Concise Racemic and Highly Enantioselective Approaches to Key Intermediates for the Syntheses of Carbocyclic Nucleosides and *pseudo*-Ribofuranoses: Formal Syntheses of Carbovir

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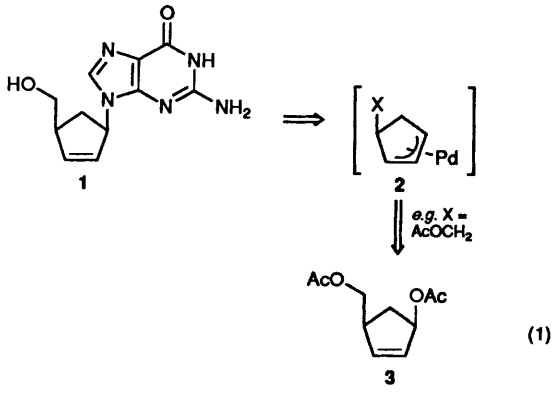
A regio- and stereo-specific synthesis of *cis*-(±)-3-acetoxy-5-(acetoxymethyl)cyclopentene **3** from cyclopent-3-enecarboxylic acid **4** *via* a bromolactonisation strategy is described. Pd-catalysed coupling of the *cis*-(±)-diacetate **3** with 2-amino-6-chloropurine or 2,6-diaminopurine leads to the formal syntheses of carbovir **1**. A synthesis of the (1*R*)-*cis*-diacetate **15** (R = Ac) is described *via* a highly enantioselective rearrangement of *cis*-6-oxabicyclo[3.1.0]hexane-3-methanol **13** (also prepared from the acid **4**) using the dilithium salt of (1*S*,2*R*)-norephedrine.

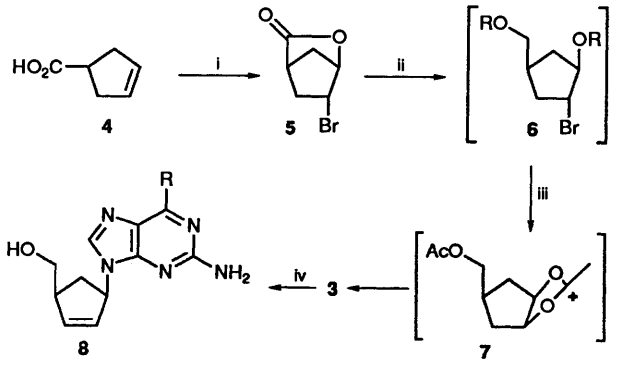
The development of synthetic routes to carbocyclic nucleosides is an area of considerable research interest.[1] Carbocyclic nucleosides show antiviral properties, particularly against HIV,[2] as well as herbicidal activities.[3] The most convergent approaches to these systems, which have found application in syntheses of aristeromycin and the potent anti-HIV agent carbovir **1**, couple a complete purine or pyrimidine base with a functionalised cyclopentane.[4–12] These strategies have most often been based on the chemistry of a π-allyl palladium intermediate **2** [eqn. (1)].[5–12]



(1)

Attack *anti* to the palladium centre in the intermediate **2** by the 'soft' purine or pyrimidine nucleophile determines the facial selectivity [*cis* to the substituent (X) already present] and minimisation of non-bonded interactions with this substituent results in the desired allylic regiochemistry.[5] The attractiveness of these strategies is crucially dependent on efficient ways of preparing the precursors to the π-allyl palladium intermediate **2**. Whilst the monoepoxide of cyclopentadiene or the monoacetate of *cis*-cyclopent-4-ene-1,3-diol fulfil this criteria, the hydroxymethylene group then has to be introduced after the coupling step in a stepwise fashion.[5,6] Precursors which already possess the hydroxymethylene group have also been prepared from *cis*-cyclopent-4-ene-1,3-diol,[7] or from cyclopentanone.[8] The most concise entry uses a Prins reaction between cyclopentadiene and formaldehyde in acetic acid.[9a] Unfortunately, this reaction proceeds in low yield to give an inseparable mixture of the *cis*-diacetate **3**, the corresponding *trans*-diacetate and their respective allylic regioisomers. Optimisation of this reaction has been done with respect to maximising the proportion of *cis*-diacetate **3** and its *cis*-allylic regioisomer, as they can both be used in palladium-catalysed coupling since the original allylic positional identity is destroyed on formation of the π-allyl palladium intermediate **2**. This optimisation study resulted in a 10% yield of a diacetate mixture (82:18 *cis*:*trans* diacetates) which was used directly in palladium-catalysed coupling reactions.[9a] Hydrolysis of the Prins product mixture followed by careful chromatographic separation of the diols and diacylation can provide the *cis*-diacetate **3**. However, a stereocontrolled access to the *cis*-diacetate **3** and/or its *cis*-allylic regioisomer would be desirable. Furthermore, only the former positional isomer is required for *pseudo*-ribofuranose synthesis.[13] Finally, given the interest in preparing chiral carbocyclic nucleosides,[1] an enantioselective approach to the *cis*-diacetate **3**, without recourse to a resolution procedure, would also be of value. Compounds derived from the *cis*-diacetate **3** have been enzymically resolved and used in the asymmetric syntheses of carbovir[10] and *pseudo*-ribofuranoses.[13] An enzymic resolution approach from cyclopentadiene and methyl glyoxylate has also been described; this route requires a one-carbon degradation to reveal the hydroxymethylene group.[11] Enantioselective approaches to precursors already possessing the hydroxymethylene group start with desymmetrisation of diesters of *cis*-cyclopent-4-ene-1,3-diol—either enzymically, followed by stepwise introduction of the hydroxymethylene group,[7] or by an elegant palladium-catalysed approach in which a masked form of the hydroxymethylene group is introduced in the asymmetrisation step.[12] Here we report full details of our synthesis of the racemic *cis*-diacetate **3**,[14] together with further palladium-catalysed coupling studies with purines, and full details of a highly enantioselective approach to either enantiomer of the *cis*-diacetate **3**[15] resulting in an improved general synthetic access to carbocyclic nucleosides and carbovir **1** in particular.

