Facile conversion of 4-*endo*-hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one into carbocyclic 2′-deoxyribonucleoside analogues

Anupma Dhanda,[a] Lars J. S. Knutsen,[b]† May-Britt Nielsen,[a] Stanley M. Roberts[a] and David R. Varley[c]

[a] *Department of Chemistry, University of Liverpool, Liverpool, UK L69 7ZD*
[b] *Novo Nordisk A/S, Novo Nordisk Park, DK-2760, Malov, Denmark*
[c] *Department of Chemistry, University of Exeter, Exeter, Devon, UK EX4 4QD*

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The readily available 3,5-*syn*-disubstituted cyclopentenes **9**–**13** react with *N*-bromosuccinimide (or *N*-bromoacetamide) and silver acetate in glacial acetic acid in a highly stereoselective manner to furnish the bromoacetates **14**–**18** in good yields. A plausible explanation for the observed selectivity is proposed. Hydrodebromination of compounds **14**, **17**, **18** and **19** provided the corresponding 2′-deoxyribonucleoside analogues **20**–**23**.

Introduction and background information

The disubstituted cyclopentenes **1**, **2** and simple derivatives are readily available and have been shown to be valuable building blocks in organic synthesis.[1] We have contributed to this field previously by demonstrating that both these molecules may be used to make selected 2′,3′-dideoxydidehydrocarbocyclic nucleosides of type **3** (Fig. 1) as well as aristeromycin.[2]

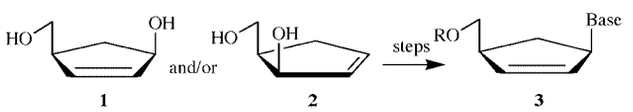
The ready availability of compounds of type **3** has encouraged researchers to investigate regio- and stereo-controlled functionalisation of the alkene unit. However, the control of stereochemistry on addition to the olefin bond can be unexpectedly capricious. For example, dihydroxylation of **3** (R = $COCH_3$, base = adenine) using osmium tetraoxide and *N*-methylmorpholine *N*-oxide gave a mixture of ribo- and lyxo-nucleoside analogues which proved to be difficult to separate.[3] Similarly, conversion of 2′,3′-dideoxydidehydrocarbocyclic nucleosides into carbocyclic deoxyribonucleosides by hydroboration followed by treatment with basic peroxide gave a mixture of 2′- and 3′-deoxycarbocyclic nucleosides.[4]

In contrast we reported recently that cyclopentene derivatives of type **3** gave bromoacetates regio- and stereo-selectively on treatment with *N*-bromosuccinimide (NBS) or *N*-bromoacetamide (NBA) and silver acetate in acetic acid at room temperature over 18 hours.[5] In this paper we detail this methodology and show how the strategy may be applied to the synthesis of a wide range of carbocyclic 2′-deoxyribonucleoside derivatives.

Results and discussion

Our preferred pathway to diol **2** and hence esters **4** and **5** involves the preparation and further transformation of the hydroxy-lactone **6** (Scheme 1) as described previously.[6] On the other hand, lithium aluminium hydride (LAH) reduction of the lactone **6** provided the triol **7** which was readily converted into the triacetate **8**.

Transformation of the esters **4** and **5** into 2′,3′-dideoxydidehydrocarbocyclic nucleosides **9**–**11** involved organopalladium chemistry, paralleling methodology introduced and popularised by Trost and co-workers.[7] Similarly the triacetate **8** was converted into the diester **12**, while the aminopurine **9** was transformed into the dichloro compound **13** through diazotization and a modified Sandmeyer reaction.



1 **2** **3**

Fig. 1

The key step in the conversion of the 2′,3′-dideoxydidehydrocarbocyclic nucleosides **9**–**13** into 2′-deoxyribonucleosides involves regio- and stereo-selective bromo-acetoxylation employing *N*-bromosuccinimide (or *N*-bromoacetamide) with silver acetate in acetic acid. The corresponding bromo-acetates **14**–**18** were formed as the sole products in 47–69% isolated yield, except in the case of the conversion of alkene **12** into bromo-acetate **18** when a small amount (13%) of an unidentified isomer of **18** was isolated by chromatography. Treatment of the 5′-tritylated compound **16** with aqueous acetic acid furnished the alcohol **19**.

The structure of the bromo-ester **14** was elucidated by X-ray crystallography[5] and the analogues **15**–**18** were assigned the same stereochemistry as **14** on account of the similarity of the spin patterns in the ^{1}H NMR spectra of all these haloesters.

Hydrodehalogenation of the bromo-compounds **14**, **17**, **18** and **19** was accomplished using tri-*n*-butyltin hydride in hot tetrahydrofuran containing azoisobutyronitrile (AIBN) (Scheme 2). The isolated yields of the carbocyclic nucleosides **20**, **21**, **22** and **23** were good to excellent (68–92%). Alternatively the bromoester **14** may be converted into the epoxide **24** in 69% yield using potassium carbonate in methanol at room temperature.[8]

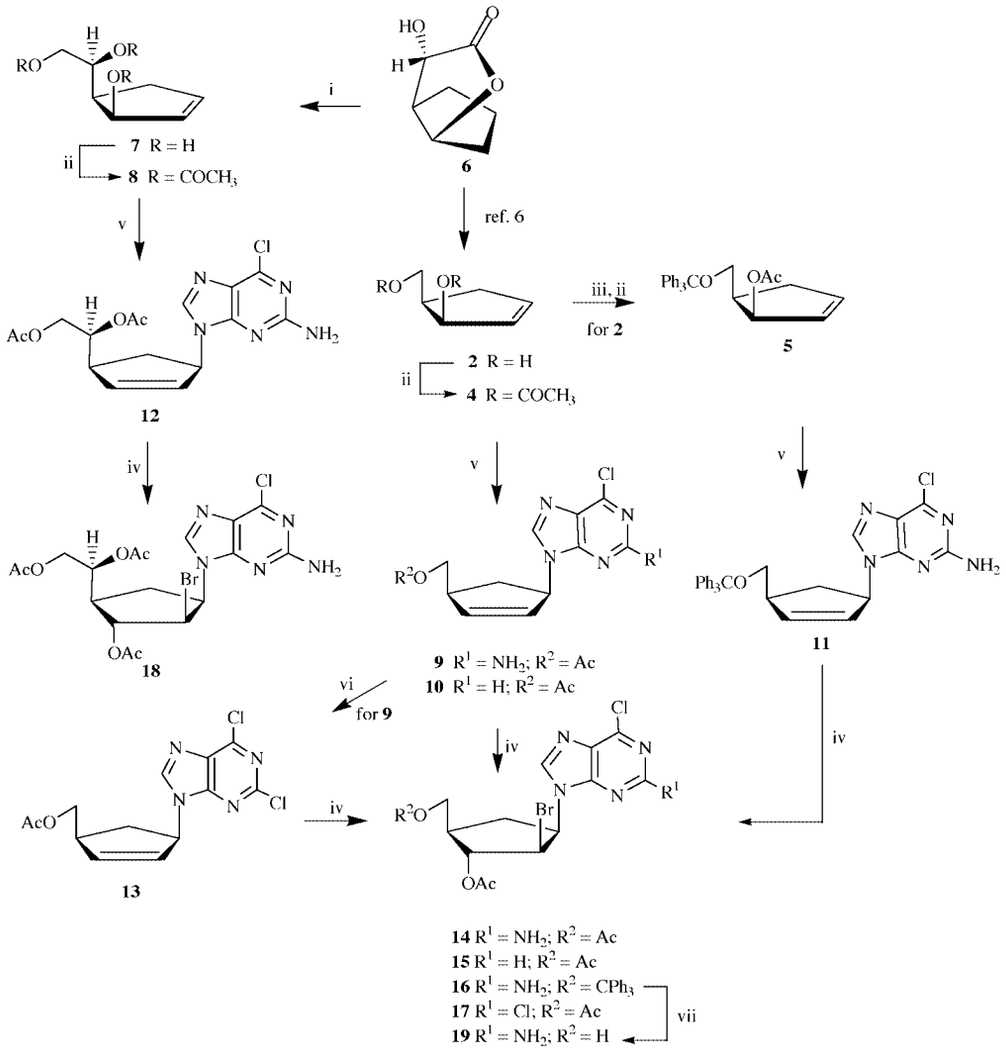
The protected carbocyclic nucleosides may be reacted further (Scheme 2), for example by removing the acetate groups directly under mild conditions (**20** ⟶ **25**) or by modifying the base unit prior to hydrolysis (*e.g.* **21** ⟶ **26** ⟶ **27**).

