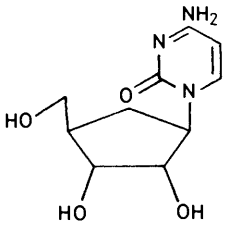
Synthesis of Carbocyclic Nucleosides: Preparation of (−)-5′-Homoaristeromycin and Analogues

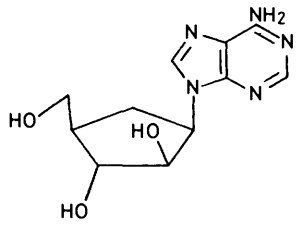
Martin F. Jones and Stanley M. Roberts
Department of Chemistry, University of Exeter, Exeter, Devon, EX4 4QD

Optically pure 5′-homoaristeromycin has been prepared from (L)-ribonolactone using an intramolecular radical cyclisation process to form the five-membered carbocyclic ring with subsequent displacement of a triflate group using a substituted purine to introduce the base moiety.

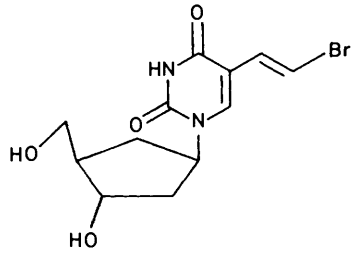
There is considerable current interest in the synthesis of carbocyclic nucleosides because of the pronounced biological activity often associated with molecules of this type. Carbodine (**1**) and cyclaradine (**2**) have interesting anti-viral properties[1] whereas carbocyclic BVDU (**3**)[2] and the 2′-deoxyguanosine analogue (**4**)[3] have noteworthy anti-herpes activity. Compound (**5**) was recently reported to have exquisite activity against herpes simplex virus types 1 and 2.[4] Aristeromycin (**6**) is a naturally occurring anti-tumour and anti-viral agent:[5] we set out to make analogues of this molecule in an effort to decrease the toxicity of the compound towards normal mammalian cells whilst maintaining the desirable anti-viral activity.



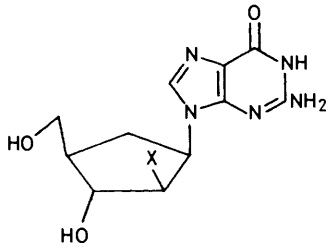
(**1**)



(**2**)



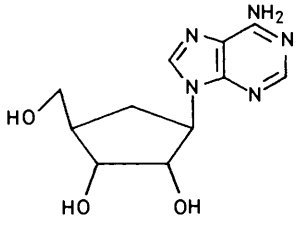
(**3**)



X

(**4**) H

(**5**) F



(**6**)

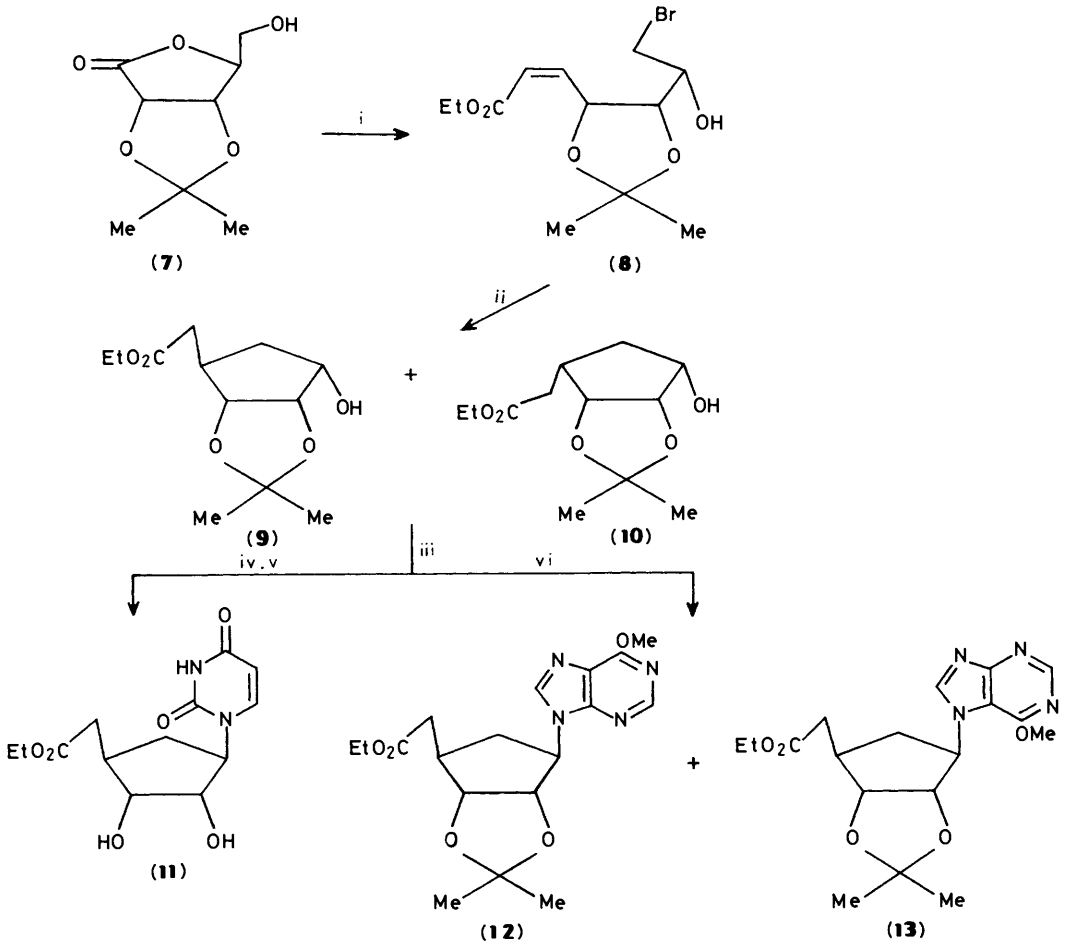
The protected (L)-ribolactone (**7**)[6] was converted into the bromide (**8**) following the procedure described by Wilcox and Thomasco (Scheme).[7] Formation of the primary radical using tributyltin hydride was followed by rapid cyclisation to give a mixture of the two cyclopentane derivatives (**9**) and (**10**). The two compounds were formed in the ratio of 6:1 and could be distinguished by ^{13}C n.m.r. [for compound (**9**) δ_C *inter alia* 84.3, 79.2, 71.1, 60.5, 38.1, 36.9, and 36.7: for compound (**10**) δ_C *inter alia* 80.1, 78.8, 72.0, 60.3, 35.6, 34.7, and 33.1].* The best yield obtained was 89% which compared favourably with the literature report. The efficient removal of tin residues by partition of the crude reaction product between hexane and acetonitrile[8] may have been a contributory factor. Compounds (**9**) and (**10**) were converted into the corresponding trifluoromethanesulphonates (triflates). Displacement of the triflate moiety by uracil using potassium carbonate in dimethyl sulphoxide (DMSO) with sonication of the mixture gave (after acid treatment) a low yield of the uracil derivative (**11**). Reaction of the same triflates with 6-methoxypurine and lithium hydride gave two products, namely the N(9)-substituted purine (**12**) (39%) and the N(7)-isomer (**13**) (27%). The substitution pattern of the two compounds (**12**) and (**13**) was established by u.v. and n.m.r. spectroscopy.[9]

Reduction of the mixture of esters (**9**) and (**10**) with di-isobutylaluminium hydride, selective protection of the primary alcohol function using dimethyl-t-butylsilyl chloride under the standard conditions, and chromatography gave a pure sample of the alcohol (**14**).