Our strategy envisaged that halogenolactonisation of the acid **4** followed by reductive ring opening, diacylation and elimination would provide a regio- and stereo-specific synthesis of the *cis*-(±)-diacetate **3** (Scheme 1). The acid **4** has been used in other approaches to carbocyclic nucleosides,[4a,c] and is an attractive starting material since it has an obvious precursor to the hydroxymethylene group already appended to a cyclopentene. Furthermore, the acid **4** is directly available (70% yield) without chromatography on a multigram scale by an optimised procedure from dimethyl malonate and (*Z*)-1,4-dichlorobut-2-ene.[16] Following Iwata's procedure,[17] bromolactonisation of the acid **4** using trimethylsilyl bromide (TMSBr), dimethyl sulfoxide (DMSO) and diisopropylethylamine reproducibly gave the bromo lactone **5** in much improved yields (70–95%) over that originally reported (40%). Reductive ring-opening of

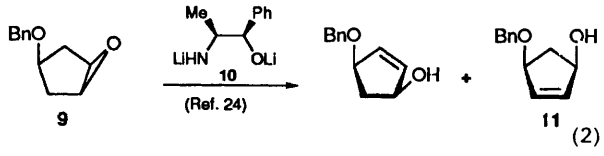


Scheme 1 *Reagents and conditions:* i, TMSBr, DMSO, Pr^i_2EtN, $CHCl_3$, reflux, 12 h; ii, (for **6**, R = H) $[(MeOCH_2CH_2O)_2AlH_2]Na$, THF, −25 °C, 2 min; iii, (for **6**, R = H) Ac_2O, sparteine, cat. DMAP, DMF, 25 °C, 12 h; then AgOAc added, reflux, 6 h; iv, (for **8**, R = Cl), NaH, 2-amino-6-chloropurine, cat. $Pd(PPh_3)_4$, DMF, 60 °C, 2 h; then MeOH added; iv, (for **8**, R = NH_2), Cs_2CO_3, 2,6-diaminopurine, cat. $Pd(PPh_3)_4$, DMSO, 60 °C, 2 h; then MeOH, K_2CO_3

the bromo lactone **5**, without loss of the halide, to give the bromo diol **6** (R = H) was initially attempted using lithium aluminium hydride, following precedent with 8-bromo-1-methyl-6-oxabicylo[3.2.1]oct-2-ene-7-one.[18] However, reaction of the bromo lactone **5** with 0.6 mole equivalent of lithium aluminium hydride in diethyl ether at −42 °C for 30 min gave 3-(hydroxymethyl)cyclopentanone (60%),[19] which has found use in a stereoselective synthesis of methyl epijasmonate.[20] In the present case, the 3-(hydroxymethyl)cyclopentanone could have arisen from formation of an epoxide and a subsequent rearrangement promoted by the aluminium salts. Variation of the reaction conditions (temperature, ratios of lithium aluminium hydride) resulted in mixtures containing the desired bromo diol **6** (R = H) and substantial quantities of 3-(hydroxymethyl)cyclopentanone. A much more satisfactory preparation used sodium bis(2-methoxyethoxy)aluminium hydride in tetrahydrofuran (THF) at −25 °C, which gave the bromo diol **6** (R = H) contaminated with traces (5%) of 3-(hydroxymethyl)cyclopentanone. The crude bromo diol **6** (R = H) was readily diacylated using acetic anhydride and pyridine in THF. However, concomitant elimination of HBr was not observed, and it was the diacetoxy bromide **6** (R = Ac) that was isolated (86% from the bromo lactone **5**) after 3 days at reflux. The crude bromo diol **6** (R = H) was eventually converted into the *cis*-diacetate **3** (66% from the bromo lactone **5**) by switching to acetic anhydride and triethylamine in dimethylformamide (DMF) and, following formation of the diacetoxy bromide **6** (R = Ac) (by TLC), addition of silver acetate. On the basis that this last step may be proceeding *via* the *meso*-acetoxonium ion **7** we repeated the reaction using (−)-sparteine as the base in an attempt to induce enantioselective desymmetrisation. Although the *cis*-diacetate **3** again formed as the racemate, this procedure reproducibly gave the highest yields (78% from the bromo lactone **5**).

