Synthesis of Carbocyclic Nucleosides: Synthesis of (±)-2,2-Bis(hydroxymethyl)cyclopropyl Nucleosides[1]

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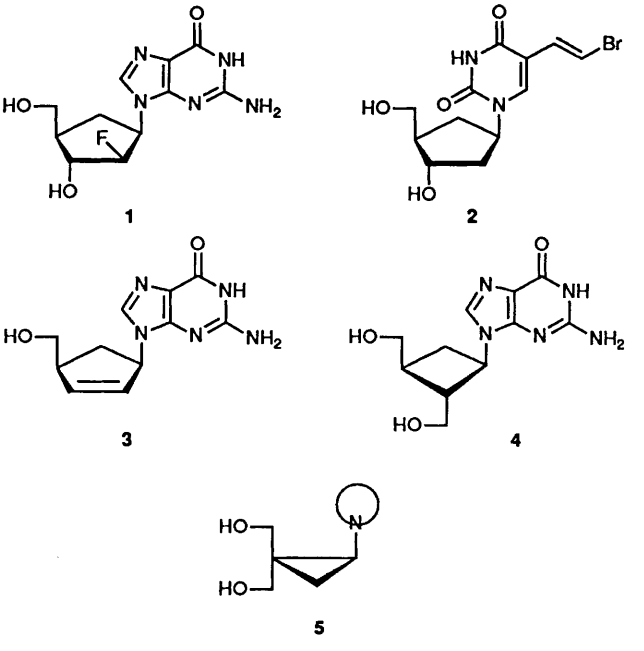
Treatment of 2,2-bis(benzyloxymethyl)cyclopropanecarboxylic acid **8** with ethyl chloroformate and sodium azide followed by thermolysis of the resulting keto azide **9** at 80 °C provided the corresponding isocyanate **10**, which was then converted into 2,2-bis(benzyloxymethyl)cyclopropylurea **11** and 2,2-bis(benzyloxymethyl)cyclopropylamine **13**. The racemic 2,2-bis(hydroxymethyl)cyclopropylpyrimidine nucleosides **16**, **21**, **22**, **23**, **26**, **29**, and **31** and the purine nucleosides **39** and **41** were prepared from compounds **11** and **13**, respectively; they showed no antiviral activity against HSV-1, HSV-2, HCMV, and HIV-1 in cell culture.

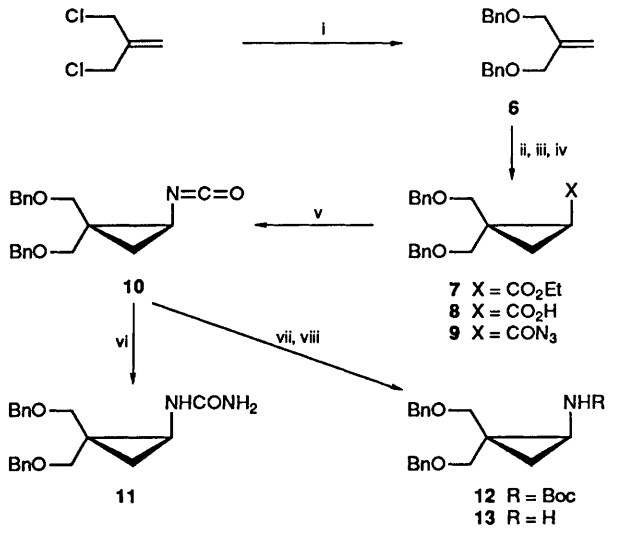
Interest has recently been growing in the synthesis of new nucleoside analogues with potential antiretroviral activity, due to the significant medical problems associated with the treatment of the acquired immunodeficiency syndrome (AIDS). Amongst the many structural types, carbocyclic nucleosides are of special interest, since they are not susceptible to degradation *in vivo* by nucleosidases and phosphorylases, and therefore much attention has been focused on the synthesis of carbocyclic nucleoside analogues and their biological properties.[2] A number of such compounds, *e.g.* carbocyclic 2′-*ara*-fluoroguanosine **1**[3] and carbocyclic 5-bromovinyl-2′-deoxyuridine **2**[4,5] have been shown to have potent antiherpetic activity, and carbovir **3**[6] and cyclobut-G **4**[7] showed potent and selective anti-HIV activity. In order to explore the structure–activity relationship of the ring size and the effect on biological activity of a hydroxymethyl substituent with a view to maintaining or improving acceptance by viral enzymes and improving selectivity, we have successfully synthesized various (±)-2,2-bis(hydroxymethyl)cyclopropyl nucleosides **5**.†



Synthesis of the Cyclopropylurea **11** *and the Cyclopropylamine* **13**.—Reaction of 1,1-bis(benzyloxymethyl)ethylene **6**, prepared from 3-chloro-2-chloromethylpropene and benzyl alcohol, with ethyl diazoacetate at 90 °C provided the cyclopropyl ester **7**, which was then hydrolysed with KOH in methanol to give the corresponding carboxylic acid **8** in 47.6% yield from **6**. Curtius rearrangement was effected as follows. Reaction of **8** successively with ethyl chloroformate in the presence of triethylamine and then sodium azide, followed by thermolysis of the keto azide **9** in toluene at 80 °C provided the isocyanate **10**. The latter was converted into the urea **11** by reaction with ammonia in ether (77% yield from **8**) and into the amine **13** by reaction with *tert*-butyl alcohol under reflux for 2 days followed by treatment with trifluoroacetic acid (85% yield from **8**) (Scheme 1). However, attempts to convert **8** into the N-Boc-cyclopropylamine **12** with diphenylphosphoryl azide (DPPA) in benzyl alcohol furnished only a low yield (< 10%) of product.