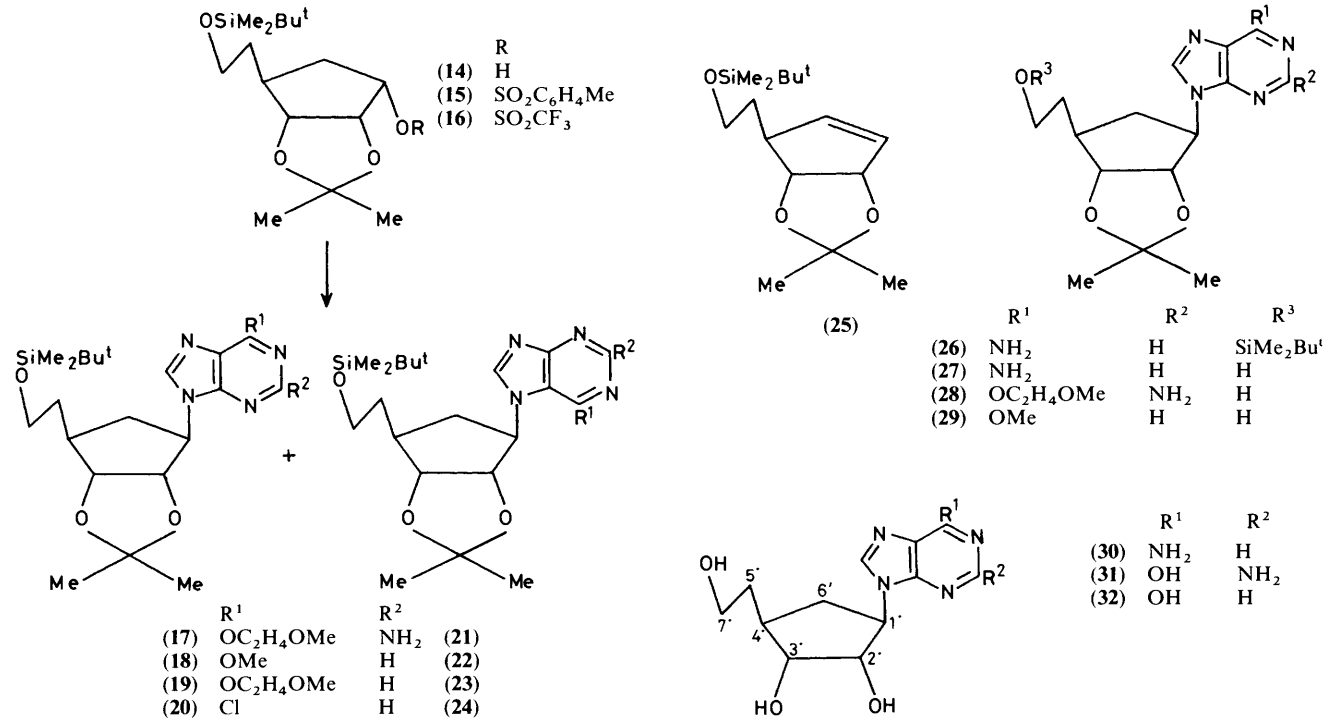
Conversion of the alcohol (**14**) into the corresponding tosylate (**15**) gave a compound which was too unreactive for our purposes. The triflate (**16**) proved to be a more useful entity. Reaction of (**16**) with 2-amino-6-methoxyethoxypurine in dimethylformamide (DMF) containing lithium hydride gave equal quantities of the 9-alkylated purine (**17**) and the 7-alkylated purine (**21**) in 52% yield. The use of the 6-methoxyethoxy group has been advocated by a Scandinavian group who achieved highly regioselective alkylation of the purine at N-9.[10] Obviously the selectivity observed by Kjellberg and Liljenberg, who were working with primary bromides, does not extend to the more complex and more reactive triflate (**16**). Lowering the temperature of the coupling reaction did not improve the selectivity in our case.

Reaction of the triflate (**16**) with 6-methoxypurine gave the corresponding 9-substituted purine (**18**) (38%) and 7-substituted purine (**22**) (36%). Some selectivity was observed on reaction of the triflate (**16**) with 6-methoxyethoxypurine; the ratio of 9-alkylated purine (**19**) to 7-alkylated purine (**23**) was 1.5:1 and the yield of the two products was 63%. The most selective reaction that we observed was that between the triflate (**16**) and 6-chloropurine, which produced the required compound (**20**) (46%) and the isomer (**24**) (9%). The N-9 substituted

* The assignments given here are different from those reported in reference 7.



Scheme. *Reagents:* i, *N*-Bromosuccinimide, Ph_3P, CH_2Cl_2, 2 h, then Bu^i_2 AlH, toluene, −70 °C, 1 h, then Ph_3PCHCO_2Et, DME, $PhCO_2H$ (cat.), 18 h; ii, Bu_3SnH, AIBN; iii, $(CF_3SO_2)_2O$, C_5H_5N, DMAP; iv, uracil, K_2CO_3, DMSO, sonication, then chromatography; v, Amberlyst 15, MeOH; vi, 6-methoxypurine, LiH, DMF, then chromatography



	R
(14)	H
(15)	$SO_2C_6H_4Me$
(16)	SO_2CF_3

	R^1	R^2	
(17)	OC_2H_4OMe	NH_2	(21)
(18)	OMe	H	(22)
(19)	OC_2H_4OMe	H	(23)
(20)	Cl	H	(24)

(25)

	R^1	R^2	R^3
(26)	NH_2	H	$SiMe_2Bu^t$
(27)	NH_2	H	H
(28)	OC_2H_4OMe	NH_2	H
(29)	OMe	H	H

	R^1	R^2
(30)	NH_2	H
(31)	OH	NH_2
(32)	OH	H

purines were very readily separated from the N-7 substituted isomers by chromatography over silica and the substitution pattern was confirmed by a combination of n.m.r. and u.v. spectroscopy. A small amount of a side-product was isolated from some of the coupling reactions; n.m.r. evidence suggested that this minor product was the cyclopentene derivative (**25**).

The chloro compound (**20**) was treated sequentially with methanolic ammonia under pressure [to give the silyl ether (**26**)] and then tetrabutylammonium fluoride to give the acetonide (**27**). Exposure to hot aqueous hydrochloric acid produced a pure sample of (−)-5′-homoaristeromycin (**30**) (70%). Treatment of the amine (**17**) with fluoride ion gave the required alcohol (**28**); warming compound (**28**) with aqueous acid, neutralisation, and recrystallisation furnished the guanosine analogue (**31**) (80%). Similar treatment of the ether (**18**) with fluoride ion gave the acetonide (**29**), which when deprotected with aqueous HCl gave a mixture which was purified by reverse phase h.p.l.c. to afford the hypoxanthine derivative (**32**) (42%).

The nucleoside analogues (**30**)—(**32**) showed disappointing biological activity. For example homoaristeromycin (**30**) was inactive at >300 μg ml^{-1} against HSV-1 and HSV-2 in a microtitre assay. Presumably the primary hydroxy group is not phosphorylated by viral or host cell kinases.[11]

Experimental

Column chromatography was carried out under pressure on MN-Kieselgel 60 230—400 mesh with the eluant specified in parentheses. All reactions requiring anhydrous conditions were conducted in oven-dried apparatus under a static atmosphere of argon. Organic extracts were dried over $MgSO_4$ unless otherwise stated and evaporated at aspirator pressure using a rotary evaporator. Light petroleum refers to the fraction boiling between 40 and 60 °C. Diethyl ether (referred to as ether) and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone ketyl using recycling stills; benzene was freshly distilled from lithium aluminium hydride; CH_2Cl_2 and DMF were distilled from CaH_2 and stored over activated 4Å sieves and amines were freshly distilled from CaH_2. Chemical shifts are reported in δ values relative to Me_4Si as an internal standard. ^1H and ^{13}C N.m.r. spectra were recorded in the solvent indicated at 250 and 62.9 MHz, respectively, on a Bruker AM250 spectrometer. I.r. and u.v. spectra were recorded on Perkin-Elmer 357 and 402 instruments, respectively. Optical rotations were determined using a Thorn-NPL automatic polarimeter Type 243. Mass spectra were recorded on a VG Micromass 16F spectrometer and accurate mass determinations were made on compounds estimated to be >95% pure by ^1H n.m.r. spectroscopy and thin layer chromatography. N.m.r. assignments are labelled according to the scheme of Madhavan and Martin;[5] the numbering system used by us to describe the n.m.r. data is shown on formulae (**30**)—(**32**).