With the *cis*-diacetate **3** in hand we sought to demonstrate its utility in a synthesis of carbovir **1**. Reaction of 2-amino-6-chloropurine with NaH, then addition of the *cis*-diacetate **3** and catalytic $Pd(PPh_3)_4$ followed, after 2 h, by addition of MeOH resulted in formation of the known chloride **8** (R = Cl) (60%),[10,21] in which base-catalysed transesterification had removed the second acetoxy group. The chloride **8** (R = Cl) can be converted into carbovir **1** by using NaOH.[10,21] Reaction of the chloride **8** (R = Cl) with ammonia under pressure is known to give the diamine **8** (R = NH_2),[21] which has been resolved using adenosine deaminase to give access to the enantiomers of carbovir **1**.[22] We were also able to prepare (82%) the diamine **8** (R = NH_2) by a more direct palladium-catalysed coupling of the *cis*-diacetate **3** with readily available 2,6-diaminopurine. For this reaction the caesium salt[8] of 2,6-diaminopurine in DMSO was used to avoid solubility problems. The selectivity for N-9- over N-7-alkylation[4b] was excellent as judged by examination of the crude ^1H NMR spectrum.

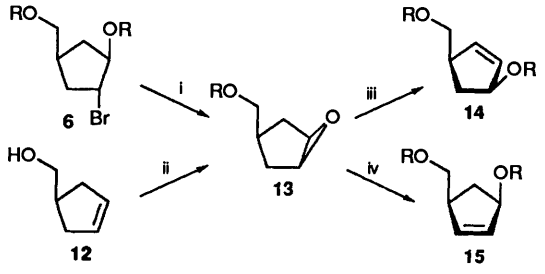
One method to synthesize the enantiomers of the *cis*-diacetate **3** individually, without recourse to a resolution procedure, would be *via* enantioselective rearrangement of a *meso*-epoxide. The enantioselective rearrangement of *meso*-epoxides to allyl alcohols using chiral bases has been the focus of much research.[23] Milne and Murphy recently used the dilithium salts of (1*R*,2*S*)- or (1*S*,2*R*)-norephedrine to effect the closely studied rearrangement of the epoxide **9** [eqn. (2)] in



(2)

higher yields and enantiomeric excesses (e.e.s) than previously recorded with other chiral bases.[24] The highest e.e. reported, which gave predominantly (86% e.e.) the allylic alcohol **11**, was obtained by warming a mixture of dilithiated (1*R*,2*S*)-norephedrine **10** (3 mol equiv.) and the epoxide **9** in THF from −78 °C to 0 °C over a period of 16 h.

In order to examine the enantioselective rearrangement strategy for the preparation of enantiomers of the *cis*-diacetate **3**, the *meso*-epoxide **13** (R = H) (previously synthesized as a 1:1 mixture with the *trans*-isomer)[25] was first made from the crude bromo diol **6** (R = H) using potassium carbonate in methanol (35% from the bromo lactone **5**) (Scheme 2). A more efficient preparation of the *meso*-epoxide **13** (R = H) also started with the acid **4**, which was first reduced[4a] with lithium aluminium hydride to give the known alcohol **12** (95%).[4a] Hydroxyl-directed epoxidation[26] of the alcohol **12** under Sharpless's conditions (*tert*-butyl hydroperoxide, cat. vanadyl acetylacetonate, CH_2Cl_2)[27] gave the *meso*-epoxide **13** (R = H) (98%) with very high stereoselectivity (*cis*:*trans* ≥ 97:3).



Scheme 2 *Reagents and conditions:* i, (for **6** and **13**, R = H) K_2CO_3, MeOH, 25 °C, 12 h; ii, (for **13**, R = H) Bu^tOOH, cat. $VO(acac)_2$, CH_2Cl_2, 25 °C, 24 h; iii, (for **13** and **14**, R = H) BuLi, (1*R*,2*S*)-norephedrine, C_6H_6–THF, 0–25 °C, 12 h; iv, (for **13** and **15**, R = H) BuLi, (1*S*,2*R*)-norephedrine, C_6H_6–THF, 0–25 °C, 12 h

There was no reaction between the derived epoxy ethers **13** (R = Tr or Bn) and dilithiated (1*R*,2*S*)-norephedrine **10** (3 mol equiv.). The epoxy ether **13** (R = Tr) was also recovered unchanged (98%) from attempted reaction with lithium diisopropylamide (LDA). In contrast, the unprotected *meso*-epoxide **13** (R = H) smoothly rearranged upon reaction with dilithiated (1*R*,2*S*)-norephedrine **10** (3 mol equiv.) in benzene–THF (2:1 v/v) on warming from 0 °C to room temperature over a period of 24 h, to give the *cis*-diol **14** (R = H) (65%) in 95% e.e., as determined by bis-Mosher's ester analysis.[28] Spectral comparisons were made with the bis-Mosher's esters from a

racemic mixture of the *cis*-diols **14** and **15** (R = H), prepared by treatment of the *meso*-epoxide **4** (R = H) with LDA. The enantiomeric *cis*-diol **15** (R = H) was similarly prepared (57%, 95% e.e.) using (1*S*,2*R*)-norephedrine. The absolute stereochemistry induced in the *cis*-diols **14** and **15** (R = H) was determined by measuring the direction of the optical rotations of the corresponding known monotritylated alcohols.[10,13] Finally, diacylation of the *cis*-diol **15** (R = H) using acetic anhydride gave the (1*R*)-*cis*-diacetate **15** (R = Ac) (95%).