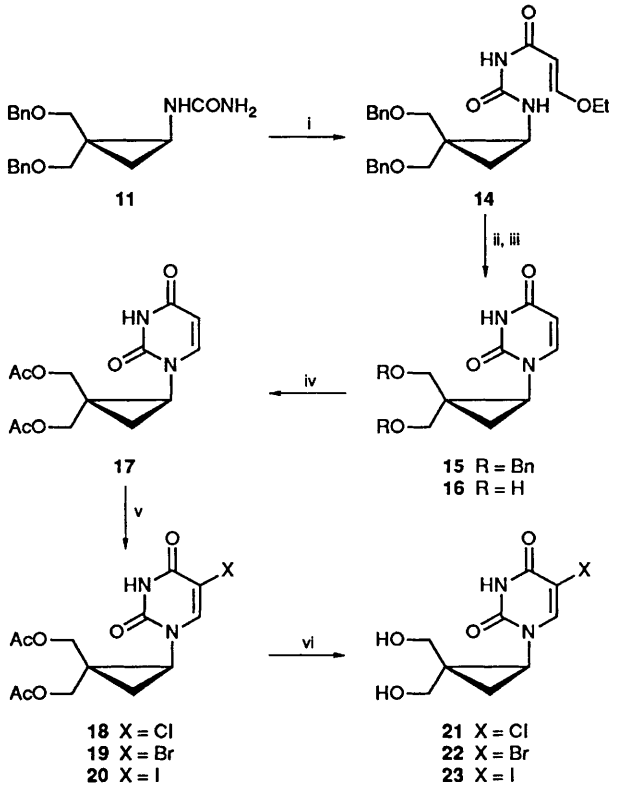
Synthesis of Pyrimidine Nucleosides.—The synthetic route (Scheme 2) to the uracil analogues from **11** was based on a variant of the general methodology for the synthesis of uracils and thymines developed initially by Shaw and Warrener.[10] Treatment of **11** with β-ethoxyacryloyl chloride in pyridine gave an intermediate acryloylurea **14**, which was cyclized with refluxing 4% aqueous ammonia to the uracil **15** (26.5% overall yield from **11**). Hydrogenolysis of **15** using catalytic hydrogen transfer from 95% formic acid provided **16** (90% yield). A number of 5-substituted uracil derivatives, especially halogen- and 2-bromovinyl-substituted uracils, have been investigated extensively for the experimental and clinical treatment of neoplastic and viral diseases. The corresponding 5-chloro, 5-bromo, 5-iodo-uridine analogues of **16** were prepared from the diacetate **17** according to the procedure for ceric ammonium nitrate (CAN)-mediated halogenation at C-5 of uracil derivatives.[11] Treatment of **17** with 1.2 mol equiv. of LiCl, LiBr, or LiI and 2 mol equiv. CAN in MeCN at 80–85 °C, followed by hydrolysis

† Very recently, a synthesis of 9-(*t*-2,*c*-3-dihydroxymethyl-*r*-1-cyclopropyl)adenine[8] and guanine[9] was reported. Both reports indicated that the compound showed no significant antiviral activity.



Scheme 1 *Reagents and conditions:* i, BnOH–NaH; ii, N_2CHCO_2Et, $CuSO_4$; iii, KOH, MeOH; iv, $ClCO_2Et$, Et_3N, NaN_3; v, toluene, 80 °C; vi, NH_3; vii, Bu^{t}OH; viii, CF_3CO_2H, then NaOH

with sodium methoxide in methanol afforded the corresponding 5-halogenouracil nucleosides **21**, **22** and **23** in 58, 51 and 93% yield, respectively.



Scheme 2 *Reagents and conditions:* i, β-ethoxyacryloyl chloride, py; ii, NH_4OH, EtOH, heat; iii, Pd-black, 95% HCO_2H, MeOH; iv, Ac_2O, py; v, LiCl, or LiBr, or LiI, CAN, MeCN, heat; vi, NaOMe, MeOH

The thymine nucleoside **26** was prepared from the tritoluoyl derivative **24** according to the procedure of Herdewijn.[12] Treatment of **24** with tetramethyltin and $Pd(Ph_3P)_4$ in HMPA at 60 °C, followed by hydrolysis with sodium methoxide in methanol gave **26** (48% from **23**). The cytosine nucleoside **31** was prepared according to the procedure of Sung.[13] Treatment of **17** with *o*-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine gave the triazole **30** which upon reaction with aqueous ammonia at room temperature gave **31** (69% yield). Conversion of the 5-iodo nucleoside **23** into the (*E*)-5-(2-bromovinyl) analogue **29** was affected by the method of Herdewijn.[5] Reaction of **23** with methyl acrylate under Heck conditions[14] resulted in isolation of the ester **27** in 45% yield, together with deiodinated product **16** in 37% yield. Hydrolysis of **27** with aqueous sodium hydroxide followed by acidification gave the acid **28** in 80% yield, which on treatment with *N*-bromosuccinimide in DMF gave the 2-bromovinyluracil **29** in 45% yield (Scheme 3).

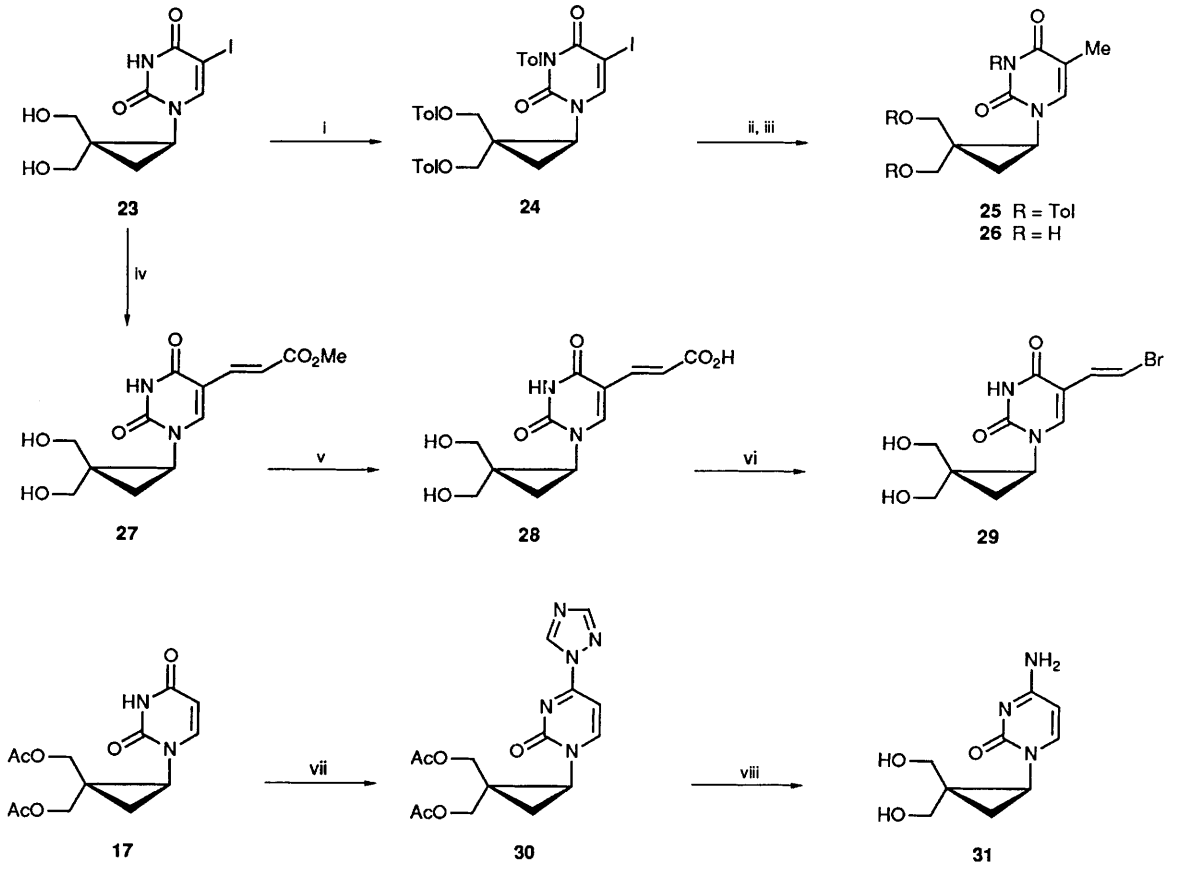
Synthesis of Purine Nucleosides.—Although direct displacement of chloride from 5-amino-4,6-dichloropyrimidine and 2,5-diamino-4,6-dichloropyrimidine with alkylamines did not occur readily,[8] their *N*-formyl derivatives **32**, and **33** were easily substituted with them in the presence of tertiary amines.[15] Accordingly, treatment of the amine **13** with **32** and **33** afforded the coupled compounds **34** and **35** (90% yields), respectively. Closure of the imidazole ring was achieved by reaction of triethyl formate and 12 mol dm^{-3} hydrochloric acid in DMF, affording the 6-chloropurines **36** and **37** (58% yield). Reaction of **36** with ammonia in methanol at 100 °C gave the 6-aminopurine **38** (94% yield). Hydrolysis of **37** with 80% formic acid at 100 °C provided the 6-ketopurine **40** (58% yield). Finally, hydrogenolysis of **38** and **40** using catalytic hydrogen transfer from 95% formic acid afforded the adenine **39** (75% yield) and the guanine **41**[16] (76% yield), respectively.