As an indication of the simplicity and efficiency of this new process, the readily available cyclopentene derivative **9** has been converted into the carbocyclic 2′-deoxyribonucleoside **25** in three steps and 50% yield overall.

Mechanistic considerations

The stereoselectivity of the addition of BrOAc across the alkene unit in the 3,5-*cis*-disubstituted cyclopent-1-ene derivatives **9**–**13** deserves comment.

† *Present address*, Cerebrus Ltd., Oakdene Court, 613 Reading Road, Winnersh, Wokingham, UK RG41 5UA.



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, THF, reflux, 4 h; ii, Ac_2O, pyridine, DMAP, room temp., 24 h, (81% for **4**, 100% for **5** and 79% for **8**); iii, triphenylmethyl chloride, dichloromethane, Et_3N, DMAP, room temp., 24 h, (78%); iv, NBS or NBA, AgOAc, AcOH, room temp., 18 h, (35% for **14**, 48% for **15**, 69% for **16**, 56% for **17** and 49% for **18**); v, 2-amino-6-chloropurine (for **9**, **11** and **12**), 6-chloropurine (for **10**), NaH, $Pd(PPh_3)_4$, DMF, 50 °C, 3 h, (48% for **9**, 28% for **10**, 55% for **11** and 48% for **12**); vi, Me_3SiCl, isopentyl nitrite, dichloromethane 0 °C, 2 h ⟶ room temp. 5 h, (61%); vii, AcOH (80%), 50 °C, 6 h, (66%).

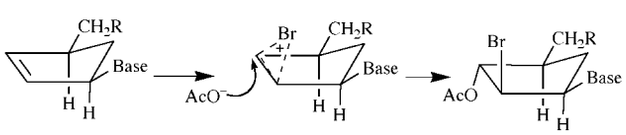


Fig. 2

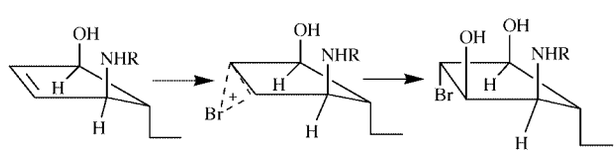


Fig. 3

Based on Kitagiri's studies[9] the compounds **9**–**13** probably adopt a conformation with the two substituents in equatorial positions (Fig. 2). The formation of the intermediate bromonium ion is probably reversible.[10] The *syn*-bromonium ion is favoured by the Cieplak effect,[11] with the axial C–H bonds donating into a low lying, vacant σ* orbital associated with the incipient bond(s) in the transition state. The acetate anion then attacks at the position distant from the C–N bond.

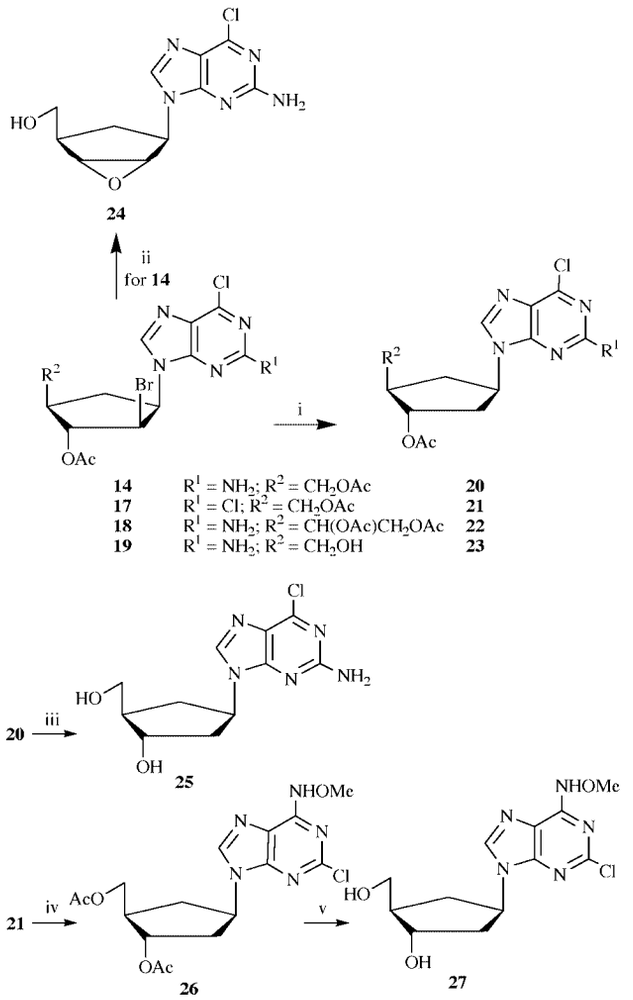
The addition of silver acetate to the reaction mixture has a beneficial effect. For example, reaction of the alkene **9** with NBA in glacial acetic acid but in the absence of silver acetate resulted in a less selective reaction; while the bromoester **14** was still a major product, NMR evidence suggested that other isomers were formed concurrently.

The recent result by Ganem *et al.*[12] (Fig. 3) seems, at first sight, to be at odds with the results obtained in these laboratories. However, according to Katagiri, the presence of two heteroatoms on the cyclopentene ring forces the five-membered ring to adopt a different conformation with the substituents in axial positions and the Cieplak effect cannot operate. In the latter case bromonium ion formation takes place on the less-hindered face and the small nucleophile attacks at the more electropositive site.

Experimental

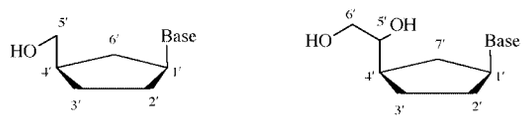
General details

All moisture-sensitive reactions were performed using freshly distilled anhydrous solvents under a static nitrogen or argon atmosphere in dried glassware. Diethyl ether and tetrahydrofuran (THF) were used freshly distilled, under a stream of nitrogen, from sodium benzophenone ketyl. Toluene was distilled over phosphorus pentoxide. Dichloromethane (DCM) was distilled over calcium hydride and stored over potassium hydroxide. Other reagents and solvents were obtained commercially and used as received without further purification unless otherwise specified.



Scheme 2 *Reagents and conditions*: i, nBu$_3$SnH, AIBN, THF, reflux, 3–7 h, (68–92%); ii, K_2CO_3, MeOH, 24 h, (69%); iii, K_2CO_3, MeOH, 2 h, (96%); iv, NH_2OCH_3·HCl, diisopropylethylamine, dioxane, 60 °C, 72 h, (57%); v, K_2CO_3, MeOH, 2 h, (90%).

