NH*Ac*), 2.10 (3 H, s, OAc) and 1.99 (1 H, m, 4′-H^b); *m*/*z* (EI) 312 (MH^+) and 269 ([MH − Ac]$^+$).

(3′R,5′R)-4-*Amino*-1-[5′-(*hydroxymethyl*)*tetrahydro*-3′-*thienyl*]*pyrimidin*-2(1H)-*one* **46**.—The acetamide **41** (110 mg, 0.35 mmol) was dissolved in a saturated solution of methanolic ammonia (20 cm^3) and the mixture was stored. After 19 h, the solution was evaporated and the residue was purified by column chromatography [$CHCl_3$–MeOH (5:1)] to give an off-white gum (51 mg). This material was purified by reversed-phase HPLC on a Dynamax C-18 column, eluted with 5% acetonitrile in water containing 0.15% TFA, and gave a residue, which was subjected further to column chromatography [$CHCl_3$–MeOH (10:1)], which furnished the *title compound* **46** (30 mg, 37%) as a foam; $[\alpha]_D^{23}$ +14.3 (*c* 0.21, DMSO); ν_{max}(DMSO)/cm^{-1} 3400br, 1711 and 1643; λ_{max}(MeOH)/nm 275 (ε 2400); δ_H([$^2H_6$]DMSO) 7.77 (1 H, d, *J* 7, 6-H), 7.10 (2 H, br d, NH_2), 5.74 (1 H, d, *J* 7, 5-H), 5.00 (2 H, m, 3′-H and OH), 3.60 (1 H, m, HOC*H*^{a}), 3.40 (2 H, m, HOC*H*^{b} and 5′-H), 2.94 (2 H, m, 2′-H_2), 2.30 (1 H, m, 4′-H^a) and 1.92 (1 H, m, 4′-H^b); *m*/*z* (EI) 228 (MH^+), 112., 97 and 85; (+ve CI, NH_3) 228 (MH^+) and 112 (Found: MH^+, 228.0802. $C_9H_{13}N_3O_2S$ requires MH, 228.0807). Indicated purity by HPLC 98.0% (t_R 7.00 min; eluent 5% acetonitrile in water containing 0.15% TFA, flow 1.0 cm^3/min; column Dynamax C-18, 280 × 4.6 mm; detection at 230 nm).

The following compounds were prepared according to General Procedure B:

(3′*R*,5′*R*)-1-[5′-(Hydroxymethyl)tetrahydro-3′-thienyl]-pyrimidine-2,4(1*H*,3*H*)-dione **40**, as a gum purified by column chromatography [$CHCl_3$–MeOH (15:1)] (65% yield), $[\alpha]_D^{23}$ −8.7 (*c* 0.23, DMSO); ν_{max}(DMSO)/cm^{-1} 3260 and 1690; λ_{max}(MeOH)/nm 265 (ε 7200); δ_H([$^2H_6$]DMSO) 11.29 (1 H, br s, NH), 7.75 (1 H, d, *J* 7, 6-H), 5.54 (1 H, d, 5-H), 4.98 (1 H, t, OH), 4.89 (1 H, m, 3′-H), 3.59–3.39 (3 H, m, HOCH_2 and 5′-H), 2.94 (2 H, m, 2′-H_2), 2.29 (1 H, m, 4′-H^a) and 1.90 (1 H, m, 4′-H^b); *m*/*z* (+ve CI, NH_3) 246 (MNH_4^+), 229 (MH^+) and 211 ([MH − H_2O]$^+$). Indicated purity by HPLC 96.6% (t_R 6.90 min; gradient elution of 5–50% acetonitrile in 0.05 mol dm^{-3} phosphate buffer, pH 1.6, during 20 min, flow 1 cm^3/min; column S5-ODS-2, 150 × 4.6 mm; detection at 270 nm).

(3′R,5′R)-1-[5′-(*Hydroxymethyl*)*tetrahydro*-3′-*thienyl*]-5-*methylpyrimidine*-2,4(1H,3H)-*dione* **42**, as a solid purified by column chromatography [$CHCl_3$–MeOH (10:1)] (53% yield), m.p. 180–181 °C; $[\alpha]_D^{23}$ +7.4 (*c* 0.27, MeOH); ν_{max}(DMSO)/cm^{-1} 3250 and 1690; λ_{max}(MeOH)/nm 271 (ε 13 000); δ_H([$^2H_6$]DMSO) 11.28 (1 H, br s, NH), 7.67 (1 H, s, 6-H), 4.98 (1 H, t, OH), 4.88 (1 H, m, 3′-H), 3.60–3.30 (3 H, m, HOCH_2 and 5′-H), 2.90 (2 H, m, 2′-H_2), 2.23 (1 H, m, 4′-H^a), 1.87 (1 H, m, 4′-H^b) and 1.76 (3 H, s, Me); *m*/*z* (EI) 243 (MH^+), 127, 126 and 116; (+ve CI, NH_3) 260 (MNH_4^+), 243 (MH^+), 225 ([MH − H_2O]$^+$) and 144 (Found: MH^+, 243.0793. $C_{10}H_{14}N_2O_3S$ requires MH, 243.0803).