(3aR,4R,6S,6aS)-*Ethyl* 4,5,6,6a-*Tetrahydro*-6-*hydroxy*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxole*-4-*acetate* (**9**) *and* (3aR, 4S, 6S, 6aS)-*Ethyl* 4,5,6,6a-*Tetrahydro*-6-*hydroxy*-2,2-*dimethyl*-3a-H-*cyclopenta*-1,3-*dioxole*-4-*acetate* (**10**).—AIBN (3 mg) and tributyltin hydride (204 μl, 0.76 mmol) were added to a solution of the bromide (**8**)[7] (223 mg, 0.69 mmol) in benzene (7 ml) and the solution was heated under reflux for 4.5 h. The solvent was removed and replaced with acetonitrile (20 ml), and this solution was washed with hexane (3 × 20 ml). The combined hexane layers were back-washed with acetonitrile (20 ml), and the combined acetonitrile layers were evaporated. Purification of the residue by flash chromatography (light petroleum–ethyl acetate, 3:1) furnished the *alcohols* (**9**) and (**10**) as a colourless gum (151 mg, 89%), homogeneous by t.l.c. analysis. (3aR,4R-6S,6aS)-*Ethyl* 4,5,6,6a-*tetrahydro*-6-*hydroxy*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxole*-4-*acetate* (**9**); $\delta_H(CDCl_3)$ 4.47 (1 H, t, *J* 6 Hz, 2′-H), 4.36 (1 H, dd, *J* 6 and 2 Hz, 3′-H), 4.12 (2 H, q, *J* 7 Hz, OCH_2Me), 4.04 (1 H, m, 1′-H), 2.48 (1 H, m, 4′-H), 2.44 (1 H, d, *J* 7 Hz, OH), 2.28 (1 H, dd, *J* 15 and 7 Hz, 5′-H_a), 2.19 (1 H, dd, *J* 15 and 8 Hz, 5′-H_b), 1.93 (1 H, ddd, *J* 13, 8, and 7 Hz, 6′-H_a), 1.67 (1 H, ddd, *J* 13, 5, and 4 Hz, 6′-H_b), 1.47 (3 H, s, Me), 1.31 (3 H, s, Me), and 1.22 (3 H, t, *J* 7 Hz, OCH_2Me); $\delta_C(CDCl_3)$ 171.8 (C-7′), 111.9 (CMe_2), 84.3 (CH, C-2′), 79.2 (CH, C-3′), 71.1 (CH, C-1′), 60.5 (OCH_2Me), 38.1 (CH, C-4′), 36.9 (CH_2, C-5′), 36.7 (CH_2, C-6′), 26.1 (Me), 24.3 (Me), and 14.2 (OCH_2Me).

(3aR,4S,6S,6aS)-*Ethyl* 4,5,6,6a-*tetrahydro*-6-*hydroxy*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxole*-4-*acetate* (**10**); $\delta_C(CDCl_3)$ 80.1 (CH, C-2′), 78.8 (CH, C-3′), 72.0 (CH, C-1′), 60.3 (OCH_2Me), 35.6 (CH_2, C-5′), 34.7 (CH, C-4′), 33.1 (CH_2, C-6′), 25.6 (Me), 24.2 (Me), and 13.5 (OCH_2Me).

(1R,2R,3S,4R)-*Ethyl* 4-(2,4-*Dioxo*-3H-*pyrimidin*-1-*yl*)-2,3-*dihydroxycyclopentane*-1-*acetate* (**11**).—Trifluoromethanesulphonic anhydride (0.167 ml, 0.99 mmol) was added dropwise, with stirring, to a chilled (−20 °C) solution of the mixture of alcohols (**9**) and (**10**) (222 mg, 0.91 mmol) in dichloromethane (6 ml) containing pyridine (0.119 ml, 1.47 mmol) and 4-dimethylaminopyridine (5 mg), and the solution was stirred at −20 °C for 15 min. After addition of ice-cold water (4 ml), the layers were separated and the organic layer was washed with water (5 ml), brine (3 ml), and dried ($MgSO_4$). The solution was evaporated, and the residue chromatographed quickly over silica gel (light petroleum–ethyl acetate, 3:1) to give the triflate as a colourless oil (326 mg, 95%) which was used directly without further characterisation. A solution of the above triflate in DMSO (3 ml) was added to a stirred suspension of uracil (115 mg, 1.03 mmol) and potassium carbonate (180 mg, 1.30 mmol) in DMSO (3 ml). The resultant mixture was sonicated at room temperature for 1.5 h, after which time t.l.c. analysis showed no starting material remained. After dilution with ethyl acetate (50 ml), the solution was washed with brine (3 × 20 ml), dried, and evaporated to yield a residue which was purified by flash chromatography (chloroform–methanol, 98:2) to furnish the acetonide as a colourless gum (58 mg, 19%), $[\alpha]_D$ −4.4° (*c* 1.6 in $CHCl_3$); $\lambda_{max.}$(EtOH) 265 nm; $\nu_{max.}(CHCl_3)$ 3 390 (NH), 1 750—1 650br (C=O), 1 455, and 1 380 cm^{-1}; $\delta_H(CDCl_3)$ 9.55 (1 H, br s, NH), 7.20 (1 H, d, *J* 7.8 Hz, 6-H), 5.70 (1 H, d, *J* 7.8 Hz, 5-H), 4.84 (1 H, dd, *J* 6.8 and 4.8 Hz, 2′-H), 4.43 (2 H, m, 1′- and 3′-H), 4.12 (2 H, q, OCH_2Me), 2.63 (1 H, m), 2.39 (3 H, m), 2.02 (1 H, m), 1.52 (3 H, s, Me), 1.26 (3 H, s, Me), and 1.23 (3 H, t, OCH_2Me); *m/z* 339 (M^+ − 1, 15%), 323 (67), 235 (57), 169 (49), and 168 (100) (Found: M^+ − 1, 339.1546. $C_{16}H_{23}N_2O_6$ requires *M* − 1, 339.1556).

Acid resin (Amberlyst 15, 100 mg) was added to a solution of the acetonide (45 mg, 0.13 mmol) in dry methanol (2 ml) and the suspension was stirred at room temperature for 5 days. Filtration and evaporation gave a residue which was purified by flash chromatography (gradient of 3—5% methanol in chloroform) to furnish the *title compound* (14 mg, 35%) as a colourless gum, $[\alpha]_D$ −16.5° (*c* 0.39 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 600—3 100br (OH and NH) and 1 690br (amide and ester C=O) cm^{-1}; $\delta_H(CDCl_3)$ 7.26 (1 H, d, *J* 8.1 Hz, 6-H), 5.71 (1 H, d, *J* 8.1 Hz, 5-H), 4.44 (1 H, dt, *J* 6.1 and 11 Hz, 1′-H), 4.29 (1 H, t, *J* 6.1 Hz, 2′-H), 4.16 (2 H, q, OCH_2Me), 3.98 (1 H, t, *J* 6.1 Hz, 3′-H), 2.57 (2 H, m), 2.32 (2 H, m), 1.65 (1 H, m), and 1.27 (3 H, t, OCH_2Me); *m/z* 299 (M^+ + 1, 11%), 169 (32), 168 (38), and 113 (100) [Found: M^+ + 1, 299.1251; (M^+ − $C_4H_4N_2O_2$, 186.0894). $C_{13}H_{19}N_2O_6$ requires *M* + 1, 299.1243; $C_9H_{14}O_4$ requires (*M* − $C_4H_4N_2O_2$, 186.0892)].