All reactions were stirred magnetically and monitored by thin layer chromatography (TLC), performed on glass-backed plates coated with Merck 60F-254 silica gel. Visualisation was achieved either *via* treatment with potassium permanganate, ceric ammonium molybdate, *p*-anisaldehyde and/or UV light (254 nm). Flash column chromatography was performed using Merck 60 silica gel (40–60 μm). Nuclear magnetic resonance (^{1}H, ^{13}C) spectra were recorded on Bruker AMX400, AM250, AC200, AC300 and Varian 300 Gemini 2000 spectrometers. All chemical shifts (δ) are quoted in parts per million (ppm) and are reported relative to an internal standard, tetramethylsilane (TMS) (δ 0.00) for ^{1}H and chloroform (δ 77.0) for ^{13}C. The following abbreviations are used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s broad singlet. Coupling constants (J) are measured in Hertz (Hz). Protons were assigned using the necessary NMR experiments (^{1}H–^{1}H COSY), whereas DEPT experiments were performed for the assignment of carbons. Melting points were determined on an electrothermal instrument and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 infrared spectrophotometer and are recorded in reciprocal centimetres (cm^{-1}, wavenumbers). Mass spectra were recorded on a TRIO1000 spectrometer at the Chemistry Department, University of Liverpool, at the EPSRC Mass Spectroscopy Centre, Swansea using a VG ZAB-E high resolution instrument as well as at the Chemistry Department, University of Exeter using a Kratos Profile HV3 high resolution instrument. Microanalyses were performed using a Carlo Erba elemental analyser. All compounds are racemic; stereodescriptors are used to indicate relative stereochemistry. The numbering of carbocyclic nucleosides and 5′ homologues, which is used in the NMR assignments, is as follows:



(1*S*,5*R*)-1-Acetoxy-5-(triphenylmethoxymethyl)cyclopent-2-ene 5

The monoprotected cyclopentenediol (1*S*,5*R*)-5-(triphenylmethoxymethyl)cyclopent-2-en-1-ol (580 mg, 1.63 mmol) was dissolved in a mixture of pyridine (15 cm^3) and acetic anhydride (15 cm^3) and stirred at room temperature for 17 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (60 cm^3). Diethyl ether (60 cm^3) was added to the mixture, the layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (30 cm^3) and brine (30 cm^3). The solution was dried ($MgSO_4$), filtered and the filtrate was evaporated *in vacuo*; the pyridine was evaporated *in vacuo* by azeotropic distillation with toluene, to give the title compound **5** as a clear oil [650 mg, 100%, R_f (dichloromethane–EtOH, 19 : 1) 0.8] (Found: C, 80.9; H, 6.6. $C_{13}H_{18}O_6$ requires C, 80.9; H, 6.6%) δ_H(300 MHz; $CDCl_3$) 1.79 (3 H, s, CH_3 of Ac), 2.17 [1 H, m, C(4)CH_2], 2.42 [1 H, m, C(4)CH_2], 2.70 [1 H, m, C(5)CH], 3.21 [2 H, m, C(1′)CH_2], 5.80 [1 H, dd, J 7.0 and 2.0, C(1)CH], 5.86 [1 H, m, C(3)CH], 6.09 [1 H, m, C(2)CH], 7.24–7.33 (9 H, m, Ph), 7.43 (6 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 34.7 (CH_2, C4), 41.3 (CH, C5), 62.4 (CH_2, C1′), 78.3 (CH, C1), 86.2 (C, Ph_3C), 126.9 (CH, Ph), 127.7 (CH, Ph), 128.8 (CH, Ph), 129.6 (CH, C3), 137.3 (CH, C2), 144.3 (C, Ph), 170.5 (C=O); m/z (EI) 321 ([M − C_6H_5]$^+$, 0.6%), 243 (Ph_3C^+, 100%), 165 (58%).

(1*R*,5*S*,1′*S*)-(1′,2′-Dihydroxyethyl)cyclopent-2-en-1-ol 7

A suspension of lithium aluminium hydride (1.42 g, 37.5 mmol) in THF (30 cm^3) was heated under reflux for 30 min. A solution of hydroxy-lactone **6** (2.37 g, 17.0 mmol) in THF (30 cm^3) was added dropwise while maintaining a gentle reflux and the mixture was then heated under reflux for 4 h. TLC analysis [EtOH–CH_2Cl_2 (1 : 9)] indicated the absence of starting material (R_f 0.40) and formation of a single product (R_f 0.02). The reaction mixture was quenched by dropwise addition of water (1.5 cm^3) at 0 °C. NaOH (2 M, 4.3 cm^3) was added dropwise at 0 °C, and the mixture was stirred for 10 min at 0 °C. Water (1.5 cm^3) was added at 0 °C. The viscous mixture was filtered; the solid material was washed with ethyl acetate and the filtrate was evaporated *in vacuo* to give the crude triol **7** as a yellow oil. To recover the triol retained in the $LiAlH_4$ suspension, the suspension was refluxed at 65 °C for 24 h in THF. The mixture was filtered while warm, and the filtrate evaporated *in vacuo* to give an additional amount of the crude triol **7** as a yellow oil (total weight of yellow oil 2.25 g). The triol **7** was carried on to the next step without purification.

(1*R*,5*S*,1′*S*)-1-Acetoxy-5-(1′,2′-diacetoxyethyl)cyclopent-2-ene 8

Triol **7** (3.62 g, 25 mmol) was dissolved in a mixture of pyridine (40 cm^3) and acetic anhydride (40 cm^3). DMAP (100 mg) was added and the solution was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (70 cm^3). Diethyl ether (100 cm^3) was added to the mixture, the layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (100 cm^3) and brine (100

cm^3). The solution was dried ($MgSO_4$), filtered and the filtrate was evaporated *in vacuo* to give a yellow oil. Crystallisation of the crude material from petroleum ether (bp 40–60 °C) (petrol) gave the title compound **8** as a white crystalline solid [3.72 g, 13.75 mmol, 55%, R_f (petrol–EtOAc, 1:4) 0.2]; mp 83–84 °C (petrol) (Found: C, 57.8; H, 6.7. $C_{13}H_{18}O_6$ requires C, 57.8; H, 6.7%) (HRMS: found: $[M + NH_4]^+$ 288.14476. $C_{13}H_{22}NO_6$ requires 288.14471); ν_{max} (CH_2Cl_2)/cm^{-1} 2948, 1734, 1371, 1227, 1017, 750; δ_H(300 MHz; $CDCl_3$) 1.98 (3 H, s, CH_3 of Ac), 2.00 (3 H, s, CH_3 of Ac), 2.02 (3 H, s, CH_3 of Ac), 2.30 [2 H, m, C(4)CH_2], 2.56 [1 H, m, C(5)CH], 3.98 [1 H, dd, *J* 12.3 and 5.5, C(2′)CH_2], 4.37 [1 H, dd, *J* 12.3 and 2.3, C(2′)CH_2], 5.22 [1 H, ddd, *J* 5.8, 5.5 and 2.3, C(1′)CH], 5.63 [1 H, m, C(1)CH], 5.84 [1 H, m, C(3)CH], 6.10 [1 H, m, C(2)CH]; δ_C(75 MHz; $CDCl_3$) 20.6 (CH_3, CH_3 of Ac), 20.7 (CH_3, CH_3 of Ac), 20.8 (CH_3, CH_3 of Ac), 33.3 (CH_2, C4), 41.9 (CH, C5), 64.5 (CH_2, C2′), 70.3 (CH, C1′), 77.1 (CH, C1), 129.7 and 137.3 (*C*H=*C*H), 170.3, 170.4, 170.7 (C=O).