It is interesting to note that the asymmetric induction found in the rearrangement of the *meso*-epoxide **13** (R = H) with the dilithium salts of (1*R*,2*S*)- or (1*S*,2*R*)-norephedrine is opposite to that observed with the epoxide **9**. In addition, the remarkably high e.e.s found for the rearrangement of the *meso*-epoxide **13** (R = H), which occur between 0 °C and room temperature, combined with the inertness of the epoxy ethers **13** (R = Tr or Bn) may indicate that the norephedrine serves to create a highly ordered transition state for the rearrangement to occur by way of an internal asymmetric deprotonation.

In conclusion, we have developed two concise routes, one racemic and one highly enantioselective, to a key intermediate for carbocyclic nucleoside synthesis and have demonstrated its utility in a synthesis of carbovir **1**.

Experimental

General.—All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under argon. Syringes and needles for the transfer of reagents were dried at 90 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl; (chlorinated) hydrocarbons, and amines, from CaH_2. DMF and DMSO were distilled from CaH_2 under reduced pressure. Internal reaction temperatures are reported unless stated otherwise. All reactions were monitored by TLC using commercially available glass-backed plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck). Organic layers were evaporated with a Buchi rotary evaporator by using water-aspirator-reduced pressure, followed by drying on a static oil pump (1 mmHg). Column chromatography was carried out on Kieselgel 60 (40–63 μm) using light petroleum (boiling range 40–60 °C) and diethyl ether. $[\alpha]_D$-Values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films unless stated otherwise, using a Perkin-Elmer 881 spectrophotometer with polystyrene film for calibration (1602 and 1029 cm^{-1}). Peak intensities are specified as strong (s), medium (m) or weak (w). ^1H NMR spectra were recorded in $CDCl_3$ unless stated otherwise with Bruker WM250, Bruker AM300 or JEOL EX400 spectrometers operating at 250.14 MHz, 300.13 MHz and 399.65 MHz respectively. Chemical shifts are reported relative to $SiMe_4$ in sample or, where stated, to $CHCl_3$ (δ 7.25). Coupling constants (J) are given in Hz. ^{13}C NMR spectra were recorded in $CDCl_3$ unless stated otherwise on the Brukers at 62.90 MHz or 75.47 MHz or on the JEOL at 100.40 MHz. Chemical shifts are reported relative to $CDCl_3$ (central line of triplet, δ_C 77.0) unless stated otherwise. A mixture of off-resonance, DEPT 135, and DEPT 90 pulse sequences were used to aid spectral interpretation. Mass spectra were obtained from the EPSRC Mass Spectrometry Service Centre, Swansea with a VG Micromass ZAB-E instrument.

exo-(±)-6-*Bromo*-2-*oxabicyclo*[2.2.1]*heptan*-3-*one* **5**.—TMSBr (1.20 cm^3, 9.1 mmol) was added dropwise to a stirred solution of DMSO (0.64 cm^3, 9.0 mmol) in $CHCl_3$ (15 cm^3) at 0 °C. After 3 h a solution of cyclopent-3-enecarboxylic acid **4**[16] (0.784 g, 7.0 mmol) in $CHCl_3$ (5 cm^3) was added dropwise over a period of 15 min. After an additional 10 min, diisopropylethylamine (1.57 cm^3, 9.0 mmol) was added to the reaction mixture, which was then refluxed for 12 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (30 cm^3) and washed successively with water (2 × 40 cm^3) and brine (40 cm^3). The organic layer was dried ($MgSO_4$), and was then evaporated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave an oil, the *bromo lactone* **5** (1.276 g, 95%); b.p. 150–160 °C/0.1 mmHg [Found: $(M + NH_4)^+$, 207.9973. $C_6H_{11}{}^{79}BrNO_2$ requires m/z, 207.997 31]; ν_{max}/cm^{-1} 2925m, 2875m, 1785s and 1045m; δ_H(400 MHz) 4.90 (1 H, br s, BrCH), 4.44 (1 H, ddd, J 10, 4 and 2, CHO), 2.91–2.90 (1 H, m, CH), 2.73 (1 H, ddd, J 14, 10 and 4, H of bridge CH_2), 2.31 (1 H, ddd, J 14, 2 and 2, H of CH_2), 1.92 (1 H, d, J 14, H of CH_2) and 1.88 (1 H, ddd, J 14, 4 and 4, H of bridge CH_2); δ_C(100 MHz) 176.3 (C=O), 81.9 (CH), 45.4 (CH), 42.0 (CH), 38.9 (CH_2) and 34.7 (CH_2); m/z (CI) 210 (100%) and 208 (100).

(±)-3-(*Hydroxymethyl*)*cyclopentanone*.—Lithium aluminium hydride (1.0 mol dm^{-3} in THF; 1.45 cm^3, 1.45 mmol) was added dropwise over a period of 60 s to a stirred solution of the bromo lactone **5**[17] (0.475 g, 2.49 mmol) in diethyl ether (5 cm^3) at −42 °C (acetonitrile/CO_2-bath). After a further 30 min water (0.055 cm^3) was added to the mixture, followed by aq. sodium hydroxide (15% w/v; 0.055 cm^3) and further water (0.167 cm^3). The reaction mixture was filtered, and the filtrate diluted with EtOAc (10 cm^3) and saturated ammonium chloride (10 cm^3) and extracted with EtOAc (2 × 10 cm^3). The combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–Et_2O) gave an oil, 3-(*hydroxymethyl*)*cyclopentanone* (0.170 g, 60%); R_f 0.25 (20% EtOAc–Et_2O (Found: M^+, 114.0681. $C_6H_{10}O_2$ requires M, 114.068 08); ν_{max}/cm^{-1} 3415m, 2950m, 1745s and 1050w; δ_H(250 MHz; $CHCl_3$) 3.66 (2 H, d, J 6, CH_2O), 2.79 (1 H, s, OH), 2.53–1.66 (6 H, m, 3 × CH_2) and 1.84–1.63 (1 H, m, CH); δ_C(63 MHz) 219.9 (C=O), 65.5 (CH_2O), 41.6 (CH_2), 38.9 (CH), 37.9 (CH_2) and 25.5 (CH_2); m/z (EI) 115 (100%) and 97 (60).