(3aR,4R,6R,6aS)-*Ethyl* 4,5,6,6a-*Tetrahydro*-6-(6-*methoxy*-9H-*purin*-9-*yl*)-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxole*-4-

acetate (**12**) *and* (3aR,4R,6R,6aS)-*Ethyl* 4,5,6,6a-*Tetrahydro*-6-(6-*methoxy*-7H-*purin*-7-*yl*)-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxole*-4-*acetate* (**13**).—6-Methoxypurine (47 mg, 0.31 mmol) in dry DMF (1.0 ml) was added to a stirred suspension of lithium hydride (30% suspension in oil, washed thrice with sodium-dried light petroleum, 16 mg, 0.6 mmol) in dry DMF (0.5 ml) and the resultant mixture was stirred for 2.5 h. This lithio-6-methoxypurine solution (1.06 ml, 0.22 mmol) was added, *via* a syringe, to a solution of the freshly prepared triflate (see previous experiment) and this solution was stirred for 3.5 h. The reaction mixture was diluted with ethyl acetate (20 ml) and washed with water (3 × 10 ml), dried and concentrated to afford a syrup. Separation by flash chromatography gave two fractions, the first (eluted with light petroleum–ethyl acetate, 1:2) contained the pure N-9 alkylated isomer (**12**) (26 mg, 39%) and the second (eluted with ethyl acetate) contained the N-7 alkylated isomer (**13**) (18 mg, 27%).

(3aR,4R,6R,6aS)-*Ethyl* 4,5,6,6a-*tetrahydro*-6-(6-*methoxy*-9H-*purin*-9-*yl*)-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxole*-4-*acetate* (**12**), $[\alpha]_D$ −11.7° (*c* 2.2 in $CHCl_3$); $\lambda_{max.}$(EtOH) 248 nm; $\nu_{max.}$($CHCl_3$) 1 728 (ester C=O), 1 673, 1 600, and 1 578 cm^{-1}; δ_H($CDCl_3$) 8.50 (1 H, s, 2-H), 7.95 (1 H, s, 8-H), 5.08 (1 H, dd, *J* 5.5 and 7.5 Hz, 2′-H), 4.80 (1 H, ddd, *J* 5.5, 11, and 6.5 Hz, 1′-H), 4.59 (1 H, dd, *J* 7.5 and 5 Hz, 3′-H), 4.18 (3 H, s, OMe), 4.15 (2 H, q, OCH_2Me), 2.79—2.31 (5 H, m, 4′-H, 2 × 5′-H and 2 × 6′-H), 1.55 (3 H, s, Me), 1.29 (3 H, s, Me), and 1.23 (3 H, t, OCH_2Me); *m/z* 377 (M^+ + 1, 14%), 361 (14), 318 (31), 231 (100), and 151 (23) (Found: M^+ + 1, 377.1823. $C_{18}H_{25}N_4O_5$ requires *M* + 1, 377.1825).

(3aR,4R,6R,6aS)-*Ethyl* 4,5,6,6a-*tetrahydro*-6-(6-*methoxy*-7H-*purin*-7-*yl*)-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxole*-4-*acetate* (**13**), $[\alpha]_D$ −2.5° (*c* 0.5 in $CHCl_3$); $\lambda_{max.}$(EtOH) 258 nm; $\nu_{max.}$($CHCl_3$) 1 729 (ester C=O), 1 610, and 1 560 cm^{-1}; δ_H($CDCl_3$) 8.66 (1 H, s, 2-H), 8.14 (1 H, s, 8-H), 4.93 (1 H, m, 1′-H), 4.89 (1 H, m, 2′-H), 4.56 (1 H, dd, 3′-H), 4.18 (3 H, s, OMe), 4.15 (2 H, q, OCH_2Me), 2.79—2.39 (4 H, m), 2.16 (1 H, m), 1.55 (3 H, s, Me), 1.29 (3 H, s, Me), and 1.26 (3 H, t, OCH_2Me); *m/z* 376 (M^+, 47%), 361 (67), 176 (58), 151 (67), and 150 (100) (Found: M^+, 376.1745. $C_{18}H_{24}N_4O_5$ requires *M*, 376.1746).

(3aS,4S,6S,6aR)-6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,-6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*ol* (**14**).—Di-isobutylaluminium hydride (1.2M in toluene; 9.6 ml, 11.5 mmol) was added dropwise *via* a syringe to a stirred solution of the alcohols (**9**) and (**10**) (891 mg, 3.65 mmol) in ether (35 ml) at −78 °C. The solution was stirred at −78 °C for 15 min, then warmed to 0 °C, and stirred for 45 min. The excess of reducing agent was quenched by slow addition of methanol (2 ml) and aqueous sodium hydroxide (4M; 100 ml) was added. Stirring at 0 °C was continued for a further 30 min, whereupon the mixture was extracted with dichloromethane (4 × 100 ml). The combined organic extracts were dried and evaporated to furnish a colourless syrup (686 mg). This crude diol was dissolved in dichloromethane (15 ml) and cooled with stirring to 0 °C. 4-Dimethylaminopyridine (20 mg) and triethylamine (0.72 ml, 5.2 mmol), were added, followed by dimethyl-t-butylsilyl chloride (570 mg, 3.77 mmol). The solution was then stirred for 15 h, and allowed to warm to room temperature. T.l.c. analysis showed a single major product, and the mixture was diluted with dichloromethane (50 ml) and washed with water (20 ml), dried, and evaporated. Flash chromatography of the residue (light petroleum–ethyl acetate, 3:1) furnished the silyl ether (**14**) as a colourless gum (820 mg, 71% for the two steps), $[\alpha]_D$ −10.0° (*c* 1.97 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 540 cm^{-1} (OH); δ_H(C_6D_6) 4.15—4.05 (2 H, m, 2′- and 3′-H), 3.92 (1 H, m, 1′-H), 3.48 (2 H, t, *J* 6 Hz, 7′-H_a and 7′-H_b), 2.24 (1 H, m, *J* 7.5 and 5 Hz, 4′-H), 1.93 (1 H, dt, *J* 12.5, 7.5, and 7.5 Hz, 6′-H_a), 1.47 (1 H, dt, *J* 12.5, 5, and 5 Hz, 6′-H_b), 1.35 (3 H, s, Me), 1.22 (2 H, m, 5′-H_a and 5′-H_b), 1.17 (3 H, s, Me), 0.97 (9 H, s, Bu^t), and 0.05 (6 H, s, $SiMe_2$); *m/z* (c.i.) 317 (M^+ + 1, 10%), 301 (96), 259 (58), 202 (54), and 201 (100) (Found: M^+ + 1, 317.2148. $C_{16}H_{33}O_4Si$ requires *M* + 1, 317.2148).