Biological Data.—The cyclopropylnucleoside analogues **16**, **21**–**23**, **26**, **29**, **31**, **39** and **41** were evaluated for activity against representative RNA and DNA viruses in cell cultures. At concentrations up to 10 μg cm^{-3} (100 μg cm^{-3} against HIV-1), no inhibition of replication was observed against HSV-1, HSV-2, cytomegalovirus cells, and HIV-1. At the concentration examined, none of the compounds was toxic to the cell monolayer.

Experimental

^1H NMR spectra were recorded at 90 MHz with JEOL FX-90A or at 400 MHz with JEOL JNM-GX 400. Chemical shifts (δ) are expressed in ppm from Me_4Si as an internal standard. Coupling constants *J* are in Hz. IR spectra were recorded with JASCO A-202 Infrared Spectrophotometer. TLC was performed on precoated plates of Silica Gel 60 F254 (E. Merck, Darmstadt). Silica gel column chromatography was carried out on Katayama K.K. Silica (60–200 mesh). Reaction progress was monitored by either UV (254 nm) or spraying the plates with a solution of 10% phosphomolybdic acid–ethanol, followed in the latter case by heating on an electric plate. Dichloromethane, 1,4-dioxane, pyridine, *N*,*N*-dimethylformamide and toluene were distilled over calcium hydride. THF and diethyl ether were distilled over sodium benzophenone ketyl prior to use. Reactions were carried out under argon atmosphere unless otherwise stated. During work-up, organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated under reduced pressure.

1,1-*Bis*(*benzyloxymethyl*)*ethylene* **6**.—To a stirred suspension of sodium hydride (60% in mineral oil; 48.4 g, 1.21 mol) in anhydrous THF (400 cm^3) was added benzyl alcohol (143 cm^3, 0.38 mol) dropwise with ice–water cooling. After the evolution of hydrogen gas had ceased, 3-chloro-2-chloromethylpropene (40 cm^3, 0.35 mol) was added slowly to this reaction vessel. The reaction mixture was stirred at room temperature overnight and then refluxed for 5 h. The solution was cooled, and acidified with 2 mol dm^{-3} hydrochloric acid (350 cm^3) and extracted with ethyl acetate (500 cm^3 × 2). The combined extracts were washed and dried. The solvent was removed and the residue was purified by column chromatography (SiO_2 1900 g, hexane–



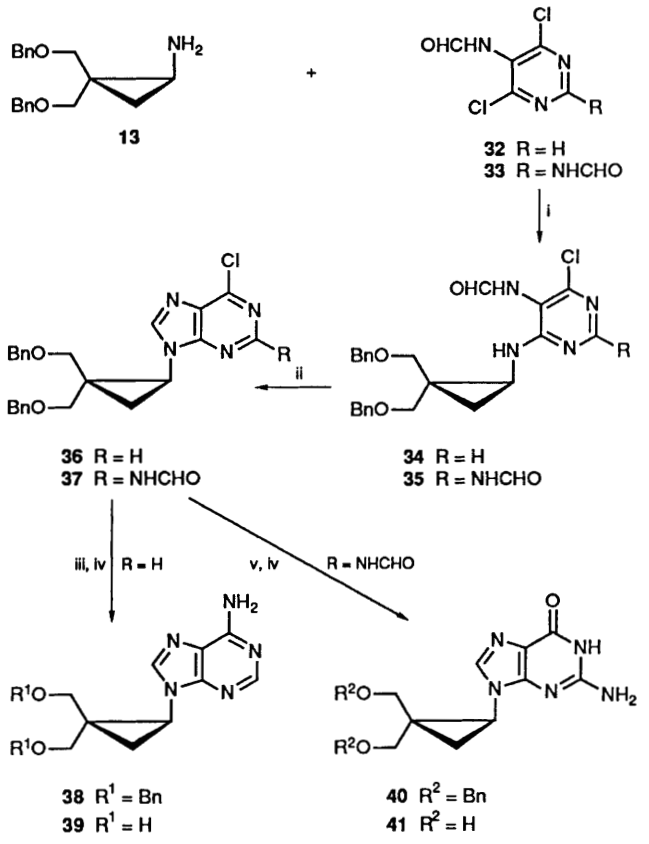
Scheme 3 *Reagents and conditions:* i, toluoyl chloride, py; ii, Me_4Sn, $(Ph_3P)_4Pd$, HMPA, heat; iii, NaOMe, MeOH; methyl acrylate, $Pd(OAc)_2$, Ph_3P, 1,4-dioxane, heat; v, NaOH; vi, NBS, K_2CO_3, DMF; vii, 1,2,4-triazole, *o*-chlorophenyl dichlorophosphate, py; viii, NH_4OH

ethyl acetate, 10:1) to afford the title compound as a colourless oil (91 g, 98%): ν_{max}(film)/cm^{-1} 1660, 1500, 1095 and 740; δ_H(90 MHz, $CDCl_3$) 4.06 (4 H, s, 2 × OCH_2), 4.52 (4 H, s, 2 × PhCH_2), 5.25 (2 H, s, CH_2=) and 7.32 (10 H, s, 2 × Ph).