(1α,3β,4α)-(±)-3-*Bromo*-4-*hydroxycyclopentanemethanol* **6** (R = H).—Preparation as previously described.[14] R_f 0.25 (20% EtOAc–Et_2O) (Found: M^+, 193.9943. $C_6H_{11}{}^{79}BrO_2$ requires M, 193.994 24); ν_{max}/cm^{-1} 3440s, 2925s and 1045w; δ_H(250 MHz; $CHCl_3$) 4.18 (1 H, m, CHBr), 4.05 (1 H, apparent q, J 1.5, C*H*OH), 3.63 (2 H, d, J 4.5, CH_2OH), 2.78 (1 H, s, OH), 2.56 (1 H, s, OH) and 2.50–1.72 (5 H, m, 2 × CH_2 and CH); δ_C(63 MHz) 73.5 (CHOH), 65.7 (CH_2OH), 56.1 (CHBr), 37.5 (CH_2), 35.0 (CH_2) and 34.3 (CH); m/z (CI) 196 (60%), 194 (55), 112 (20), 98 (20), 79 (50) and 67 (100).

(1α,2β,4α)-(±)-1-*Acetoxy*-4-(*acetoxymethyl*)-2-*bromocyclopentane* **6** (R = Ac).—Acetic anhydride (0.10 cm^3, 1.06 mmol) was added to a stirred solution of crude bromo diol **6** (R = H) (50 mg) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (20 mg, 0.16 mmol) in pyridine (1 cm^3). The reaction mixture was then heated to reflux for 72 h after which time it was diluted with diethyl ether (10 cm^3), and washed successively with water (10 cm^3) and brine (2 × 10 cm^3). The organic layer was dried ($MgSO_4$), and was then evaporated under reduced pressure. Purification of the residue by column chromatography (35% diethyl ether–light petroleum) gave an oil, the *diacetoxy bromide* **6** (R = Ac) (65 mg, 86%); R_f 0.35 (35% diethyl ether–light petroleum) [Found: $(M + NH_4)^+$, 296.0497. $C_{10}H_{19}{}^{79}BrNO_4$ requires m/z, 296.049 74]; ν_{max}/cm^{-1} 2950w, 1740s, 1440w, 1370m, 1140s and 1035m; δ_H(250 MHz; $CHCl_3$) 5.08–5.00 (1 H, m, CHO), 4.41–4.32 (1 H, m, CHBr), 4.13–4.07 (2 H, m, CH_2O), 2.59–1.95 (4 H, m, 2 × CH_2), 2.13 (3 H, s, Me), 2.07 (3 H, s, Me) and 1.88–1.72 (1 H, m, CH); δ_C(63 MHz) 170.6 (C=O), 169.9 (C=O), 77.5 (CHO), 67.8 (CH_2O),

50.3 (CHBr), 36.8 (CH), 33.7 (CH_2), 32.2 (CH_2), 20.8 (Me) and 20.7 (Me); *m/z* (CI) 298 (100%), 296 (100) and 218 (17).

cis-(±)-3-*Acetoxy*-5-(*acetoxymethyl*)*cyclopentene* **3**.—Preparation and characterisation as previously described.[14] R_f 0.30 (35% diethyl ether–light petroleum).

cis-(±)-4-(2-*Amino*-6-*chloro*-9H-*purin*-9-*yl*)*cyclopent*-2-*enemethanol* **8** (R = Cl).—2-Amino-6-chloropurine (85 mg, 0.5 mmol) was added to a stirred solution of sodium hydride (80% w/w in mineral oil; 15 mg, 0.5 mmol, pre-washed with light petroleum) in DMF (5 cm^3) at 25 °C. The reaction mixture was heated to 60 °C and after 0.5 h it was cooled to ambient temperature before the *cis*-diacetate **3** (80 mg, 0.4 mmol) and $Pd(PPh_3)_4$[29] (100 mg, 0.1 mmol) were added. The flask was covered in tin foil to exclude light and the mixture was heated to 60 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with MeOH (10 cm^3), filtered, and evaporated under reduced pressure. Purification of the residue by column chromatography (5% MeOH–CH_2Cl_2) gave a yellow solid, which was recrystallised to give the chloride **8** (R = Cl) (64 mg, 60%); R_f 0.25 (5% MeOH–CH_2Cl_2); m.p. 140–143 °C (from EtOH) (lit.,[21] 145–147 °C); $\nu_{max}(CHCl_3)$/cm^{-1} 3345m, 2995m, 1600s, 1310s, 1220s, 1080s and 750s; δ_H(400 MHz; [$^2H_6$]DMSO) 8.10 (1 H, s, HC=N), 6.98 (2 H, s, NH_2), 6.16 (1 H, ddd, *J* 5.5, 2 and 2, =CH), 5.91 (1 H, ddd, *J* 5.5, 2 and 2, CH=), 5.50–5.45 (1 H, m, CHN), 4.69 (1 H, t, *J* 5.5, OH), 3.46 (2 H, d, *J* 5.5, OCH_2), 2.94–2.85 (1 H, m, CH), 2.64 (1 H, ddd, *J* 13, 8.5 and 8.5, H of CH_2) and 1.64 (1 H, ddd, *J* 13, 5.5 and 5.5, H of CH_2); δ_C(100 MHz; [$^2H_6$]DMSO) 159.5, 153.5, 149.2 (HC=N), 141.1, 138.8, 129.1 (=CH), 123.4 (CH=), 63.6 (OCH_2), 58.9 (CHN), 47.6 (CH) and 33.8 (CH_2).