(3aS,4S,6S,6aR)-6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,-6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl* *Toluene*-p-*sulphonate* (**15**).—Toluene-*p*-sulphonyl chloride (652 mg, 3.4 mmol) was added to a cooled (0 °C) solution of the silyl ether (**14**) (346 mg, 1.1 mmol) in pyridine (5 ml), and the mixture was stirred for 18 h after removing the ice-bath. The solvent was removed under reduced pressure, and the residue taken up in dichloromethane (50 ml). This solution was washed with water (2 × 25 ml), dried, and evaporated to yield a gum which was purified by flash chromatography, eluting first with chloroform and then with chloroform–ethyl acetate (2:1) to furnish the *title compound* (488 mg, 95%), $[\alpha]_D$ −26° (*c* 1.36 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 600, 1 460, and 1 370 cm^{-1}; δ_H($CDCl_3$) 7.81 (2 H, d, Ar), 7.34 (2 H, d, Ar), 4.66 (1 H, m, 1′-H), 4.45 (1 H, t, *J* 5 Hz, 2′-H), 4.32 (1 H, d, *J* 5 Hz, 3′-H), 3.60 (2 H, t, *J* 7 Hz, 7′-H_a and 7′-H_b), 2.39 (3 H, s, Ar-Me), 2.14 (2 H, m, 4′-H and 6′-H_a), 1.65 (1 H, m, 6′-H_b), 1.55—1.25 (2 H, m, 5′-H_a and 5′-H_b), 1.43 (3 H, s, Me), 1.24 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.05 (6 H, s, $SiMe_2$); *m/z* (c.i.) 471 (M^+ + 1, 11%), 457 (36), 456 (75), 455 (100), 415 (85), and 355 (92) (Found: M^+ + 1, 471.2237. $C_{23}H_{39}O_6SSi$ requires *M* + 1, 471.2237).

(3aS,4R,6S,6aR)-9-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-(2-*methoxyethoxy*)-9H-*purin*-2-*amine* (**17**) *and* (3aS,4R,6S,6aR)-7-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-(2-*methoxyethoxy*)-7H-*purin*-2-*amine* (**21**).—Trifluoromethanesulphonic anhydride (0.175 ml, 1.04 mmol) was added dropwise with stirring to a chilled (−20 °C) solution of silyl ether (**14**) (288 mg, 0.91 mmol) in dichloromethane (9 ml) containing pyridine (0.095 ml, 1.18 mmol) and 4-dimethylaminopyridine (5 mg). After 15 min, ice-cold water (5 ml) was added, and the layers were separated. The organic layer was further washed with water (5 ml) and dried. Evaporation furnished a gum which was rapidly purified by flash chromatography, giving the triflate (**16**) (384 mg, 94%) which was used directly. A solution of 2-amino-6-methoxyethoxypurine (325 mg, 1.55 mmol) in DMF (8 ml) was added to a stirred suspension of lithium hydride (30% suspension in oil, washed thrice with sodium-dried light petroleum, 83 mg, 3.11 mmol) in dry DMF (2 ml) and the mixture was stirred at room temperature for 2 h. This yellow solution (9.0 ml, *ca.* 1.4 mmol) was added *via* a syringe to a stirred solution of the freshly prepared triflate (**16**) (384 mg, 0.86 mmol) in dry DMF (3 ml), and stirring was continued for 3 h. The mixture was diluted with ethyl acetate (100 ml) and washed with water (3 × 40 ml), dried, and concentrated to a syrup. Separation by flash chromatography gave two fractions; the first (eluted with ethyl acetate–light petroleum, 2:1) contained the pure N-9 alkylated isomer (**17**) (114 mg, 26%), and the second (eluted with chloroform–methanol, 9:1) contained the N-7 alkylated isomer (**21**) (114 mg, 26%). (3aS,4R,6S,6aR)-9-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6*a*-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-(2-*methoxyethoxy*)-9H-*purin*-2-*amine* (**17**), $[\alpha]_D$ −6.5° (*c* 1.91 in $CHCl_3$); $\lambda_{max.}$(EtOH) 248 and 283 nm; $\nu_{max.}$($CHCl_3$) 3 530 (NH_2), 3 420, 1 612, and 1 588 cm^{-1}; δ_H($CDCl_3$) 7.60 (1 H, s, 8-H), 4.97 (1 H, dd, *J* 5 and 7 Hz, 2′-H), 4.80 (2 H, br s, NH_2), 4.64 (2 H, t, *J* 5 Hz, OCH_2CH_2OMe), 4.61 (1 H, m, 1′-H), 4.46 (1 H, dd, *J* 7 and 6 Hz, 3′-H), 3.80 (2 H, t, *J* 5 Hz, OCH_2CH_2OMe), 3.70 (2 H, t, *J* 6 Hz, 7′-H_a and 7′-H_b), 3.42 (3 H, s, OMe), 2.41 (1 H, m, 6′-H_a), 2.20 (1 H, m, 4′-H), 2.15 (1 H, m, 6′-H_b), 1.87 (1 H, m, 5′-H_a), 1.66 (1 H, m, 5′-H_b), 1.53 (3 H, s, Me), 1.28 (3 H, s, Me), 0.89 (9 H, s,

Bu^t), and 0.08 (6 H, s, $SiMe_2$); *m/z* 507 (M^+, 19%), 492 (13), 450 (54), 210 (71), and 183 (100) (Found: M^+, 507.2876. $C_{24}H_{41}N_5O_5Si$ requires *M*, 507.2877).

(3aS,4R,6S,6aR)-7-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-(2-*methoxyethoxy*)-7H-*purin*-2-*amine* (**21**), $[\alpha]_D$ + 0.9° (*c* 1.88 in $CHCl_3$); $\lambda_{max.}$(EtOH) 297 nm; $\nu_{max.}$($CHCl_3$) 3 520 (NH_2), 3 420, 1 620, and 1 570 cm^{-1}; δ_H($CDCl_3$) 7.84 (1 H, s, 8-H), 4.94 (1 H, dd, *J* 7 and 5 Hz, 2′-H), 4.83 (2 H, br s, NH_2), 4.78—4.52 (3 H, m, 1′-H and OCH_2CH_2OMe), 4.49 (1 H, dd, *J* 7 and 6 Hz 3′-H), 3.74 (2 H, m, OCH_2CH_2OMe), 3.69 (2 H, t, *J* 7 Hz, 7′-H_a and 7′-H_b), 3.39 (3 H, s, OMe), 2.36 (1 H, m, 6′-H_a), 2.18 (1 H, m, 4′-H), 2.14 (1 H, m, 6′-H_b), 1.87 (1 H, m, 5′-H_a), 1.68 (1 H, m, 5′-H_b), 1.52 (3 H, s, Me), 1.29 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.08 (6 H, s, $SiMe_2$); *m/z* 507 (M^+, 18%), 492 (8), 450 (100), 210 (44), and 183 (62) (Found: M^+, 507.2877. $C_{24}H_{41}N_5O_5Si$ requires *M*, 507.2877).

The alkylated purines (**18**)—(**20**) and (**22**)—(**24**) were prepared using analogous procedures: (3aS,4R,6S,6aR)-9-{6-[2-(*dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-*methoxy*-9H-*purine* (**18**) was obtained in 38% yield as a gum, $[\alpha]_D$ −13.42° (*c* 1.54 in $CHCl_3$); $\lambda_{max.}$(EtOH) 249 nm; $\nu_{max.}$($CHCl_3$) 1 605, 1 578, and 1 480 cm^{-1}; δ_H($CDCl_3$) 8.51 (1 H, s, 2-H), 7.95 (1 H, s, 8-H), 5.05 (1 H, dd, *J* 5 and 7 Hz, 2′-H), 4.76 (1 H, m, *J* 5 Hz, 1′-H), 4.53 (1 H, dd, *J* 7 and 5 Hz, 3′-H), 4.18 (3 H, s, OMe), 3.72 (2 H, t, *J* 6 Hz, 7′-H_a and 7′-H_b), 2.51 (1 H, m, 6′-H_a), 2.32 (1 H, m, 6′-H_b), 2.28 (1 H, m, 4′-H), 1.88 (1 H, m, *J* 14 Hz, 5′-H_a), 1.73 (1 H, m, *J* 14 Hz, 5′-H_b), 1.55 (3 H, s, Me), 1.29 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.08 (6 H, s, $SiMe_2$); *m/z* 449 (M^+ + 1, 14%), 448 (M^+, 7%), 433 (20), 391 (27), 333 (12), and 183 (100) (Found: M^+ + 1, 449.2578. $C_{22}H_{37}N_4O_4Si$ requires *M* + 1, 449.2584).