Ethyl 1,1-*Bis*(*benzyloxymethyl*)*cyclopropane*-2-*carboxylate* **7**.—To a magnetically stirred solution of the olefin **6** (74.9 g, 0.28 mol) containing powdered anhydrous cupric sulfate (1 g) was added ethyl diazoacetate (190 cm^3, 1.81 mol) dropwise at 90 °C over 30 min. Stirring was continued for a further 30 min after the evolution of nitrogen gas had ceased. The solution was cooled to room temperature, and purified by column chromatography (SiO_2 1900 g, hexane–ethyl acetate, 5:1) to give the title compound as a colourless oil (55.6 g, 56.2%) (Found: C, 74.7; H, 7.4. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.39%); ν_{max}(film)/cm^{-1} 1728, 1450, 1300 and 740; δ_H(90 MHz, $CDCl_3$) 1.12 (1 H, dd, *J* 7.9, 4.5, CH_2), 1.23 (3 H, t, *J* 7.0, CH_2CH_3), 1.28 (1 H, dd, *J* 5.7, 4.5, CH_2), 1.77 (1 H, dd, *J* 7.9, 5.7, CH), 3.29 (1 H, d, *J* 9.7, OCH_2), 3.57 (1 H, d, *J* 10.1, OCH_2), 3.73 (1 H, d, *J* 9.7, OCH_2), 3.89 (1 H, d, *J* 10.1, OCH_2), 4.10 (2 H, q, *J* 7.0, CH_2CH_3), 4.43 (2 H, s, PhCH_2), 4.50 (2 H, s, PhCH_2) and 7.30 (10 H, complex, 2 × Ph).

1,1-*Bis*(*benzyloxymethyl*)*cyclopropane*-2-*carboxylic Acid* **8**.—A solution of the ester **7** (28.7 g, 0.081 mol), 20% methanolic KOH solution (330 cm^3) in methanol (150 cm^3) was stirred overnight at room temperature. The solution was diluted with water (500 cm^3), and extracted with ether (200 cm^3). The aqueous solution was then acidified with 2 mol dm^{-3} hydrochloric acid and extracted with ethyl acetate (500 cm^3 × 2). The combined ethyl acetate extracts were washed, dried and evaporated. The residue was purified by column chromatography (SiO_2 1200 g, hexane–ethyl acetate, 1:1) to give the title compound as a colourless oil (22.4 g, 84.7%) (Found: C, 73.8; H, 6.6. $C_{20}H_{22}O_4$ requires C, 73.60; H, 6.79%); ν_{max}(film)/cm^{-1} 3400–2600br, 1730 and 1690; δ_H(400 MHz, $CDCl_3$) 1.19 (1 H, dd, *J* 7.8, 4.4, CH_2), 1.28 (1 H, dd, *J* 5.9, 4.4, CH_2), 1.79 (1 H, dd, *J* 7.8, 5.9, CH), 3.34 (1 H, d, *J* 9.8, OCH_2), 3.59 (1 H, d, *J* 9.8, OCH_2), 3.71 (1 H, d, *J* 9.8, OCH_2), 3.86 (1 H, d, *J* 9.8, OCH_2), 4.43 (2 H, s, PhCH_2), 4.50 (2 H, s, PhCH_2), and 7.24–7.36 (10 H, complex, 2 × Ph).

N-[2,2-*Bis*(*benzyloxymethyl*)*cyclopropyl*]*urea* **11**.—A solution of the acid **8** (12.4 g, 38.1 mmol), triethylamine (6.6 cm^3, 47.6 mmol) and ethyl chloroformate (5.1 cm^3, 53.3 mmol) in acetone (250 cm^3) was stirred at 0 °C for 1 h and then to this solution was added sodium azide (4.0 g, 60.9 mmol) in water (70 cm^3). After 1 h at room temperature, the reaction mixture was diluted with water (200 cm^3) and extracted with ether (250 cm^3 × 2). The organic extracts were washed, dried and evaporated to give the keto azide compound **9** as a yellow oil (12.1 g). A solution of the latter in anhydrous toluene (30 cm^3) was heated at 90–100 °C for 1 h and then evaporated to dryness to give the isocyanate **10** (12.8 g). This was dissolved in ether (150 cm^3). Through this ethereal solution was bubbled ammonia gas for 30 min to give a white precipitate. This was filtered off and washed with cold ether (10 cm^3 × 2) to give the title compound as white crystals (9.95 g, 76.7%): m.p. 126–128 °C (Found: C, 70.8; H, 7.0; N, 8.4. $C_{20}H_{24}N_2O_3$ requires C, 70.56; H, 7.11; N, 8.23%); ν_{max}(Nujol)/cm^{-1} 3445, 3180, 1680, 1620 and 1095; δ_H(90 MHz, $CDCl_3$) 0.83 (1 H, dd, *J* 4.4, 5.3, CH_2), 1.08 (1 H, dd, *J* 5.3, 7.7, CH_2), 2.50 (1 H, dd, *J* 4.4, 7.7, CH), 3.05 (1 H, d, *J* 9.7, OCH_2), 3.42 (1 H, d, *J* 9.7, OCH_2), 3.73 (1 H, d, *J* 9.7, OCH_2), 3.79 (1 H, d, *J* 9.7, OCH_2), 4.48 (4 H, s, 2 × PhCH_2), 4.90 (1 H, br s, D_2O exchangeable, NH), 5.45–



Scheme 4 *Reagents and conditions*: i, diisopropylethylamine, 1,4-dioxane, heat; ii, $HC(OEt)_3$, aq. HCl, heat; iii, NH_3, MeOH, heat; iv, Pd-black, 95% HCO_2H, MeOH; v, 80% HCO_2H, heat

5.60 (2 H, br s, D_2O exchangeable, NH_2) and 7.30 (10 H, s, 2 × Ph).

N-tert-*Butoxycarbonyl*-2,2-*bis*(*benzyloxymethyl*)*cyclopropylamine* **12**.—A solution of the isocyanate (2.0 g) in anhydrous *tert*-butyl alcohol was heated at 90–100 °C for 2 days and then evaporated. The residue was purified by column chromatography (SiO_2 35 g, chloroform–methanol, 35:1) to give the title compound as white crystals (2.2 g, 84.8%), m.p. 61–62 °C (Found: C, 72.3; H, 7.8; N, 3.4. $C_{24}H_{31}NO_4$ requires C, 72.51; H, 7.86; N, 3.52%); ν_{max}(Nujol)/cm^{-1} 3430, 3350, 1705 and 1490; δ_H(90 MHz, $CDCl_3$) 0.71 (1 H, dd, *J* 6.5, 5.6, CH_2), 1.00 (1 H, dd, *J* 7.5, 6.5, CH_2), 1.45 (9 H, s, *tert*-butyl), 2.57 (1 H, m, CH), 3.12 (1 H, d, *J* 10.3, OCH_2), 3.40 (1 H, d, *J* 10.3, OCH_2), 3.80 (1 H, d, *J* 10.3, OCH_2), 3.85 (1 H, d, *J* 10.3, OCH_2), 4.49 (4 H, br s, 2 × PhCH_2) and 7.31 (10 H, complex, 2 × Ph).