(1′*R*,4′*S*)-2-Amino-6-chloro-9-[4′-(acetoxymethyl)cyclopent-2′-en-1′-yl]purine 9

2-Amino-6-chloropurine (1.07 g, 6.3 mmol) and sodium hydride (60% dispersed in mineral oil, 252 mg, 6.3 mmol) in DMF (10 cm^3) were stirred for 20 min at room temperature and for 10 min at 50 °C. The resultant solution was added to a suspension of **4** (1.13 g, 5.7 mmol) and tetrakis(triphenylphosphine)palladium (728 mg, 0.630 mmol) in DMF (10 cm^3) *via* cannula, rinsing with DMF (2 × 3 cm^3). The reaction mixture was stirred in the dark for 3 h at 50 °C and then cooled to room temperature whereupon water (40 cm^3) was added. The mixture was extracted with dichloromethane (3 × 50 cm^3) and the combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo* to give a yellow crude oil. The oil was purified by column chromatography over silica gel, eluting first with petrol–EtOAc (4:1) to give recovered starting material **4** [339 mg, 33% recovered, R_f (petrol–EtOAc, 4:1) 0.30], then with petrol–EtOAc (1:2) which provided the title compound **9** as a clear oil [843 mg, 48%, R_f (petrol–EtOAc, 1:2) 0.30] (Found: C, 50.7; H, 4.6, N, 22.6; M^+ 307.08343. $C_{13}H_{14}ClN_5O_2$ requires C, 50.7; H, 4.6, N, 22.8%; M^+ 307.08359); ν_{max} (CH_2Cl_2)/cm^{-1} 3325, 3310, 2950, 2850, 1750, 1625, 1575, 1410, 1230, 775, 730; δ_H(200 MHz; $CDCl_3$) 1.65–1.80 [1 H, m, C(6′)CH_2], 2.10 (3 H, s, CH_3 of Ac), 2.87 [1 H, dt, *J* 14.2, 8.9 and 8.4, C(6′)CH_2], 3.20 [1 H, m, C(4′)CH], 4.15 [1 H, dd, *J* 11.1 and 5.6, C(5′)CH_2], 4.25 [1 H, dd, *J* 11.1 and 5.6, C(5′)CH_2], 5.18 (2 H, br s, NH_2), 5.60 [1 H, m, C(1′)CH], 5.91 [1 H, ddd, *J* 5.5, 4.3 and 2.1, C(2′)CH], 6.18 [1 H, ddd, *J* 5.5, 4.1 and 2.1, C(3′)CH], 7.82 [1 H, s, C(8) CH]; δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 34.6 (CH_2, C6′), 44.5 (CH, C4′), 59.6 (CH, C1′), 66.2 (CH_2, C5′), 125.7 (C, C5), 129.9 (CH, C2′), 137.9 (CH, C3′), 140.6 (CH, C8), 151.4 and 153.5 (C, C4 and C, C6), 159.1 (C, C2), 171.0 (C, C=O).

(1′*R*,4′*S*)-6-Chloro-9-[4′-(acetoxymethyl)cyclopent-2′-en-1′-yl]purine 10

Compound **10** was prepared in a similar manner to that described for compound **9** using 6-chloropurine (154 mg, 1.0 mmol) and (1*R*,5*R*)-5-(acetoxymethyl)cyclopent-2-en-1-ol **2** (487 mg, 2.5 mmol) to give the desired product **10** as colourless solid [82 mg, 28%, R_f (petrol–EtOAc, 1:2) 0.35]; mp 107–108 °C (HRMS: found: M^+ 293.0805. $C_{13}H_{13}ClN_4O_2$ requires 293.0805); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 1742, 1487; δ_H(300 MHz; $CDCl_3$) 1.66 [1 H, m, C(6′)CH_2], 2.00 (3 H, s, CH_3 of Ac), 2.87 [1 H, m, C(6′)CH_2], 3.15 [1 H, ddddd, *J* 8.8, 5.5, 5.5, 2.2 and 2.0 C(4′)CH], 4.04 [1 H, dd, *J* 11.2 and *J* 5.4, C(5′)CH_2], 4.12 [1 H, dd, *J* 11.2 and *J* 5.5, C(5′)CH_2], 5.76 [1 H, dddd, *J* 8.8, 5.7, 2.0 and 2.0, C(1′)CH], 5.92 [1 H, ddd, *J* 5.5, 2.2 and 2.0, C(2′)CH], 6.16 [1 H, ddd, *J* 5.5, 2.2 and 2.2, C(3′)CH], 8.02 [1 H, s, C(2)CH or C(8)CH], 8.70 [1 H, s, C(2)CH or C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 34.9 (CH_2, C6′), 44.5 (CH, C4′), 60.1 (CH, C1′), 66.0 (CH_2, C5′), 129.3 (CH, C2′), 131.8 (C, C5), 138.7 (CH, C3′), 148.4 (CH, C8), 150.8 and 151.4 (C, C4 and C, C6), 151.7 (CH, C2), 170.7 (C, C=O).

(1′*R*,4′*S*)-2-Amino-6-chloro-9-[4′-(triphenylmethoxymethyl)-cyclopent-2′-en-1′-yl]purine 11

Compound **11** was prepared in a similar manner to that described for compound **9** using 2-amino-6-chloropurine (119 mg, 0.70 mmol), (1*R*,2*R*)-1-acetoxy-2-(triphenylmethoxymethyl)cyclopent-4-ene **5** (307 mg, 0.77 mmol) and tetrakis-(triphenylphosphine)palladium (40 mg, 0.035 mmol) to give the desired product **11** as a clear oil [194 mg, 55%, R_f (petrol–EtOAc, 1:4) 0.51] (HRMS: found: M^+ 507.18292. $C_{30}H_{26}ClN_5O$ requires 507.18259); δ_H(300 MHz; $CDCl_3$) 1.59 [1 H, m, C(6′)CH_2], 2.77 [1 H, ddd, *J* 14.0, 7.0 and 7.0, C(6′)CH_2], 3.16 [3 H, m, C(4′)CH and C(5′)CH_2], 5.03 (2 H, br s, NH_2), 5.56 [1 H, m, C(1′)CH], 5.84 [1 H, m, C(2′)CH], 6.26 [1 H, m, C(3′)CH], 7.26–7.53 (15 H, m, Ph), 7.65 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 35.1 (CH_2, C6′), 45.6 (CH, C4′), 59.4 (CH, C1′), 65.9 (CH_2, C5′), 86.3 (C, Ph_3C), 125.8 (C, C5), 127.1 (CH, Ph), 127.8 (CH, Ph), 128.6 (CH, Ph), 128.9 (CH, C2′), 139.4 (CH, C3′), 140.5 (CH, C8), 143.9 (C, Ph), 151.7 (C, C4), 153.9 (C, C6), 159.0 (C, C2).

(1′*R*,4′*S*,5′*S*)-2-Amino-6-chloro-9-[4′-(1″,2″-diacetoxyethyl)-cyclopent-2′-en-1′-yl]purine 12

Compound **12** was prepared in a similar manner to that described for compound **9** using 2-amino-6-chloropurine (3.04 g, 17.4 mmol) and triacetate **8** (3.92 g, 14.5 mmol) to give the desired product **12** as a clear oil [2.62 g, 48%, R_f (petrol–EtOAc, 1:2) 0.30] (HRMS: found: M^+ 379.10474. $C_{16}H_{18}ClN_5O_4$ requires 379.10495); δ_H(200 MHz; $CDCl_3$) 1.85 [1 H, m, C(7′)CH_2], 2.05 (3 H, s, CH_3 of Ac), 2.10 (3 H, s, CH_3 of Ac), 2.75 [1 H, m, C(7′)CH_2], 3.20 [1 H, m, C(4′)CH], 4.10 [1 H, dd, *J* 12.2 and 6.0, C(6′)CH_2], 4.35 [1 H, dd, *J* 12.2 and 4.0, C(6′)CH_2], 5.45 [4 H, m, C(1′)CH, C(5′)CH, NH_2], 5.83 [1 H, ddd, *J* 5.5, 4.4 and 2.1, C(2′)CH], 6.05 [1 H, ddd, *J* 5.5, 4.1 and 2.1, C(3′)CH], 7.75 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.5 (CH_3, CH_3 of Ac), 20.8 (CH_3, CH_3 of Ac), 33.0 (CH_2, C7′), 45.6 (CH, C4′), 60.4 (CH, C1′), 64.1 (CH, C5′), 73.0 (CH_2, C6′), 125.8 (C, C5), 130.2 (CH, C2′), 136.0 (CH, C3′), 141.0 (CH, C8), 151.6 (C, C4), 153.6 (C, C6), 159.1 (C, C2), 170.6 and 170.8 (C, C=O).