cis-(±)-4-(2,6-*Diamino*-9H-*purin*-9-*yl*)*cyclopent*-2-*enemethanol* **8** (R = NH_2).—2,6-Diaminopurine (92 mg, 0.61 mmol) was added to a stirred solution of caesium carbonate (199 mg, 0.61 mmol) in DMSO (5 cm^3) at 25 °C and the mixture was then heated to 60 °C for 2 h. After this mixture had cooled to room temperature, the *cis*-diacetate **3** (81 mg, 0.41 mmol) and $Pd(PPh_3)_4$[29] (100 mg, 0.1 mmol) were added. The flask was covered in tin foil to exclude light and the reaction mixture was heated to 60 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with MeOH (10 cm^3), filtered through a pad of Celite 545 (Fluka), and evaporated under reduced pressure. The residue was preadsorbed onto silica (40 mg) and purified by column chromatography (10% MeOH–CH_2Cl_2) to yield the diamine **8** and its O-acylated derivative (111 mg of a 1:3 mixture respectively by ^1H NMR analysis). The mixture was diluted with MeOH (5 cm^3) before potassium carbonate (200 mg) was added and the reaction mixture was stirred for 1 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was adsorbed onto silica (40 mg) and purified by column chromatography (15% MeOH–$CHCl_3$) to give a yellow solid, which was recrystallised to give the diamine **8** (R = NH_2) (83 mg, 82%); R_f 0.25 (15% MeOH–$CHCl_3$); m.p. 150–153 °C (from EtOH) (lit.,[21] 152–155 °C); $\nu_{max}(CHCl_3)$/cm^{-1} 3345m, 2995m, 1600s, 1310s, 1220s, 1080s and 750s; δ_H(400 MHz; [$^2H_6$]DMSO) 7.68 (1 H, s, HC=N), 6.76 (2 H, s, NH_2), 6.16 (1 H, ddd, *J* 6, 2.5 and 2.5, =CH), 5.92 (1 H, ddd, *J* 5.5, 2 and 2, CH=), 5.85 (2 H, s, NH_2) and 5.46–5.42 (1 H, m, CH), 3.54 (2 H, d, *J* 11.5, OCH_2), 3.50 (1 H, s, OH), 2.92 (1 H, m, CH), 2.66 (1 H, ddd, *J* 13, 8.5 and 8.5, H of CH_2) and 1.63 (1 H, ddd, *J* 13, 5.5 and 5.5, H of CH_2); δ_C(100 MHz; [$^2H_6$]DMSO; $SiMe_4$) 160.2, 156.2, 151.4, 138.1 (HC=N or =C), 135.3 (=C or HC=N), 130.1 (C=), 113.3, 64.2 (OCH_2), 58.3 (CHN), 47.7 (CH) and 34.4 (CH_2).

(1α,3α,5α)-6-*Oxabicyclo*[3.1.0]*hexane*-3-*methanol* **13** (R = H).—*Method A*. Potassium carbonate (451 mg, 3.26 mmol) was added in one portion to a stirred solution of the crude bromo diol **6** (R = H) (187 mg) in MeOH (2 cm^3) at 25 °C. After 12 h the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography (15% diethyl ether–light petroleum) gave, first, an oil, the *meso*-epoxide **13** (R = H) (41 mg, 35%), followed by unchanged bromo diol **6** (92 mg); data for the *meso*-epoxide **13** (R = H): R_f 0.30 (Et_2O); ν_{max}/cm^{-1} 3400s, 2925s, 2855s and 1035s; δ_H(400 MHz) 3.53 (2 H, s, 2 × CHO), 3.46 (2 H, d, *J* 5, CH_2OH), 3.20 (1 H, s, OH), 2.42–2.37 (1 H, m, CH) and 2.10–1.98 (4 H, m, 2 × CH_2); δ_C(100 MHz) 67.0 (2 × CHO), 59.2 (CH_2OH), 36.6 (CH) and 31.2 (2 × CH_2).