2,2-*Bis*(*benzyloxymethyl*)*cyclopropylamine* **13**.—A solution of the N-Boc amine **12** (413 mg) in trifluoroacetic acid (4 cm^3) was stirred for 20 min at room temperature and then evaporated. The residue was basified with 2 mol dm^{-3} sodium hydroxide (10 cm^3) and extracted with ethyl acetate (10 cm^3 × 2). The combined extracts were washed, dried, and evaporated to give the title compound as a colourless oil (310 mg, 100%) (Found: C, 76.9; H, 7.5; N, 4.9. $C_{19}H_{23}NO_2$ requires C, 76.73; H, 7.80; N, 4.71%); ν_{max}(Nujol)/cm^{-1} 3400, 2860 and 1450; δ_H(90 MHz, $CDCl_3$) 0.48 (1 H, dd, *J* 5.3, 4.4, CH_2), 0.74 (1 H, dd, *J* 7.0, 5.3, CH_2), 2.37 (1 H, dd, *J* 7.0, 4.4, CH), 3.14 (1 H, d, *J* 9.7, OCH_2), 3.57 (1 H, d, *J* 9.7, OCH_2), 3.61 (1 H, d, *J* 9.7, OCH_2), 3.85 (1 H, d, *J* 9.7, OCH_2), 4.48 (2 H, s, PhCH_2), 4.52 (2 H, s, PhCH_2) and 7.30 (10 H, complex, 2 × Ph).

1-[2,2-*Bis*(*benzyloxymethyl*)*cyclopropyl*]*uracil* **15**.—To a solution of the urea **11** (840 mg, 2.5 mmol) in methylene dichloride–pyridine (2:1; 18 cm^3) at −30 °C was added β-ethoxyacryloyl chloride (960 mg, 7.1 mmol). The reaction mixture was warmed to room temperature and stirred for 16 h, and then poured onto ice–water and extracted with chloroform (15 cm^3 × 2). The combined extracts were washed, dried and evaporated to give a dark brown oil, which was purified by column chromatography (SiO_2 40 g, toluene–ethanol, 10:1) to afford a yellow oil **14** (1.04 g). This compound was heated in 4% aqueous ammonia (20 cm^3) and ethanol (20 cm^3) at 80–85 °C for 5 h in a sealed tube. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2 50 g, hexane–ethyl acetate, 1:1–1:3) to give the title compound as an oil (365 mg, 37.3%) (Found: C, 70.3; H, 6.0; N, 6.9. $C_{23}H_{24}N_2O_4$ requires C, 70.39; H, 6.16; N, 7.14%); ν_{max}(film)/cm^{-1} 3200, 1710, 1690, 1380 and 1290; δ_H(400 MHz, $CDCl_3$) 1.17 (1 H, dd, *J* 6.7, 4.8, CH_2), 1.34 (1 H, dd, *J* 7.9, 6.7, CH_2), 3.09 (1 H, dd, *J* 7.9, 4.8, CH), 3.41 (1 H, d, *J* 10.1, OCH_2), 3.42 (1 H, d, *J* 9.7, OCH_2), 3.55 (1 H, d, *J* 10.1, OCH_2), 3.73 (1 H, d, *J* 9.7, OCH_2), 4.40 (2 H, br s, PhCH_2), 4.55 (2 H, s, PhCH_2), 5.54 (1 H, d, *J* 8.43, 5-H), 7.27–7.33 (11 H, complex, 2 × Ph, 6-H) and 8.36 (1 H, br s, NH).

1-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]*uracil* **16**.—A solution of the benzyl ether **15** (350 mg) in 95% formic acid–methanol (1:1; 5 cm^3) was hydrogenolized over palladium black (10 mg) at atmospheric pressure for 4 h. The mixture was filtered and the catalyst was washed with methanol (3 cm^3). The combined filtrate and washings were evaporated and the residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 4:1) to give the title compound as white crystals (170 mg, 90%); m.p. 165–167 °C (Found: C, 51.1; H, 5.8; N, 13.1. $C_9H_{12}N_2O_4$ requires C, 50.94; H, 5.70; N, 13.20%); ν_{max}(Nujol)/cm^{-1} 3400, 1695, 1660, 1310, 1290 and 995; δ_H(400 MHz; CD_3OD) 1.11 (1 H, dd, *J* 6.6, 4.6, CH_2), 1.24 (1 H, dd, *J* 7.6, 6.6, CH_2), 3.09 (1 H, dd, *J* 7.6, 4.6, CH), 3.50 (2 H, s, OCH_2), 3.58 (1 H, d, *J* 10.5, OCH_2), 3.73 (1 H, d, *J* 10.5, OCH_2), 5.64 (1 H, d, *J* 8.1, 5-H) and 7.57 (1 H, d, *J* 8.1, 6-H).

1-[2,2-*Bis*(*acetoxymethyl*)*cyclopropyl*]*uracil* **17**.—A solution of the diol **16** (36 mg) in pyridine (1 cm^3) and acetic anhydride (1 cm^3) was stirred at room temperature for 2.5 h and then evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 5:1) to give the title compound as white crystals (49 mg, 96%); m.p. 134–135°C (Found: C, 43.5; H, 6.4; N, 11.1. $C_{13}H_{16}N_2O_6$ requires C, 43.54; H, 6.50; N, 11.29%); ν_{max}(Nujol)/cm^{-1} 3150, 1740, 1660 and 1290; δ_H(400 MHz, $CDCl_3$) 1.21 (1 H, dd, *J* 7.1, 5.1, CH_2), 1.33 (1 H, dd, *J* 7.8, 7.1, CH_2), 2.06 (3 H, s, AcO), 2.14 (3 H, s, AcO), 3.29 (1 H, dd, *J* 5.1, 7.8, CH), 3.91 (1 H, d, *J* 12.2, AcOCH_2), 4.12 (1 H, d, *J* 12.0, AcOCH_2), 4.22 (1 H, d, *J* 12.0, AcOCH_2), 4.24 (1 H, d, *J* 12.2, AcOCH_2), 5.69 (1 H, d, *J* 8.1, 5-H), 7.17 (1 H, d, *J* 8.1, 6-H) and 8.65 (1 H, br s, NH).

1-[2,2-*Bis*(*acetoxymethyl*)*cyclopropyl*]-5-*chlorouracil* **18**.—A mixture of the diacetate **17** (19.9 mg, 0.07 mmol), lithium chloride (3.5 mg, 0.08 mmol) and ceric ammonium nitrate (73.5 mg, 0.13 mmol) in acetonitrile–acetic acid (1:1; 2 cm^3) was heated at 80 °C for 6 h. The mixture was then cooled, poured into a mixture of brine (5 cm^3) and 5% aqueous sodium bisulfite (5 cm^3) and extracted with ethyl acetate (10 cm^3 × 3). The organic solution was washed, dried and evaporated and the residue was purified by column chromatography (SiO_2 3 g, chloroform–methanol, 15:1) to give the title compound as an oil (15.65 mg, 70.6%) (Found: C, 47.5; H, 4.4; N, 8.3. $C_{13}H_{15}ClN_2O_6$ requires C, 47.21; H, 4.57; N, 8.47%); ν_{max}(film)/cm^{-1} 3200, 1740, 1720, 1700, 1630 and 1440; δ_H(400 MHz, $CDCl_3$)

1.24 (1 H, dd, *J* 4.9, 7.3, CH_2), 1.36 (1 H, dd, *J* 7.3, 7.8, CH_2), 2.07 (3 H, s, AcO), 2.14 (3 H, s, AcO), 3.32 (1 H, dd, *J* 4.9, 7.8, CH), 4.95 (1 H, d, *J* 12.0, AcOcH_2), 4.10 (1 H, d, *J* 12.0, AcOCH_2), 4.21 (1 H, d, *J* 5.0, AcOCH_2), 4.24 (1 H, d, *J* 5.0, AcOCH_2), 7.42 (1 H, s, 6-H) and 8.97 (1 H, br s, NH).