(1′*R*,4′*S*)-2,6-Dichloro-9-[4′-(acetoxymethyl)cyclopent-2′-en-1′-yl]purine 13

2-Amino-6-chloropurine **9** (475 mg, 1.54 mmol) was dissolved in dichloromethane (8 cm^3) and the solution was cooled to 0 °C. Trimethylchlorosilane (0.58 cm^3, 4.62 mmol) was added rapidly followed by slow addition of isopentyl nitrite (0.62 cm^3, 4.62 mmol) maintaining the temperature at 0 °C. The mixture was stirred for 2 h at 0 °C and then for 5 h at room temperature. The reaction was quenched with water (6 cm^3) and extracted with dichloromethane (2 × 10 cm^3). The combined organic layers were washed with saturated aqueous sodium hydrogencarbonate solution (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give a yellow oil. The oil was purified by column chromatography over silica gel eluting with petrol–EtOAc (1:2) to give the 2,6-dichloropurine **13** as a yellow oil [309 mg, 0.944 mmol, 61%, R_f (petrol–EtOAc, 1:2) 0.30] (Found: C, 47.6; H, 3.7; N, 17.0. $C_{13}H_{12}Cl_2N_4O_2$ requires C, 47.7; H, 3.7; N, 17.1%) (HRMS: found: $[M + H]^+$ 327.04181. $C_{13}H_{13}Cl_2N_4O_2$ requires 327.04156); δ_H(200 MHz; $CDCl_3$) 1.70 [1 H, m, C(6′)CH_2], 2.15 (3 H, s, CH_3 of Ac), 2.96 [1 H, dd, *J* 14.3 and 8.9, C(6′)CH_2], 3.20 [1 H, m, C(4′)CH], 4.11 [1 H, dd, *J* 11.1 and 5.1, C(5′)CH_2], 4.23 [1 H, dd, *J* 11.1 and 5.1, C(5′)CH_2], 5.80 [1 H, m, C(1′)CH], 5.95 [1 H, ddd,

J 5.5, 4.3 and 2.1, C(2′)CH], 6.20 [1 H, ddd, *J* 5.5, 4.0 and 2.1, C(3′)CH], 8.20 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 35.1 (CH_2, C6′), 44.7 (CH, C4′), 60.3 (CH, C1′), 66.0 (CH, C5′), 123.2 (C, C5), 129.2 (CH, C2′), 139.1 (CH, C3′), 143.9 (CH, C8), 151.9 and 152.8 (C, C4 and C, C6), 153.1 (C, C2), 171.7 (C, C=O).

(1′*R*,2′*R*,3′*R*,4′*R*)-2-Amino-6-chloro-9-[3′-acetoxy-4′-(acetoxymethyl)-2′-bromocyclopentan-1′-yl]purine 14

To a solution of **9** (215 mg, 0.70 mmol) in glacial acetic acid (8 cm^3) was added *N*-bromoacetamide (112 mg, 0.77 mmol) and silver acetate (130 mg, 0.77 mmol) and the reaction mixture was stirred at room temperature overnight. Saturated aqueous sodium hydrogen carbonate solution and solid sodium hydrogen carbonate were added until neutral pH was obtained. The solid material was removed by filtration and the filtrate was extracted with dichloromethane (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give a red oil. Purification of the crude oil by column chromatography over silica gel using gradient elution [CH_2Cl_2 (100%) then EtOH–CH_2Cl_2 (5:95)] gave the bromoacetate **14** as a clear oil. The oil was crystallised from dichloromethane and petrol to give compound **14** as fine long white crystals [109 mg, 35%, R_f (EtOH–CH_2Cl_2, 5:95) 0.26]; mp 136–137 °C (Found: C, 40.3; H, 3.8; N, 15.5. $C_{15}H_{17}BrClN_5O_4$ requires C, 40.3; H, 3.8; N, 15.7%) (HRMS: found: $[M + H]^+$ 446.02259. $C_{15}H_{18}BrClN_5O_4$ requires 446.02307); ν_{max} ($CHCl_3$)/cm^{-1} 3523, 3009, 1743, 1608, 1208; δ_H(300 MHz; $CDCl_3$) 2.11 (3 H, s, CH_3 of Ac), 2.15 (3 H, s, CH_3 of Ac), 2.37–2.58 [3 H, m, C(6′)CH_2 and C(4′)CH], 4.33 [1 H, dd, *J* 11.4 and 6.0, C(5′)CH_2], 4.42 [1 H, dd, *J* 11.4 and 6.0, C(5′)CH_2], 4.75 [1 H, m, C(2′)CH], 4.92 [1 H, m, C(1′)CH], 5.17 (2 H, br s, NH_2), 5.44 [1 H, m, C(3′)CH], 7.90 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.7 (CH_3, CH_3 of Ac), 20.8 (CH_3, CH_3 of Ac), 30.0 (CH_2, C6′), 42.5 (CH, C4′), 55.1 (CH, C2′), 55.7 (CH, C1′), 65.0 (CH_2, C5′), 80.5 (CH, C3′), 125.4 (C, C5), 140.5 (CH, C8), 149.1 and 152.0 (C, C4 and C, C6), 159.2 (C, C2), 169.7 and 170.9 (C, C=O) [*Crystal data*:[5] colourless prism, monoclinic, $P2_1/n$, 0.15 × 0.20 × 0.25 mm, a = 15.597(5), b = 7.077(2), c = 17.178(2) Å, β = 96.13(2)°, U = 1885.4 Å^3, T = −120 °C, Z = 4, μ(Mo-Kα) = 23.29 cm^{-1}; 3769 reflections measured, 3630 unique, R = 0.055, R_w = 0.080. CCDC 182/834].

(1′*R*,2′*R*,3′*R*,4′*R*)-6-Chloro-9-[3′-acetoxy-4′-(acetoxymethyl)-2′-bromocyclopentan-1′-yl]purine 15

Compound **15** was prepared in a similar manner to that described for compound **14** using compound **10** (73 mg, 0.25 mmol) and *N*-bromoacetamide (35 mg, 0.25 mmol) to give the desired product **15** as a colourless glassy solid [52 mg, 48%, R_f (dichloromethane–MeOH–NH_3, 94:5:1) 0.30] (HRMS: found: M^+ 430.0034. $C_{15}H_{16}BrClN_4O_4$ requires 430.0043); δ_H(300 MHz; $CDCl_3$) 2.08 (3 H, s, CH_3 of Ac), 2.17 (3 H, s, CH_3 of Ac), 2.55 [3 H, m, C(6′)CH_2 and C(4′)CH], 4.35 [2 H, m, C(5′)CH_2], 4.79 [1 H, m, C(2′)CH], 5.13 [1 H, m, C(1′)CH], 5.40 [1 H, m, C(3′)CH], 8.26 [1 H, s, C(2)CH], 8.70 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 20.9 (CH_3, CH_3 of Ac), 30.1 (CH_2, C6′), 42.5 (CH, C4′), 55.1 (CH, C2′), 56.2 (CH, C1′), 64.9 (CH_2, C5′), 80.5 (CH, C3′), 125.4 (C, C5), 143.6 (CH, C8), 150.8 (C, C4), 151.6 (C, C6), 152.0 (CH, C2), 169.5 and 170.7 (C, C=O).