(3aS,4R,6S,6aR)-7-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-dimethyl-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-*methoxy*-7H-*purine* (**22**) was obtained in 36% yield, $[\alpha]_D$ + 0.41° (*c* 0.8 in $CHCl_3$); $\lambda_{max.}$(EtOH) 259 nm; $\nu_{max.}$($CHCl_3$) 1 610, 1 560, and 1 480 cm^{-1}; δ_H($CDCl_3$) 8.66 (1 H, s, 2-H), 8.12 (1 H, s, 8-H), 4.87 (1 H, m, 1′-H), 4.83 (1 H, m, *J* 6 Hz, 2′-H), 4.47 (1 H, br t, *J* 6 Hz, 3′-H), 4.18 (3 H, s, OMe), 3.72 (2 H, t, *J* 6 Hz, 7′-H_a and 7′-H_b), 2.52 (1 H, m, *J* 12, 7, and 7 Hz, 6′-H_a), 2.29 (1 H, m, *J* 7 and 6 Hz, 4′-H), 2.05 (1 H, m, 6′-H_b), 1.87 (1 H, m, 5′-H_a), 1.69 (1 H, m, 5′-H_b), 1.55 (3 H, s, Me), 1.31 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.05 (6 H, s, $SiMe_2$); *m/z* 449 (M^+ + 1, 10%), 433 (10), 391 (98), 333 (50), and 183 (100) (Found: M^+ + 1, 449.2584. $C_{22}H_{37}N_4O_4Si$ requires *M* + 1, 449.2584).

(3aS,4R,6S,6aR)-9-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-(2-*methoxyethoxy*)-9H-*purine* (**19**) was obtained 38% yield, $[\alpha]_D$ −11.8° (*c* 1.17 in $CHCl_3$); $\lambda_{max.}$(EtOH) 249 nm; $\nu_{max.}$($CHCl_3$) 1 604, 1 575, and 1 470 cm^{-1}; δ_H($CDCl_3$) 8.47 (1 H, s, 2-H), 7.90 (1 H, s, 8-H), 5.04 (1 H, dd, *J* 7 and 5 Hz, 2′-H), 4.75 (3 H, m, OCH_2CH_2OMe and 1′-H), 4.52 (1 H, dd, *J* 7 and 5 Hz, 3′-H), 3.84 (2 H, t, *J* 5 Hz, OCH_2CH_2OMe), 3.71 (2 H, t, *J* 7 Hz, 7′-H_a and 7′-H_b), 3.40 (3 H, s, OMe), 2.47 (1 H, m, 6′-H_a), 2.28 (2 H, m, 6′-H_b and 4′-H), 1.88 (1 H, m, 5′-H_a), 1.68 (1 H, m, 5′-H_b), 1.52 (3 H, s, Me), 1.29 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.08 (6 H, s, $SiMe_2$); *m/z* (c.i.) 493 (M^+ + 1, 100%), 435 (15), 195 (25), and 183 (57) (Found: M^+ + 1, 493.2857. $C_{24}H_{41}N_4O_5Si$ requires *M* + 1, 493.2846).

(3aS,4R,6S,6aR)-7-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-6-(2-*methoxyethoxy*)-7H-*purine* (**23**) was obtained in 25% yield, $[\alpha]_D$ + 4.7° (*c* 0.86 in $CHCl_3$); $\lambda_{max.}$(EtOH) 259 nm; $\nu_{max.}$($CHCl_3$) 1 608, 1 555, and 1 480 cm^{-1}; δ_H($CDCl_3$) 8.63 (1 H, s, 2-H), 8.10 (1 H, s, 8-H), 4.98 (1 H, dd, *J* 5 and 7 Hz, 2′-H), 4.90—4.64 (3 H, m, OCH_2CH_2OMe and 1′-H), 4.53 (1 H, dd, *J* 7 and 6 Hz, 3′-H), 3.79 (2 H, m, OCH_2CH_2OMe), 3.71 (2 H, t, *J* 6 Hz, 7′-H_a and 7′-H_b), 3.40 (3 H, s, OMe), 2.42 (1 H, m, 6′-H_a), 2.21 (2 H, m, 6′-H_b and 4′-H), 1.92 (1 H, m, 5′-H_a), 1.71 (1 H, m, 5′-H_b), 1.52 (3 H, s, Me), 1.29 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.05 (6 H, s, $SiMe_2$); *m/z* (c.i.) 493 (M^+ + 1, 100%), 435 (32), 195 (18), and 183 (23) (Found: M^+ + 1, 493.2852. $C_{24}H_{41}N_4O_5Si$ requires *M* + 1, 493.2846).

(3aS,4R,6S,6aR)-6-*Chloro*-9-{6-[2-(*dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-9H-*purine* (**20**) was obtained in 46% yield, $[\alpha]_D$ −17.0° (*c* 1.3 in $CHCl_3$); $\lambda_{max.}$(EtOH) 265 nm; $\nu_{max.}$($CHCl_3$) 1 590, 1 560, and 1 490 cm^{-1}; δ_H($CDCl_3$) 8.74 (1 H, s, 2-H), 8.16 (1 H, s, 8-H), 5.04 (1 H, dd, *J* 7 and 6 Hz, 2′-H), 4.79 (1 H, m, *J* 6 Hz, 1′-H), 4.54 (1 H, dd, *J* 7 and 5 Hz, 3′-H), 3.73 (2 H, t, *J* 6 Hz, 7′-H_a and 7′-H_b), 2.54 (1 H, m, 6′-H_a), 2.34 (1 H, m, 6′-H_b), 2.32 (1 H, m, 4′-H), 1.88 (1 H, m, 5′-H_a), 1.74 (1 H, m, 5′-H_b), 1.52 (3 H, s, Me), 1.29 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.08 (6 H, s, $SiMe_2$); *m/z* (c.i.) 455 (M^+ + 1, 42%), 454 (30), 453 (M^+ + 1, 100%), and 419 (95) (Found: M^+ + 1, 453.2092. $C_{21}H_{34}{}^{35}ClN_4O_3$ requires *M* + 1, 453.2089).

(3aS,4R,6S,6aR)-6-*Chloro*-7-{6-[2-(*t-butyldimethylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-7H-*purine* (**24**) was obtained in 9% yield, $[\alpha]_D$ −4.4° (*c* 1.22 in $CHCl_3$); $\lambda_{max.}$(EtOH) 272 nm; $\nu_{max.}$($CHCl_3$) 1 593, 1 540, and 1 475 cm^{-1}; δ_H($CDCl_3$) 8.88 (1 H, s, 2-H), 8.38 (1 H, s, 8-H), 5.33 (1 H, m, *J* 6, 6, and 12 Hz, 1′-H), 4.85 (1 H, br t, *J* 6 and 7 Hz, 2′-H), 4.55 (1 H, dd, *J* 7 and 5 Hz, 3′-H), 3.73 (2 H, t, *J* 7 Hz, 7′-H_a and 7′-H_b), 2.68 (1 H, dt, *J* 6, 6, and 12 Hz, 6′-H_a), 2.39 (1 H, m, 4′-H), 1.99 (1 H, m, *J* 12 and 12 Hz, 6′-H_b), 1.88 (1 H, m, 5′-H_a), 1.72 (1 H, m, 5′-H_b), 1.58 (3 H, s, Me), 1.31 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.08 (6 H, s, $SiMe_2$); *m/z* (c.i.) 455 (M^+ + 1, 28%), 454 (22), 453 (M^+ + 1, 71%), 419 (46), and 417 (100) (Found: M^+ + 1, 453.2092. $C_{21}H_{34}{}^{35}ClN_4O_3$ requires *M* + 1, 453.2089).