Method B. *tert*-Butyl hydroperoxide [~3.0 mol dm^{-3} in CH_2Cl_2, prepared from a mixture of *tert*-butyl hydroperoxide (70% by weight in water; 41 cm^3, 0.3 mol) and CH_2Cl_2 (59 cm^3) by drying (2 × $MgSO_4$) and storage over oven-dried 4 Å molecular sieves[30] (13X sieves are not recommended);[27] 10 cm^3, ~30 mmol] was added dropwise to a stirred solution of the alcohol **12**[4a] (1.470 g, 15.0 mmol) and vanadyl acetylacetonate (15 mg, 0.06 mmol) in CH_2Cl_2 (40 cm^3) at 25 °C. After 24 h, aq. sodium sulfite (15% w/v; 100 cm^3) was added and the reaction mixture was stirred for a further 6 h. It was then filtered, and the filtrate was washed successively with aq. sodium hydrogen carbonate (3 × 20 cm^3) and brine (20 cm^3), and dried ($MgSO_4$). The solvent was evaporated off under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave an oil, the *meso*-epoxide **13** (R = H) (1.677 g, 98%; *cis*:*trans* ≥ 97:3 by ^1H NMR); b.p. 80–100 °C/2.0 mmHg; data for the *trans*-epoxide: R_f 0.30 (Et_2O); δ_H(400 MHz) 3.57 (2 H, d, *J* 6, CH_2OH), 3.49 (2 H, s, 2 × CHO), 3.20 (1 H, s, OH), 2.15–2.10 (2 H, m, 2 × H of CH_2), 2.10–1.98 (1 H, m, CH) and 1.50–1.43 (2 H, m, 2 × H of CH_2); δ_C(100 MHz) 65.0 (CH_2OH), 57.0 (2 × CHO), 35.5 (CH) and 31.0 (2 × CH_2).

(1R)-cis-4-*Hydroxycyclopent*-2-*enemethanol* **14** (R = H).—Butyllithium (2.5 mol dm^{-3} in hexanes; 6.5 cm^3, 16.2 mmol) was added dropwise to a stirred solution of (1*R*,2*S*)-norephedrine (1.221 g, 8.1 mmol) in benzene (15 cm^3)–THF (10 cm^3) at 0 °C. After 0.5 h a solution of the *meso*-epoxide **13** (R = H) (0.276 g, 2.4 mmol) in THF (3 cm^3) was added dropwise to the reaction mixture over a period of 0.25 h. The solution was then allowed to warm to room temperature overnight. MeOH (10 cm^3) was added, and the solution was filtered through Celite 545 (Fluka) and evaporated under reduced pressure. The residue was adsorbed onto SiO_2 (1.0 g) and purified by suction-flash chromatography (gradient elution, Et_2O to 10% Et_2O–EtOAc, 40 cm^3 fractions) to give an oil, the *cis*-diol **14** (R = H) (0.179 g, 65%); R_f 0.25 (10% Et_2O–EtOAc); $[\alpha]_D^{20}$ +46.7 (*c* 1.55 in CH_2Cl_2); ν_{max}/cm^{-1} 3330s, 2930s, 1640w, 1140m, 1370m and 1040m; δ_H(300 MHz) 5.98 (1 H, ddd, *J* 5.5, 2 and 2, =CH), 5.83 (1 H, dd, *J* 5.5 and 2.5, CH=), 4.67 (1 H, ddd, *J* 7, 2 and 2, CHO), 3.89–3.44 (2 H, m, OCH_2), 3.20–2.45 (3 H, m, 2 × OH and CH), 2.40–2.27 (1 H, m, H of CH_2) and 1.57 (1 H, ddd, *J* 14, 2 and 2, H of CH_2); δ_C(69.5 MHz) 134.9 (=C), 134.8 (C=), 75.5 (CHO), 63.1 (OCH_2), 46.5 (CH) and 37.1 (CH_2).

(1S)-cis-4-*Hydroxycyclopent*-2-*enemethanol* **15** (R = H).—Following the procedure for the *cis*-diol **14** (R = H) using butyllithium (2.5 mol dm^{-3} in hexanes; 4.7 cm^3, 11.7 mmol), (1*S*,2*R*)-norephedrine (888 mg, 5.87 mmol) and the *meso*-epoxide **13** (R = H) (200 mg, 1.75 mmol) gave an oil, the *cis*-diol **15** (R = H) (115 mg, 57%); $[\alpha]_D^{25}$ −44.3 (*c* 1.55 in CH_2Cl_2) {lit.,[7] $[\alpha]_D^{20}$ −36 (*c* 0.07 in $CHCl_3$)}.