(1′*R*,2′*R*,3′*R*,4′*R*)-2-Amino-6-chloro-9-[3′-acetoxy-2′-bromo-4′-(triphenylmethoxymethyl)cyclopent-1′-yl]purine 16

Compound **16** was prepared in a similar manner to that described for compound **14** using compound **11** (141 mg, 0.28 mmol) and *N*-bromoacetamide (45 mg, 0.31 mmol) to give the desired product **16** as a yellow oil [125 mg, 69%, R_f (dichloromethane–EtOH, 19:1) 0.58]; δ_H (200 MHz; $CDCl_3$) 2.11 [4 H, m, CH_3 of Ac and C(6′)CH_2], 2.40 [2 H, m, C(6′)CH_2 and C(4′)CH], 3.48 [2 H, m, C(5′)CH_2], 4.64 [1 H, m, C(2′)CH], 4.83 [1 H, m, C(1′)CH], 5.13 (2 H, br s, NH_2), 5.37 [1 H, m, C(3′)CH], 7.25–7.37 (9H, m Ph), 7.43–7.49 (6H, m, Ph), 7.74 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 30.2 (CH_2, C6′), 43.4 (CH, C4′), 55.4 (CH, C2′), 55.7 (CH, C1′), 64.8 (CH_2, C5′), 80.9 (CH, C3′), 87.0 (C, Ph_3C), 125.4 (C, C5), 127.2 (CH, Ph), 127.9 (CH, Ph), 128.7 (CH, Ph), 140.6 (CH, C8), 143.9 (C, Ph), 151.5 (C, C4), 153.8 (C, C6), 159.1 (C, C2), 169.7 (C, C=O); *m/z* (EI) 324 (15%, $M^+ - Ph_3C - Br$), 243 (81%, Ph_3C^+), 170 (100%), 43 (50%, Ac^+).

(1′*R*,2′*R*,3′*R*,4′*R*)-2,6-Dichloro-9-[3′-acetoxy-4′-(acetoxymethyl)-2′-bromocyclopentan-1′-yl]purine 17

Compound **17** was prepared in a similar manner to that described for compound **14** using compound **13** (291 mg, 0.89 mmol) and *N*-bromosuccinimide (192 mg, 1.07 mmol) to give the desired product **17** as a clear oil [233 mg, 56%, R_f (petrol–EtOAc, 1:2) 0.37] (Found: C, 38.9; H, 3.3; N, 11.8; M^+ 464.97211. $C_{15}H_{15}BrCl_2N_4O_4$ requires C, 38.7; H, 3.2; N, 12.0%; 464.97320); δ_H(300 MHz; $CDCl_3$) 2.13 (3 H, s, CH_3 of Ac), 2.18 (3 H, s, CH_3 of Ac), 2.50–2.68 [3 H, m, C(6′)CH_2 and C(4′)CH], 4.38 [2 H, dd, *J* 8.4 and 2.7, C(5′)CH_2], 4.78 [1 H, m, C(2′)CH], 5.15 [1 H, m, C(1′)CH], 5.45 [1 H, m, C(3′)CH], 8.25 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 20.9 (CH_3, CH_3 of Ac), 30.4 (CH_2, C6′), 42.7 (CH, C4′), 54.9 (CH, C2′), 56.3 (CH, C1′), 64.8 (CH_2, C5′), 80.4 (CH, C3′) 131.5 (C, C5), 143.9 (CH, C8), 149.1 and 152.0 (C, C4 and C, C6), 159.2 (C, C2), 169.9 and 170.8 (C, C=O).

(1′*R*,2′*R*,3′*R*,4′*R*,5′*S*)-2-Amino-6-chloro-9-[3′-acetoxy-2′-bromo-4′-(1″,2″-diacetoxyethyl)cyclopentan-1′-yl]purine 18

To a solution of **12** (171 mg, 0.45 mmol) in glacial acetic acid (10 cm^3) was added *N*-bromoacetamide (79 mg, 0.54 mmol) and silver acetate (91 mg, 0.54 mmol) and the reaction mixture was stirred at room temperature for 16 h. Saturated aqueous sodium hydrogen carbonate solution and solid sodium hydrogen carbonate were added until neutral pH was attained. The solid materials were removed by filtration and the filtrate was extracted with dichloromethane (2 × 40 cm^3). The combined organic layers were dried ($MgSO_4$) and solvent evaporated *in vacuo* to give a crude yellow oil. The crude oil was purified by column chromatography over silica gel eluting with dichloromethane–EtOH (19:1), affording a mixture of diastereoisomers as a clear oil. Crystallisation from *tert*-butyl methyl ether gave the bromoacetate **18** as a colourless solid [115 mg, 49%, R_f (dichloromethane–EtOH, 19:1) 0.37] (HRMS: found: M^+ 517.03581. $C_{18}H_{21}BrClN_5O_6$ requires 517.03638); δ_H(300 MHz; $CDCl_3$) 2.09 (3 H, s, CH_3 of Ac), 2.12 (3 H, s, CH_3 of Ac), 2.16 (3 H, s, CH_3 of Ac), 2.48–2.62 [3 H, m, C(7′)CH_2 and C(4′)CH], 4.12 [1 H, dd, *J* 12.0 and 6.0 C(6′)CH_2], 4.39 [1 H, dd, *J* 12.0 and 3.0, C(6′)CH_2], 4.62 [1 H, m, C(2′)CH], 4.85 [1 H, m, C(1′)CH], 5.44 (2 H, s, NH_2), 5.58 [1 H, m, C(5′)CH], 5.79 [1 H, m, C(3′)CH], 7.80 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.4 (CH_3, CH_3 of Ac), 20.7 (CH_3, CH_3 of Ac), 20.7 (CH_3, CH_3 of Ac), 29.4 (CH_2, C7′), 42.9 (CH, C4′), 54.9 (CH, C1′), 55.4 (CH, C3′), 63.5 (CH, C5′), 71.5 (CH_2, C6′), 79.0 (CH, C2′), 125.5 (CH, C5), 141.0 (C, C8), 151.6 (C, C4), 153.6 (C, C6), 159.1 (C, C2), 169.2, 170.5 and 170.6 (C, C=O).

(1′*R*,2′*R*,3′*R*,4′*R*)-2-Amino-6-chloro-9-[3′-acetoxy-2′-bromo-4′-(hydroxymethyl)cyclopentan-1′-yl]purine 19

Compound **16** (98 mg, 0.15 mmol) was dissolved in an aqueous solution of acetic acid (80%, 3 cm^3) and stirred for 6 h at 50 °C. The solvent was evaporated *in vacuo* and the resulting crude oil was purified by column chromatography over silica gel eluting with petrol–EtOAc (1:9). The title compound **19** was obtained as an oil (40 mg, 66%) (HRMS: found M^+ 403.00439. $C_{13}H_{15}$-

$BrClN_5O_3$ requires 403.00467); δ_H(400 MHz; acetone-d_6) 2.11 (3 H, s, CH_3 of Ac), 2.43 [3 H, m, C(6′)CH_2 and C(4′)CH], 3.82 [2 H, m, C(5′)CH_2], 4.14 (1 H, br s, OH), 4.88 [1 H, m, C(2′)CH], 4.99 [1 H, m, C(1′)CH], 5.45 [1 H, m, C(3′)CH], 6.30 (2 H, br s, NH_2), 8.15 [1 H, s, C(8)CH]; δ_C(100 MHz; acetone-d_6) 21.3 (CH_3, CH_3 of Ac), 30.2 (CH_2, C6′), 46.6 (CH, C4′), 56.9 (CH, C2′), 57.7 (CH, C1′), 64.9 (CH_2, C5′), 81.9 (CH, C3′), 125.4 (C, C5), 142.4 (CH, C8), 151.6 (C, C4), 155.3 (C, C6), 161.2 (C, C2), 170.8 (C, C=O).