On one occasion a non-polar, non-u.v. active product was noticed upon completion of the alkylation of 6-methoxypurine. This was isolated in 23% yield and tentatively identified as the olefin (**25**), δ_H($CDCl_3$) 5.83 (1 H, m, *J* 6 Hz, 1′-H), 5.76 (1 H, dt, *J* 6, 2, and 2 Hz, 6′-H), 5.14 (1 H, br d, *J* 6, 2, and 1 Hz, 2′-H), 4.46 (1 H, br d, *J* 6 Hz, 3′-H), 3.69 (2 H, t, *J* 7 Hz, 7′-H_a and 7′-H_b), 2.86 (1 H, m, 4′-H), 1.70—1.50 (2 H, m, 5′-H_a and 5′-H_b), 1.41 (3 H, s, Me), 1.34 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.10 (6 H, s, $SiMe_2$).

(3aS,4R,6S,6aR)-9-{6-[2-(*Dimethyl-t-butylsiloxy*)*ethyl*]-4,5,6,6a-*tetrahydro*-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*}-9H-*purin*-6-*amine* (**26**).—A solution of the 6-chloropurine (**20**) (217 mg, 0.48 mmol) in methanolic ammonia (16 ml, saturated at 0 °C) was heated in a Teflon-lined steel bomb at 100 °C for 20 h. The solution was concentrated and purified by chromatography (ethyl acetate–ethanol, 9:1) to yield the *title compound* as a glassy solid (172 mg, 83%), $[\alpha]_D$ −14.5° (*c* 1.72 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 500 (NH_2), 3 410, 1 630, and 1 592 cm^{-1}; δ_H($CDCl_3$) 8.31 (1 H, s, 2-H), 7.84 (1 H, s, 8-H), 5.74 (2 H, br s, NH_2), 5.06 (1 H, dd, *J* 6 and 7 Hz, 2′-H), 4.71 (1 H, m, *J* 6 Hz, 1′-H), 4.52 (1 H, dd, *J* 7 and 6 Hz, 3′-H), 3.71 (2 H, t, 7′-H_a and 7′-H_b), 2.47 (1 H, m, 6′-H_a), 2.30 (1 H, m, 6′-H_b), 2.28 (1 H, m, *J* 6 Hz, 4′-H), 1.88 (1 H, m, 5′-H_a), 1.72 (1 H, m, 5′-H_b), 1.55 (3 H, s, Me), 1.30 (3 H, s, Me), 0.89 (9 H, s, Bu^t), and 0.06 (6 H, s, $SiMe_2$); *m/z* 433 (M^+, 1%), 418 (7), 376 (26), 318 (13), and 183 (100) (Found: M^+, 433.2494. $C_{21}H_{35}N_5O_3Si$ requires *M*, 433.2510).

(3aS,4R,6S,6aR)-9-[4,5,6,6a-*Tetrahydro*-6-(2-*hydroxyethyl*)-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*]-9H-*purin*-6-*amine* (**27**).—A solution of tetrabutylammonium fluoride (1M; 0.70 ml, 0.70 mmol) was added to a solution of the silyl ether (**26**) (216 mg, 0.50 mmol) in THF (5 ml). After stirring for 2 h, the solution was evaporated and purified by chromatography

(ethyl acetate–ethanol, 9:1) yielding the free alcohol (**27**) as an amorphous solid (150 mg, 94%), m.p. 206—208 °C; $[\alpha]_D$ −28.4° (*c* 1.30 in MeOH); $\nu_{max.}$(Nujol) 3 450br (NH_2, OH), 3 200, 1 670, and 1 600 cm^{-1}; δ_H[$(CD_3)_2SO$, D_2O] 8.26 (1 H, s, 2-H), 8.13 (1 H, s, 8-H), 4.94 (1 H, dd, *J* 6 and 7 Hz, 2′-H), 4.75 (1 H, m, *J* 6 Hz, 1′-H), 4.42 (1 H, dd, *J* 6 and 7 Hz, 3′-H), 3.44 (2 H, t, *J* 6 Hz, 7′-H_a and 7′-H_b), 2.33 (1 H, m, 6′-H_a), 2.11 (1 H, m, *J* 6 Hz, 4′-H), 2.06 (1 H, m, 6′-H_b), 1.71 (1 H, m, 5′-H_a), 1.58 (1 H, m, 5′-H_b), 1.44 (3 H, s, Me), and 1.19 (3 H, s, Me); *m/z* 319 (M^+, 4%), 304 (11), 261 (52), 216 (100), and 136 (29) (Found: M^+, 319.1640. $C_{15}H_{21}N_5O_3$ requires *M*, 319.1644).

Analogously, silyl ethers (**17**) and (**18**) were desilylated, by exposure to tetrabutylammonium fluoride, in 88% and 98% yields, respectively, to furnish (3aS,4R,6S,6aR)-9-[4,5,6,6a-*tetrahydro*-6-(2-*hydroxyethyl*)-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*]-6-(2-*methoxyethoxy*)-9H-*purin*-2-*amine* (**28**) $[\alpha]_D$ −17.1 (*c* 1.5 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 510 (OH), 3 405, 1 610, and 1 580 cm^{-1}; δ_H($CDCl_3$) 7.60 (1 H, s, 8-H), 5.00 (1 H, dd, *J* 5 and 7 Hz, 2′-H), 4.86 (2 H, br s, NH_2), 4.63 (2 H, t, *J* 5 Hz, OCH_2CH_2OMe), 4.62 (1 H, m, *J* 5 Hz, 1′-H), 4.54 (1 H, t, *J* 7 Hz, 3′-H), 3.78 (4 H, m, OCH_2CH_2OMe, 7′-H_a and 7′-H_b), 3.42 (3 H, s, OMe), 2.38 (2 H, m, 6′-H_a and 4′-H), 2.22 (1 H, m, 6′-H_b), 1.77 (2 H, m, 5′-H_a and 5′-H_b), 1.55 (3 H, s, Me), and 1.30 (3 H, s, Me); *m/z* 393 (M^+, 31%), 378 (11), 335 (20), 290 (100), 232 (30), and 183 (13) (Found: M^+, 393.2015. $C_{18}H_{27}N_5O_5$ requires *M*, 393.2012) and (3aS,4R,6S,6aR)-9-[4,5,6,6a-*tetrahydro*-6-(2-*hydroxyethyl*)-2,2-*dimethyl*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*]-6-*methoxy*-9H-*purine* (**29**) $[\alpha]_D$ −26.2° (*c* 1.56 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450br (OH), 1 602, and 1 580 cm^{-1}; δ_H($CDCl_3$) 8.50 (1 H, s, 2-H), 7.95 (1 H, s, 8-H), 5.08 (1 H, dd, *J* 7 and 5 Hz, 2′-H), 4.79 (1 H, m, *J* 5 Hz, 1′-H), 4.60 (1 H, dd, *J* 7 and 6 Hz, 3′-H), 4.18 (3 H, s, OMe), 3.80 (2 H, m, 7′-H_a and 7′-H_b), 2.46 (1 H, m, 6′-H_a), 2.38 (1 H, m, 6′-H_b), 2.29 (1 H, m, 4′-H), 1.82 (2 H, m, 5′-H_a and 5′-H_b), 1.58 (3 H, s, Me), and 1.32 (3 H, s, Me); *m/z* 335 (M^+ + 1, 5%), 334 (M^+, 1%), 319 (11), 276 (64), 231 (100), and 151 (43) (Found: M^+ + 1, 335.1713. $C_{16}H_{23}N_4O_4$ requires *M* + 1, 335.1719).