1-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]-5-*chlorouracil* **21**.—A solution of the chlorodiacetate **18** (27.0 mg, 0.08 mmol) and sodium methoxide (18 mg, 0.33 mmol) in dry methanol (2 cm^3) was stirred at room temperature for 30 min, after which it was neutralized with 1 mol dm^{-3} hydrochloric acid, and evaporated. The residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 5:1) to give the title compound as a white solid glass (16.6 mg, 81.8%); m.p. 119–120 °C (Found: C, 43.7; H, 4.5; N, 11.2. $C_9H_{11}ClN_2O_4$ requires C, 43.82; H, 4.50; N, 11.36%); ν_{max}(Nujol)/cm^{-1} 3400, 3050, 1690, 1625 and 1435 cm^{-1}; δ_H(400 MHz, CD_3OD) 1.16 (1 H, dd, *J* 4.4, 6.4, CH_2), 1.24 (1 H, dd, *J* 6.4, 7.8, CH_2), 3.11 (1 H, dd, *J* 4.4, 7.8, CH), 3.51–3.57 (3 H, complex, OCH_2, OC*H*H), 3.73 (1 H, d, *J* 11.2, OCH_2) and 7.90 (1 H, s, 6-H).

1-[2,2-*Bis*(*acetoxymethyl*)*cyclopropyl*]-5-*iodouracil* **20**.—A mixture of the diacetate **17** (27.0 mg, 0.09 mmol), lithium iodide (15.2 mg, 0.11 mmol) and ceric ammonium nitrate (100 mg, 0.18 mmol) in acetonitrile (1.5 cm^3) was heated at 80–85 °C for 30 min after which it was cooled and evaporated. The residue was purified by column chromatography (SiO_2 3 g, chloroform–methanol, 8:1) to give the title compound as a light yellow oil (38.1 mg, 99.0%) (Found: C, 36.7; H, 3.9; N, 6.5. $C_{13}H_{15}IN_2O_6$ requires C, 36.98; H, 3.58; N, 6.64%); ν_{max}(film)/cm^{-1} 3500, 3220, 1720, 1690, 1610 and 1420; δ_H(400 MHz, $CDCl_3$) 1.24 (1 H, dd, *J* 4.9, 7.1, CH_2), 1.37 (1 H, dd, *J* 7.1, 7.8, CH_2), 2.07 (3 H, s, AcO), 2.13 (3 H, s, AcO), 3.31 (1 H, dd, *J* 4.9, 7.8, CH), 3.97 (1 H, d, *J* 12.0, AcOCH_2), 4.10 (1 H, d, *J* 12.0, AcOCH_2), 4.20 (1 H, d, *J* 18.3, AcOCH_2), 4.23 (1 H, d, *J* 18.3, AcOCH_2), 7.63 (1 H, s, 6-H) and 8.75 (1 H, s, NH).

1-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]-5-*iodouracil* **23**.—A mixture of the iodo diacetate **20** (550 mg, 1.30 mmol) and sodium methoxide (155 mg, 2.86 mmol) in dry methanol (18 cm^3) was stirred at room temperature for 1.5 h after which it was neutralized with 1 mol dm^{-3} hydrochloric acid and evaporated. The residue was purified by column chromatography (SiO_2 10 g, chloroform–methanol, 5:1) to give the title compound as a white solid glass (387 mg, 88.8%); m.p. 117–119 °C (Found: C, 32.2; H, 3.1; N, 8.0. $C_9H_{11}IN_2O_4$ requires C, 31.97; H, 3.28; N, 8.29%); ν_{max}(Nujol)/cm^{-1} 3400, 3200, 1660, 1600 and 1290 cm^{-1}; δ_H(400 MHz, CD_3OD) 1.14 (1 H, dd, *J* 4.9, 6.4, CH_2), 1.25 (1 H, dd, *J* 6.4, 7.8, CH_2), 3.11 (1 H, dd, *J* 4.9, 7.8, CH), 3.50 (1 H, d, *J* 12.2, OCH_2), 3.54 (1 H, d, *J* 12.2, OCH_2), 3.57 (1 H, d, *J* 11.2, OCH_2), 3.72 (1 H, d, *J* 11.2, OCH_2) and 8.02 (1 H, s, 6-H).

5-*Bromo*-1-[2,2-*bis*(*hydroxymethyl*)*cyclopropyl*]*uracil* **22**.—A mixture of the diol **16** (25.5 mg, 0.12 mmol), lithium bromide (12.5 mg, 0.14 mmol) and ceric ammonium nitrate (132 mg, 0.24 mmol) in acetic acid (3 cm^3) was heated at 75–80 °C for 1.5 h, after which it was cooled and evaporated. The residue was purified by column chromatography (SiO_2 3 g, chloroform–methanol, 4:1) to give the title compound as white crystals (17.7 mg, 50.6%); m.p. 119–121 °C (Found: C, 36.8; H, 3.6; N, 9.7. $C_9H_{11}BrN_2O_4$ requires C, 37.13; H, 3.81; N, 9.62%); ν_{max}(Nujol)/cm^{-1} 3400, 3050, 1685, 1615 and 1285; δ_H(400 MHz, CD_3OD) 1.15–1.25 (2 H, complex, CH_2), 3.11 (1 H, m, CH), 3.51–3.61 (3 H, complex, OCH_2, OC*H*H), 3.72 (1 H, d, *J* 11.2, OCH_2) and 7.98 (1 H, s, 6-H).