(3S)-cis-3-[α-*Methoxy*-α-(*trifluoromethyl*)*phenylacetoxy*]-5-{[α-*methoxy*-α-(*trifluoromethyl*)*phenylacetoxy*]*methyl*}*cyclopentene*.—A solution of the *cis*-diol **14** (R = H) (28 mg, 0.25 mmol), DMAP (8 mg, 0.06 mmol), (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (120 mg, 0.51 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (105 mg, 0.51 mmol) in CH_2Cl_2 (5 cm^3) was stirred at 25 °C. After 24 h the reaction mixture was filtered, the filter cake was washed with diethyl ether (3 × 10 cm^3), and the combined filtrates were washed successively with 1 mol dm^{-3} hydrochloric acid (2 × 20 cm^3) and saturated aq. sodium hydrogen carbonate (2 × 20 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (20% diethyl ether–light petroleum) gave an oil, the *bis-Mosher's esters* [126 mg, 94%; 1*S*:1*R* ⩾ 97.5:2.5 by ^1H NMR analysis (in 4:1:1 $CDCl_3$–[$^2H_6$]benzene–[$^2H_6$]DMSO) of the diastereoisomeric H of CH_2s in the δ 1.6–1.7 region]; R_f 0.20 (20% diethyl ether–light petroleum) [Found: $(M + NH_4)^+$, 564.1820. $C_{26}H_{28}F_6NO_6$ requires *m*/*z*, 564.177 47]; ν_{max}/cm^{-1} 2960m, 1750s, 1450m, 1275s, 1175s and 1030s; *m*/*z* (CI) 564 (80%), 391 (35), 330 (86), 313 (72), 252 (45), 189 (68), 96 (54) and 79 (100); discernible data for major diastereoisomer: δ_H(300 MHz) 7.61–7.25 (10 H, m, ArH), 6.10–5.91 (2 H, m, 2 × CH=), 5.91–5.78 (1 H, m, CHO), 4.31–4.08 (2 H, m, OCH_2), 3.52 (3 H, s, J_{H-F} not discernible, Me), 3.51 (3 H, s, J_{H-F} not discernible, Me), 3.08–3.04 (1 H, m, CH), 2.53 (1 H, ddd, *J* 14.5, 8.5 and 8.5, H of CH_2) and 1.70 (1 H, ddd, *J* 14.5, 3.5 and 3.5, H of CH_2); δ_C(69.5 MHz) 167.7 (C=O), 167.6 (C=O), 137.7 (=C), 132.2 (Ar, quat.), 132.1 (Ar, quat.), 131.3 (C=), 129.5 (Ar), 129.4 (Ar), 128.9 (2 × Ar), 128.8 (2 × Ar), 127.3 (4 × Ar), 125.2 (q, J_{C-F} 288, 2 × CF_3), 85.1 (q, J_{CC-F} 28, 2 × CCF_3), 81.4 (CHO), 68.7 (OCH_2), 55.4 (Me), 55.3 (Me), 43.5 (CH) and 33.0 (CH_2). Discernible data for minor diastereoisomer: δ_H(300 MHz) 1.60 (1 H, ddd, *J* 14.5, 3.5 and 3.5, H of CH_2); δ_C(69.5 MHz) 138.0 (=C), 131.2 (C=), 81.3 (CHO), 68.8 (OCH_2), 43.4 (CH) and 32.9 (CH_2).

(1R)-cis-4-(*Triphenylmethoxymethyl*)*cyclopent*-2-*enol*.—A solution of the *cis*-diol **15** (R = H) (42.2 mg, 0.37 mmol), chlorotriphenylmethane (103 mg, 0.37 mmol), triethylamine (0.21 cm^3, 1.5 mmol) and DMAP (4 mg, 0.03 mmol) in DMF (2 cm^3) was stirred at 25 °C. After 72 h the reaction mixture was diluted with diethyl ether (10 cm^3), and washed successively with water (10 cm^3), saturated aq. sodium hydrogen carbonate (2 × 10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–light petroleum) gave a solid, the monotritylated alcohol (125.3 mg, 95%); R_f 0.18 (20% EtOAc–light petroleum); $[\alpha]_D^{20}$ −73.9 (*c* 1.4 in $CHCl_3$) {lit.,[13] $[\alpha]_D^{24}$ −72 (*c* 1.2 in $CHCl_3$) for material determined (by NMR using a chiral shift reagent) to have a 95.5% e.e.}; m.p. 110–112 °C (from Et_2O) (lit.,[13] 113–114 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400s, 1960s, 1710m, 1490s, 1460s, 1090s and 1040m; δ_H(300 MHz) 7.51–7.38 (6 H, m, ArH), 6.00–5.94 (2 H, m, HC=), 4.75–4.68 (1 H, m, CHO), 3.28 (1 H, dd, *J* 9 and 4, H of OCH_2), 3.06 (1 H, dd, *J* 9 and 4, H of OCH_2), 2.37 (1 H, ddd, *J* 16, 7.5 and 7.5, H of CH_2), 2.09 (1 H, d, *J* 9, OH) and 1.42 (1 H, ddd, *J* 14, 3 and 3, H of CH_2).

(1S)-cis-4-(*Triphenylmethoxymethyl*)*cyclopent*-2-*enol*.—Prepared following the procedure for the *cis*-diol **15** (R = H) using the *cis*-diol **14** (R = H); $[\alpha]_D^{20}$ +71.8 (*c* 1.4 in $CHCl_3$) {lit.,[13] $[\alpha]_D^{26}$ +63.2 (*c* 0.5 in $CHCl_3$) for material determined (by NMR using a chiral shift reagent) to have a >95% e.e.}.

(3R)-cis-3-*Acetoxy*-5-(*acetoxymethyl*)*cyclopentene* **15** (R = Ac).—A solution of the *cis*-diol **15** (R = H) (39.1 mg, 0.34 mmol), acetic anhydride (0.13 cm^3, 1.4 mmol), and DMAP (4 mg, 0.03 mmol) in pyridine (2 cm^3) was stirred at 25 °C. After 12 h the reaction mixture was diluted with diethyl ether (10 cm^3), and washed successively with water (10 cm^3), saturated aq. ammonium chloride (2 × 10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography (35% diethyl ether–light petroleum) gave a white semi-solid, the (1*R*)-*cis*-diacetate **15** (R = Ac) (66.0 mg, 97%); R_f 0.30 (35% diethyl ether–light petroleum); $[\alpha]_D^{22}$ −85.7 (*c* 0.5 in $CHCl_3$).

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