(1′*R*,3′*S*,4′*R*)-2-Amino-6-chloro-9-[3′-acetoxy-4′-(acetoxymethyl)cyclopentan-1′-yl]purine 20

THF (10 cm^3) was degassed by cooling it to 0 °C and bubbling nitrogen through for 15 min. The bromoacetate **14** (120 mg, 0.27 mmol), AIBN (9.0 mg, 0.06 mmol) and tri-*n*-butyltin hydride (0.72 cm^3, 2.69 mmol) were added to the degassed THF and the reaction mixture was stirred under reflux for 3 h. TLC analysis did not indicate any conversion and further tri-*n*-butyltin hydride (0.36 cm^3, 1.35 mmol) was added to the reaction mixture and stirring under reflux was continued for another 60 min. After cooling to room temperature, EtOAc (25 cm^3), saturated potassium fluoride solution (5 cm^3) and solid potassium fluoride (1 g) were added and the mixture was stirred for 30 min to precipitate the unreacted tributyltin hydride as the fluoride salt. The solid material was removed by filtration and the filtrate was washed with water (3 × 30 cm^3) and brine (20 cm^3) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude material was purified by column chromatography over silica gel, eluting with dichloromethane–EtOH (29:1), followed by dichloromethane–EtOH (19:1) to give the product **20** as a white crystalline solid [88 mg, 92%, R_f (dichloromethane–EtOH, 19:1) 0.26]; mp 121–124 °C (*tert*-butyl methyl ether) (HRMS: found: M^+ 367.10470. $C_{15}H_{18}ClN_5O_4$ requires 367.10473); δ_H(400 MHz; $CDCl_3$) 1.98 [1 H, m, C(6′)CH_2], 2.08 (6 H, s, 2 × CH_3 of Ac), 2.30 [1 H, dd, *J* 13.0 and 8.0, C(6′)CH_2], 2.52–2.62 [3 H, m, C(2′)CH_2 and C(4′)CH], 4.30 [2 H, m, C(5′)CH_2], 4.90 [1 H, m, C(1′)CH], 5.22 [3 H, m, C(3′)CH and NH_2], 7.78 [1 H, s, C(8)CH]; δ_C(100 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 21.1 (CH_3, CH_3 of Ac), 33.0 (CH_2, C6′), 37.3 (CH, C2′), 43.6 (CH, C4′), 54.1 (CH, C1′), 64.8 (CH_2, C5′), 75.4 (CH, C3′), 126.0 (C, C5), 140.9 (CH, C8), 151.6 (C, C4), 153.4 (C, C6), 158.7 (C, C2), 170.3 and 171.0 (C, C=O).

(1′*R*,3′*S*,4′*R*)-2,6-Dichloro-9-[3′-acetoxy-4′-(acetoxymethyl)-cyclopentan-1′-yl]purine 21

THF (10 cm^3) was degassed by cooling it to 0 °C and bubbling nitrogen through for 15 min. The degassed THF was added to the bromoacetate **17** (148 mg, 0.318 mmol), AIBN (83 mg, 0.636 mmol) and tris(trimethylsilyl)silane (0.20 cm^3, 0.636 mmol) *via* a cannula. The reaction mixture was stirred under reflux for 24 h. The solvent was removed *in vacuo* and the crude material purified by column chromatography over silica gel eluting with petrol–EtOAc (1:2) yielding the title compound **21** as a yellow oil [81 mg, 68%, R_f (petrol–EtOAc, 1:2) 0.40] (Found: C, 46.8; H, 4.3, N, 14.8; M^+ 386.05520. $C_{15}H_{16}Cl_2N_4O_4$ requires C, 46.5; H, 4.2, N, 14.5%; 386.05487); δ_H(300 MHz; $CDCl_3$) 1.99 [1 H, m, C(6′)CH_2], 2.10 (6 H, s, 2 × CH_3 of Ac), 2.45 [1 H, m, C(6′)CH_2], 2.60 [3 H, m, C(2′)CH_2 and C(4′)CH], 4.15–4.30 [2 H, ABX, J_{AB} 18.0, J_{AX} 5.1 and J_{BX} 5.4, C(5′)CH_2], 5.10 [1 H, m, C(1′)CH], 5.25 [1 H, m, C(3′)CH], 8.10 [1 H, s, C(8)CH]; δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3, CH_3 of Ac), 21.0 (CH_3, CH_3 of Ac), 33.7 (CH_2, C6′), 38.0 (CH, C2′), 43.8 (CH, C4′), 54.6 (CH, C1′), 64.4 (CH_2, C5′), 75.0 (CH, C3′), 130.1 (C, C5), 144.1 (CH, C8), 152.1 and 153.1 (C, C4 and C, C6), 159.4 (C, C2), 170.4 and 170.9 (C, C=O).

(1′*R*,3′*S*,4′*R*,5′*S*)-2-Amino-6-chloro-9-[3′-acetoxy-4′-(1″,2″-diacetoxyethyl)cyclopentan-1′-yl]purine 22

THF (3 cm^3) was degassed by cooling it to 0 °C and bubbling nitrogen through for 15 min The bromoacetate **18** (34 mg, 0.07 mmol), AIBN (21 mg, 0.13 mmol) and tri-*n*-butyltin hydride (0.26 cm^3, 0.99 mmol) were added to the degassed THF and the reaction mixture was stirred under reflux for 7 h. The solvent was evaporated *in vacuo* and the crude material was purified by column chromatography over silica gel eluting with hexane (to remove tin residues) followed by dichloromethane–MeOH (24:1) to give the product **22** as a colourless oil [26 mg, 90%, R_f (dichloromethane–MeOH, 24:1) 0.17] (HRMS: found: M^+ 439.12555. $C_{18}H_{22}ClN_5O_6$ requires 439.12585); δ_H(300 MHz; $CDCl_3$) 2.08 (6 H, s, 2 × CH_3 of Ac), 2.12 (3 H, s, CH_3 of Ac), 2.15–2.27 [2 H, m, C(7′)CH_2], 2.51–2.71 [3 H, m, C(4′)CH and C(2′)CH_2], 4.12 [1 H, dd, *J* 12.0 and 7.0, C(6′)CH_2], 4.39 [1 H, dd, *J* 12.0 and 3.0, C(6′)CH_2], 4.87 [1 H, m, C(1′)CH], 5.30 (2 H, s, NH_2), 5.40 [1 H, m, C(3′)CH], 5.53 [1 H, m, C(5′)CH], 7.73 [1 H, s, C(8)CH]; δ_C(100 MHz; $CDCl_3$) 20.9 (CH_3, CH_3 of Ac), 21.0 (CH_3, CH_3 of Ac), 21.2 (CH_3, CH_3 of Ac), 32.3 (CH_2, C7′), 37.6 (CH_2, C2′), 45.1 (CH, C4′), 54.6 (CH, C1′), 63.9 (CH, C5′), 71.8 (CH_2, C6′), 74.7 (CH, C3′), 126.0 (CH, C5), 141.3 (C, C8), 151.7 (C, C4), 153.3 (C, C6), 158.8 (C, C2), 170.0, 170.7 and 170.8 (C, C=O).