1-[2,2-*Bis*(*toluoyloxymethyl*)*cyclopropyl*]-5-*iodo*-3-*toluoyluracil* **24**.—A solution of the iodide **23** (88.3 mg, 0.261 mmol), ethyldiisopropylamine (0.09 cm^3, 0.522 mmol) and *p*-toluoyl chloride (0.21 cm^3, 1.57 mmol) in dry pyridine (3 cm^3) was stirred at room temperature for 3 h, after which it was poured onto ice–water and extracted with chloroform (10 cm^3 × 3). The combined extracts were washed, dried and evaporated and the residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 20:1) to give the title compound as a white solid (138.8 mg, 76.8%); m.p. 227–229 °C (Found: C, 57.5; H, 4.4; N, 3.8. $C_{33}H_{29}IN_2O_7$ requires C, 57.23; H, 4.22; N, 4.05%); ν_{max}(Nujol)/cm^{-1} 1740, 1705, 1660 and 1600; δ_H(400 MHz, $CDCl_3$) 1.44 (1 H, dd, *J* 5.4, 4.9, CH_2), 1.56 (1 H, dd, *J* 5.4, 7.8, CH_2), 2.35 (3 H, s, ArCH_3), 2.37 (3 H, s, ArCH_3), 2.39 (3 H, s, ArCH_3), 3.45 (1 H, dd, *J* 4.9, 7.8, CH), 4.24 (1 H, d, *J* 11.7, OCH_2), 4.41 (1 H, d, *J* 12.2, OCH_2), 4.51 (1 H, d, *J* 11.7, OCH_2), 4.66 (1 H, d, *J* 12.2, OCH_2), 7.11–7.19 (6 H, complex, 3 × Ar), 7.71 (2 H, d, *J* 7.8, Ar), 7.79 (1 H, s, 6-H), 7.82 (2 H, d, *J* 8.3, Ar), and 7.88 (2 H, d, *J* 8.3, Ar).

1-[2,2-*Bis*(*toluoyloxymethyl*)*cyclopropyl*]-3-*toluoylthymine* **25**.—A solution of the iodouracil **24** (84.73 mg, 0.122 mmol), tetramethyltin (0.034 cm^3, 0.245 mmol) and tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol) in hexamethylphosphoric triamide (2.5 cm^3) was stirred at 60 °C for 16 h, after which it was poured into water and extracted with ethyl acetate (20 cm^3 × 3). The combined extracts were washed, dried and evaporated and the residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 25:1) to give the title compound as a white solid (54.3 mg, 76.7%); m.p. 73–79 °C (Found: C, 70.6; H, 5.4; N, 4.8. $C_{34}H_{32}N_2O_7$ requires C, 70.33; H, 5.56; N, 4.83%); ν_{max}(Nujol)/cm^{-1} 1745, 1720, 1665 and 1625; δ_H(400 MHz, $CDCl_3$) 1.43 (1 H, dd, *J* 5.1, 7.0, CH_2), 1.53 (1 H, dd, *J* 7.0, 7.8, CH_2), 1.88 (3 H, d, *J* 1.0, 5-CH_3), 2.34 (3 H, s, ArCH_3), 2.36 (3 H, s, ArCH_3), 2.39 (3 H, s, ArCH_3), 3.39 (1 H, dd, *J* 5.1, 7.8, CH), 4.24 (1 H, d, *J* 12.2, OCH_2), 4.41 (1 H, d, *J* 11.9, OCH_2), 4.53 (1 H, d, *J* 11.9, OCH_2), 4.61 (1 H, d, *J* 12.2, OCH_2), 7.11–7.19 (7 H, complex, 3 × Ar, 6-H), 7.74 (2 H, d, *J* 8.3, Ar), 7.82 (2 H, d, *J* 8.0, Ar) and 7.89 (2 H, d, *J* 8.3, Ar).

1-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]*thymine* **26**.—The toluoylthymine **25** (68.5 mg, 0.118 mmol) was stirred with sodium methoxide (23.5 mg, 0.43 mmol) in methanol (3 cm^3) at room temperature for 2.5 h, after which the solution was acidified with 1 mol dm^{-3} hydrochloric acid and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2 10 g, chloroform–methanol, 4:1) to afford the title compound as a white solid (21.3 mg, 79.8%); m.p. 162–163 °C (Found: C, 52.9; H, 6.1; N, 12.1. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38%); ν_{max}(Nujol)/cm^{-1} 3420, 1690 and 1300; δ_H(400 MHz, CD_3OD) 1.09 (1 H, dd, *J* 4.6, 6.6, CH_2), 1.24 (1 H, dd, *J* 6.6, 7.8, CH_2), 1.86 (3 H, d, *J* 1.0, 5-CH_3), 3.04 (1 H, dd, *J* 4.6, 7.8, CH), 3.46 (1 H, d, *J* 11.7, OCH_2), 3.51 (1 H, d, *J* 11.7, OCH_2), 3.57 (1 H, d, *J* 11.2, OCH_2), 3.74 (1 H, d, *J* 11.2, OCH_2) and 7.41 (1 H, q, *J* 1.0, 6-H).

(E)-5-1-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*] [2-(*Methoxycarbonyl*)*vinyl*]*uracil* **27**.—Triphenylphosphine (33.8 mg, 0.13 mmol), palladium(II) acetate (9.6 mg, 0.043 mmol), and triethylamine (0.06 cm^3, 0.43 mmol) were combined in dry 1,4-dioxane (3.6 cm^3) and the mixture was stirred and heated at 70 °C for 5 min. To this violet coloured solution were added, in turn, the iodouracil **23** (104 mg, 0.305 mmol) in dry 1,4-dioxane (12 cm^3) and methyl acrylate (0.28 cm^3, 3.1 mmol); the temperature was then increased to reflux for 1 h. While still hot, the solution was decanted from the brown–black residue and the supernatant cooled. Solvent was removed under reduced pressure to give a brown gum which was dissolved with methanol (5 cm^3). The solution was cooled to give a brown powder precipitate. This precipitate was dissolved with 1,4-

dioxane–water (15:1; 50 cm^3) by heating. Whilst still hot, the solution was filtered and the filtrate was concentrated under reduced pressure to give a pale yellow powder (44.8 mg). This was recrystallized from chloroform to give the title compound as a white powder (41.0 mg, 45.1%); m.p. 243–245 °C (decomp.) (Found: C, 52.6; H, 5.6; N, 9.2. $C_{13}H_{16}N_2O_6$ requires C, 52.70; H, 5.44; N, 9.46%); ν_{max}(Nujol)/cm^{-1} 3480, 1690, 1620 and 1165; δ_H(400 MHz, [$^2H_6$]-DMSO) 1.08 (1 H, dd, *J* 6.3, 7.8, CH_2), 1.23 (1 H, dd, *J* 4.6, 6.3, CH_2), 3.11 (1 H, dd, *J* 4.6, 7.8, CH), 3.35 (2 H, complex, OCH_2), 3.62 (2 H, complex, OCH_2), 3.67 (3 H, s, CO_2CH_3), 4.42 (1 H, t, *J* 5.6, OH), 4.53 (1 H, t, *J* 5.5, OH), 6.87 (1 H, d, *J* 15.9, CH=), 7.39 (1 H, d, *J* 15.9, CH=) and 8.18 (1 H, s, 6-H). The combined mother liquors were concentrated, and the residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 4:1) to give compound **16** (24.2 mg, 37.3%).