(2R,4R)-4-(6′-*Amino*-9′H-*purin*-9′-*yl*)*tetrahydrothiophene*-2-*methanol* **43**, as crystals (from EtOH) (47% yield), m.p. 160–162 °C; $[\alpha]_D^{23}$ −1.3 (*c* 1.13, MeOH); ν_{max}(Nujol)/cm^{-1} 3400–3100br, 1666, 1601 and 1575; λ_{max}(MeOH)/nm 261 (ε 13 100); δ_H([$^2H_6$]DMSO), 8.27 (1 H, s, 2′-H), 8.15 (1 H, s, 8′-H), 7.25 (2 H, br s, NH_2), 5.02 (2 H, m, 4-H and OH), 3.60–3.15 (5 H, m, 2-H and HOCH_2 and 5-H_2), 2.58 (1 H, m, 3-H^a) and 2.31 (1 H, m,

3-H^b) (Found: C, 47.6; H, 5.25; N, 27.8. $C_{10}H_{13}N_5OS$ requires C, 47.79; H, 5.21; N, 27.87%).

(2R,4R)-4-(*2'-Amino-6'-chloro-9'H-purin-9'-yl*)*tetrahydrothiophene-2-methanol* **44**, a gum purified by column chromatography [$CHCl_3$–MeOH (10:1)] (79% yield), $[\alpha]_D^{23}$ −11 (*c* 1.05, $CHCl_3$); ν_{max}(DMSO)/cm^{-1} 3600–3200, 1609 and 1556; λ_{max}(MeOH)/nm 248 (ε 5700) and 312 (7400); δ_H([$^2H_6$]DMSO) 8.23 (1 H, s, 8'-H), 7.40 (2 H, br s, NH_2), 4.98 (1 H, t, OH), 4.89 (1 H, m, 4-H), 3.60–3.45 (3 H, m, HOCH_2 and 2-H), 3.16 (2 H, m, 5-H_2), 2.54 (1 H, m, 3-H^a) and 2.20 (1 H, m, 3-H^b); *m/z* (EI) 287, 285, 172, 170 and 134; (+ve CI, NH_3) 288, 286 and 170 (Found: M$^+$, 285.0426. $C_{10}H_{12}ClN_5OS$ requires M, 285.0451).

(3'R,5'R)-2-*Amino*-1,9-*dihydro*-9-[*5'-(hydroxymethyl)tetrahydro-3'-thienyl*]-6H-*purin*-6-*one* **45**. A stirred solution of the chloride **44** (146 mg) in 1 mol dm^{-3} hydrochloric acid (6 cm^3) was heated at 80 °C for 1 h. Addition of sodium hydrogencarbonate (504 mg) to the cooled solution caused precipitation of a solid, which was recrystallised from water to give the *title compound* **45** as a hygroscopic solid (63 mg, 46%), m.p. 288–291 °C; $[\alpha]_D^{23}$ −12.5 (*c* 0.20, DMSO); ν_{max}(Nujol)/cm^{-1} 3600–3000br, 1727, 1631 and 1462; λ_{max}(MeOH)/nm 255 (ε 13 100); δ_H([$^2H_6$]DMSO) 10.58 (1 H, br s, NH), 7.86 (1 H, s, 8-H), 6.50 (2 H, br s, NH_2), 5.02 (1 H, br s, OH), 4.80 (1 H, m, 3'-H), 3.60–3.10 (5 H, m, 5'-H and 2'-H_2 and HOCH_2), 2.48 (1 H, m, 4'-H^a) and 2.14 (1 H, m, 4'-H^b) (Found: C, 41.1; H, 5.1; N, 23.7. $C_{10}H_{13}N_5O_2S$·1.3H_2O requires C, 41.31; H, 5.41; N, 24.09%); *m/z* (EI) 267 (M$^+$), 152 and 151 (Found: M$^+$, 267.0804. $C_{10}H_{13}N_5O_2S$ requires M, 267.0790).

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