(1′*R*,3′*S*,4′*R*)-2-Amino-6-chloro-9-[3′-acetoxy-4′-(hydroxymethyl)cyclopentan-1′-yl]purine 23

THF (2 cm^3) was degassed by cooling it to 0 °C while nitrogen was bubbled through the solvent for 15 min. The bromoacetate **19** (20 mg, 0.05 mmol), AIBN (16 mg, 0.10 mmol) and tri-*n*-butyltin hydride (0.14 cm^3, 0.50 mmol) were added to the degassed THF and the reaction mixture was stirred under reflux for 3 h. No products were detectable by TLC analysis and further tri-*n*-butyltin hydride (0.07 cm^3, 0.25 mmol) was added to the reaction mixture, which was stirred for another 2 h. The solvent was evaporated *in vacuo* and the crude material was purified by column chromatography on silica gel eluting with hexane (to remove tin residues) followed by dichloromethane–MeOH (19:1) to give the product **23** as an oil, still contaminated with traces of tributyltin hydride [13 mg, R_f (dichloromethane–EtOH, 19:1) 0.36]; δ_H(200 MHz; acetone-d_6) 2.10 (3 H, s, CH_3 of Ac), 2.22–2.43 [2 H, m, C(6′)CH_2], 2.43–2.65 [2 H, m, C(2′)CH_2], 3.72 [2 H, dd, *J* 5.5 and 5.2, C(5′)CH_2], 4.00 (1 H, t, *J* 5.0, OH), 5.00 [1 H, m, C(1′)CH], 5.19 [1 H, m, C(3′)CH], 6.24 (2 H, br s, NH_2), 8.12 [1 H, s, C(8)CH].

(1′*R*,2′*S*,3′*R*,4′*R*)-2-Amino-6-chloro-9-[4′-(hydroxymethyl)-2′,3′-epoxycyclopentan-1′-yl]purine 24

To a stirred, cooled solution (0 °C) of the acetoxy bromide **13** (89 mg, 0.20 mmol) in methanol (10 cm^3) was added potassium carbonate (27 mg, 0.20 mmol). The reaction was stirred at room temperature for 24 h. Methanol (10 cm^3) was added and the solution adsorbed onto silica gel. Column chromatography over silica (Merck 7729) eluting with dichloromethane–methanol (9:1) gave the title compound **24** as a colourless powder (39 mg, 69%) (HRMS: found: M^+ 281.06824. $C_{11}H_{12}ClN_5O_2$ requires 281.06795); δ_H(400 MHz; $CDCl_3$) 1.80 [1 H, ddd, *J* 15.0, 7.0 and 7.0, C(6′)CH_2], 2.11 [1 H, ddd, *J* 15.0, 7.0 and 7.0, C(6′)CH_2], 2.40 [1 H, m, C(4′)CH], 3.37 [2 H, m, C(5′)CH_2], 3.72 [1 H, m, C(3′)CH], 3.98 [1 H, d, *J* 2.0, C(2′)CH], 4.80 (1 H, br s, OH), 4.84 [1 H, m, C(1′)CH], 6.93 (2 H, s, NH_2), 8.19 [1 H, s, C(8)CH]; δ_C(100 MHz; $CDCl_3$) 32.4 (CH_2, C6′), 42.3 (CH, C4′), 54.4 (CH, C1′), 58.3 (CH, C2′), 61.3 (CH, C3′), 61.9 (CH_2, C5′), 123.8 (C, C5), 141.5 (CH, C8), 149.9 (C, C4), 154.5 (C, C6), 160.2 (C, C2).

(1′*R*,3′*S*,4′*R*)-2-Amino-6-chloro-9-[3′-hydroxy-4′-(hydroxymethyl)cyclopentan-1′-yl]purine 25

A solution of **20** (43 mg, 0.12 mmol) and potassium carbonate (9 mg, 0.07 mmol) in methanol (5.0 cm^3) was stirred at room temperature for 2 h. The reaction mixture was neutralised with

saturated aqueous ammonium chloride solution and stirred for a further 15 min. The solvent was evaporated *in vacuo* and the crude material was purified by column chromatography over silica gel, eluting with dichloromethane–MeOH (9:1). The diol **25** was obtained as a clear oil [32.0 mg, 96%, R_f (dichloromethane–MeOH, 9:1) 0.17] (HRMS: found: M^+ 283.08416. $C_{11}H_{14}ClN_5O_2$ requires 283.08359); δ_H(300 MHz; CD_3OD) 1.93 [1 H, m, C(6′)CH_2], 2.17–2.25 [2 H, m, C(4′)CH and C(2′)CH_2], 2.36–2.53 [2 H, m, C(2′)CH_2 and C(6′)CH_2], 3.72 [2 H, m, C(5′)CH_2], 4.31 [1 H, m, C(3′)CH], 5.06 [1 H, m, C(1′)CH], 8.19 [1 H, s, C(8)CH]; δ_C(75 MHz; CD_3OD) 32.2 (CH_2, C6′), 38.9 (CH_2, C2′), 48.4 (CH, C4′), 52.8 (CH, C1′), 62.1 (CH, C5′), 71.5 (CH, C3′), 123.3 (CH, C5), 141.1 (C, C8), 149.4 (C, C4), 153.1 (C, C6), 159.2 (C, C2).

(1′*R*,3′*S*,4′*R*)-2-Chloro-6-*N*-methoxyamino-9-[3′-acetoxy-4′-(acetoxymethyl)cyclopentan-1′-yl]purine 26

Compound **21** (15 mg, 0.04 mmol), diisopropylethylamine (0.04 cm^3, 0.25 mmol) and methoxylamine hydrochloride (16 mg, 0.19 mmol) were dissolved in dioxane (5 cm^3). The reaction mixture was stirred at 60 °C for 3 days then cooled to room temperature and the solvent evaporated *in vacuo*. Purification of the crude product by column chromatography over silica gel eluting with petrol–EtOAc (1:2) gave the title compound **26** as a clear oil [9 mg, 0.02 mmol, 57%, R_f (petrol–EtOAc, 1:2) 0.25] (HRMS: found: M^+ 397.11496. $C_{16}H_{20}ClN_5O_5$ requires 397.11530); δ_H(200 MHz; $CDCl_3$) 1.99 [1 H, m, C(6′)CH_2], 2.10 (3 H, s, CH_3 of Ac), 2.11 (3 H, s, CH_3 of Ac), 2.40 [1 H, m, C(6′)CH_2], 2.60 [3 H, m, C(2′)CH_2 and C(4′)CH], 4.00 (3 H, s, OCH_3), 4.20 [2 H, m, C(5′)CH_2], 5.10 [1 H, m, C(1′)CH], 5.30 [1 H, m, C(3′)CH], 7.98 [1 H, s, C(8)CH], 9.00 (1 H, br s, NH); δ_C(75 MHz; $CDCl_3$) 20.7 (CH_3, CH_3 of Ac), 21.0 (CH_3, CH_3 of Ac), 33.9 (CH_2, C6′), 38.0 (CH, C2′), 43.7 (CH, C4′), 53.8 (CH, C1′), 64.5 (CH_2, C5′), 65.0 (CH_3, CH_3 of $HNOCH_3$), 75.0 (CH, C3′) 129.0 (C, C5), 146.0 (CH, C8), 152.0 and 153.5 (C, C4 and C, C2), 161.0 (C, C6), 170.1 and 170.3 (C, C=O).

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