(−)-5′-*Homoaristeromycin* (**30**).—The acetonide (**27**) (130 mg, 0.41 mmol) was dissolved in hydrochloric acid (3M; 8 ml) and heated to 85 °C. After 1 h the solvent was evaporated and azeotroped thrice with benzene under reduced pressure to remove residual water. The flask was then evacuated to 0.1 torr for 2 h to yield the title compound as its hydrochloride salt, which was then dissolved in water (5 ml) and neutralised with basic resin [Amberlite 1RA 400 (OH)]. The beads were filtered off and the filtrate evaporated to yield the *title compound* (106 mg, 93%) as a hygroscopic amorphous solid, $[\alpha]_D$ −26.6° (*c* 1.9 in EtOH); $\lambda_{max.}$(EtOH) 260 nm; δ_H[$(CD_3)_2SO$, D_2O] 8.18 (1 H, s, 2-H), 8.10 (1 H, s, 8-H), 4.63 (1 H, dt, *J* 8, 10, and 8 Hz, 1′-H), 4.33 (1 H, dd, *J* 8 and 6 Hz, 2′-H), 3.74 (1 H, dd, *J* 6 and 5 Hz, 3′-H), 3.46 (2 H, m, 7′-H_a and 7′-H_b), 2.27 (1 H, dt, *J* 8, 8, and 12 Hz, 6′-H_a), 1.96 (1 H, m, 4′-H), 1.74 (1 H, m, 5′-H_a), 1.66 (1 H, m, *J* 10 and 12 Hz, 6′-H_b), and 1.54 (1 H, m, 5′-H_b), *m/z* 280 (M^+ + 1, 3%), 279 (M^+, 3%), 262 (7), 162 (36), 136 (100), and 135 (53) (Found: M^+, 279.1321. $C_{12}H_{17}N_5O_3$ requires *M*, 279.1331).

(1R,2S,3R,5S)-3-(2-*Amino*-6-*hydroxy*-9H-*purin*-9-*yl*)-5-(2-*hydroxyethyl*)*cyclopentane*-1,2-*diol* (**31**).—The acetonide (**28**) (74 mg, 0.19 mmol) was dissolved in hydrochloric acid (3M; 5 ml) and heated at 85 °C for 0.5 h, whereupon t.l.c. analysis showed no starting material remained. The solvent was evaporated and the flask was evacuated to 0.1 torr for 2 h before redissolving the residue in water (1 ml). Aqueous sodium hydroxide (2M) was then added dropwise to pH 8, whereupon the product precipitated as a white solid. The solid was filtered off and recrystallised from water (0.5 ml), yielding the *title compound* as a fine white powder (41 mg, 78%), m.p. 245—250 °C (decomp.); $[\alpha]_D$ −21.4° (*c* 0.49 in DMSO); $\lambda_{max.}$(water, pH 1) 255 and 280 nm, (water, pH 12) 257 and 269 nm; δ_H[$(CD_3)_2SO$, D_2O] 7.76 (1 H, s, 8-H), 4.45 (1 H, dt, *J* 8, 8, and 10 Hz, 1′-H), 4.20 (1 H, dd, *J* 8 and 5 Hz, 2′-H), 3.68 (1 H, t, *J* 5 Hz, 3′-H), 3.44 (2 H, m, 7′-H_a and 7′-H_b), 2.21 (1 H, dt, *J* 8, 8, and 12 Hz, 6′-H_a), 1.90 (1 H, m, 4′-H), 1.72 (1 H, m, 5′-H_a), and 1.50 (2 H, m, 5′-H_b and 6′-H_b).

(1R,2S,3R,5S)-5-(2-*Hydroxyethyl*)-3-(6-*hydroxy*-9H-*purin*-9-*yl*)*cyclopentane*-1,2-*diol* (**32**).—The acetonide (**29**) (94 mg, 0.28 mmol) was dissolved in hydrochloric acid (3M; 8 ml) and heated at 85 °C for 0.5 h. The solution was evaporated, and the residue dissolved in water (0.5 ml) before adjusting the pH to 8 with aqueous sodium hydroxide (2M). The resultant solution was purified by reverse phase h.p.l.c. on a column packed with Spherisorb S50DS2, eluting with 15% acetonitrile in water to give the *title compound* as a white amorphous powder (33 mg, 42%), $[\alpha]_D$ −25.1° (*c* 0.32 in water); $\lambda_{max.}$(water, pH 1), 252 nm, (water, pH 11) 256 nm; δ_H[$(CD_3)_2SO$, D_2O] 8.17 (1 H, s, 2-H), 8.02 (1 H, s, 8-H), 4.64 (1 H, dt, *J* 8, 8, and 10 Hz, 1′-H), 4.29 (1 H, dd, *J* 8 and 5 Hz, 2′-H), 3.72 (1 H, t, *J* 5 Hz, 3′-H), 3.46 (2 H, m, 7′-H_a and 7′-H_b), 2.28 (1 H, dt, *J* 8, 12, and 8 Hz, 6′-H_a), 1.97 (1 H, m, 4′-H), 1.75 (1 H, m, 5′-H_a), 1.60 (1 H, m, *J* 10 and 12 Hz, 6′-H_b), and 1.53 (1 H, m, 5′-H_b).

Acknowledgements

We thank Glaxo Group Research (GGR) for a post-doctoral Fellowship (to M. F. J.) and Drs. Biggadike, Borthwick, Kirk, and Myers (GGR, Greenford) for helpful discussions.

References

1 R. Vince and S. J. Daluge, *J. Med. Chem.*, 1977, **20**, 612; see also V. E. Marquez and M. I. Lim, *Med. Chem. Rev.*, 1986, **6**, 1.
2 P. Herdewijn, E. De Clercq, J. Balzarini, and H. Vanderhaeghe, *J. Med. Chem.*, 1985, **28**, 550; P. Ravenscroft, R. F. Newton, D. I. C. Scopes, and C. Williamson, *Tetrahedron Lett.*, 1986, **27**, 747.
3 Y. F. Shealy, C. A. O'Dell, W. M. Shannon, and G. Arnett, *J. Med. Chem.*, 1984, **27**, 1416; J. A. Secrist III, J. A. Montgomery, Y. F. Shealy, C. A. O'Dell, and C. J. Clayton, *ibid.*, 1987, **30**, 746; K. Biggadike, A. D. Borthwick, A. M. Exall, B. E. Kirk, S. M. Roberts, and P. Youds, *J. Chem. Soc., Chem. Commun.*, 1987, 1083.
4 S. M. Roberts, K. Biggadike, A. D. Borthwick, and B. E. Kirk, 'Proceedings of the 4th Medicinal Chemistry Symposium,' ed. P. R. Leeming, RSC, 1988.
5 G. V. B. Madhavan and J. C. Martin, *J. Org. Chem.*, 1986, **51**, 1287; Y. Arai, Y. Hayashi, M. Yamamoto, H. Takayama, and T. Koizumi, *Chem. Lett.*, 1987, 185.
6 'Carbohydrates,' ed. P. M. Collins, Chapman and Hall, London, 1987, p. 443.
7 C. S. Wilcox and L. M. Thomasco, *J. Org. Chem.*, 1985, **50**, 547.
8 J. M. Berge and S. M. Roberts, *Synthesis*, 1979, 471.
9 J. Zemlicka, *Nucleosides, Nucleotides*, 1984, **3**, 245; K. Ogilvie, U. Cheriyan, B. Radatus, K. Smith, K. Galloway, and W. Kennell, *Can. J. Chem.*, 1982, **60**, 3005.
10 J. Kjellberg and M. Liljenberg, *Tetrahedron Lett.*, 1986, **27**, 877.
11 *Cf.* P. Lassoto, J. T. Kusmierek, R. Stolarski, and D. Shugar, *Z. Naturforsch., C*, 1987, **42**, 589.

Received 18*th January* 1988; *Paper* 8/00183I