(E)-1-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]-5-(2-*carboxyvinyl*)*uracil* **28**.—A solution of the methyl ester **27** (41.1 mg, 0.14 mmol) in 1 mol dm^{-3} aqueous sodium hydroxide (1.7 cm^3) was stirred at room temperature for 1.5 h, after which it was cooled in an ice-bath and acidified to pH 2 with 6 mol dm^{-3} hydrochloric acid. With time, precipitation occurred and the precipitate was filtered off to give the title compound (31.7 mg, 80.3%); m.p. 219–221 °C (Found: C, 53.2; H, 4.7; N, 9.4. $C_{12}H_{14}N_2O_6$ requires C, 53.06; H, 4.80; N, 9.52%); ν_{max}(Nujol)/cm^{-1} 3450, 1730, 1690, 1665, 1600 and 1315; δ_H(400 MHz, [^{2}H]-DMSO) 1.09 (1 H, dd, *J* 6.3, 7.8, CH_2), 1.22 (1 H, dd, *J* 4.6, 6.3, CH_2), 3.10 (1 H, dd, *J* 4.6, 7.8, CH), 3.2–3.5 (3 H, complex, OCH_2, OC*H*H), 3.62 (1 H, br d, *J* 11.0, OCH_2), 4.42 (1 H, br s, D_2O exchangeable, OH), 4.54 (1 H, br s, D_2O exchangeable, OH), 6.78 (1 H, d, *J* 15.9, CH=), 7.31 (1 H, d, *J* 15.9, CH=) and 8.12 (1 H, s, 6-H).

(E)-1-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]-5-(2-*bromovinyl*)*uracil* **29**.—The acid **28** (39 mg, 0.14 mmol) was dissolved with dry DMF (1 cm^3) and potassium carbonate (42 mg, 0.3 mmol) was added. The mixture was stirred at room temperature for 15 min. *N*-Bromosuccinimide (25.2 mg, 0.14 mmol) in dry DMF (0.8 cm^3) was then added dropwise over 10 min. After a further 30 min the DMF solution was evaporated under high vacuum, and the residue was triturated with chloroform–methanol (2:1; 50 cm^3). The suspension was filtered and the filtrate was evaporated to give the solid, which was purified by column chromatography (SiO_2 2.0 g, chloroform–methanol, 2:1) to give the title compound as a white glass solid (19.5 mg, 44.6%); m.p. 71–74 °C (Found: C, 41.5; H, 4.3; N, 8.7. $C_{11}H_{13}BrN_2O_4$ requires C, 41.66; H, 4.13; N, 8.83%); ν_{max}(Nujol)/cm^{-1} 3450, 1670, 1450 and 1310; δ_H(400 MHz, CD_3OD) 1.17 (1 H, dd, *J* 4.4, 6.8, CH_2), 1.25 (1 H, dd, *J* 6.8, 7.8, CH_2), 3.11 (1 H, dd, *J* 4.4, 7.8, CH), 3.49 (2 H, complex, OCH_2), 3.58 (1 H, d, *J* 11.2, OCH_2), 3.74 (1 H, d, *J* 11.2, OCH_2), 6.79 (1 H, d, *J* 13.7, CH=), 7.33 (1 H, d, *J* 13.7, CH=) and 7.68 (1 H, s, 6-H).

1-[2,2-*Bis*(*acetoxymethyl*)*cyclopropyl*]-4-(1,2,4-*triazol*-1-*yl*)-*pyrimidin*-2(1H)-*one* **30**.—To a stirred solution of the diacetate **17** (89.1 mg, 0.3 mmol) in pyridine (3 cm^3) was added 1,2,4-triazole (115 mg, 1.66 mmol) and *o*-chlorophenyl phosphorodichloridate (0.13 cm^3, 0.813 mmol). The mixture was stirred at room temperature for 72 h and then evaporated under reduced pressure. The residue was dissolved in dichloromethane (30 cm^3) and the solution was washed successively with saturated aqueous sodium hydrogencarbonate and water, dried and evaporated. The residue was purified by column chromatography (SiO_2 5 g, ethyl acetate) to give the title compound as a white solid (93.2 mg, 89.1%); m.p. 183–184 °C (Found: C, 51.6; H, 5.0; N, 19.9. $C_{15}H_{17}N_5O_5$ requires C, 51.87; H, 4.93; N, 20.17%); ν_{max}(Nujol)/cm^{-1} 3150, 1740, 1725, 1675, 1620 and 1545; δ_H(400 MHz, $CDCl_3$) 1.35 (1 H, dd, *J* 3.2, 5.4, CH_2), 1.45 (1 H, dd, *J* 3.2, 7.4, CH_2), 2.04 (3 H, s, AcO), 2.19 (3 H, s, AcO), 3.62 (1 H, dd, *J* 5.4, 7.4, CH), 3.86 (1 H, d, *J* 12.2, AcOCH_2), 4.18 (1 H, d, *J* 11.7, AcOCH_2), 4.21 (1 H, d, *J* 12.2, AcOCH_2), 4.37 (1 H, d, *J* 11.7, AcOCH_2), 7.03 (1 H, d, *J* 7.1, 5-H), 7.81 (1 H, d, *J* 7.1, 6-H), 8.13 (1 H, s, 3′-H) and 9.26 (1 H, s, 5′-H).

4-*Amino*-1-[2,2-*bis*(*hydroxymethyl*)*cyclopropyl*]*pyrimidin*-2(1H)-*one* **31**.—The triazole **30** (81.3 mg, 0.234 mmol) was stirred in 35% aqueous ammonia (4 cm^3) at room temperature for 22 h, after which the solution was evaporated under reduced pressure to leave an off-white solid. This residue was stirred with hot methanol (1 cm^3) for 20 min and cooled to room temperature. The product was collected and dried *in vacuo* at room temperature to give the title compound as a white solid (38.6 mg, 78.1%); m.p. 225–227 °C (Found: C, 51.0; H, 6.2; N, 19.7. $C_9H_{13}N_3O_3$ requires C, 51.17; H, 6.20; N, 19.90%); ν_{max}(Nujol)/cm^{-1} 3360, 3200, 1665, 1610 and 1310; δ_H(400 MHz, CD_3OD) 1.04 (1 H, dd, *J* 4.9, 6.3, CH_2), 1.26 (1 H, dd, *J* 6.3, 7.8, CH_2), 3.09 (1 H, dd, *J* 4.9, 7.8, CH), 3.31 (1 H, d, *J* 11.7, OCH_2), 3.48 (1 H, d, *J* 11.7, OCH_2), 3.55 (1 H, d, *J* 11.2, OCH_2), 3.83 (1 H, d, *J* 11.2, OCH_2), 5.88 (1 H, d, *J* 7.3, 5-H) and 7.58 (1 H, *J* 7.3, 6-H).

6-{[2,2-*Bis*(*benzyloxymethyl*)*cyclopropyl*]*amino*}-4-*chloro*-5-*formamidopyrimidine* **34**.—A solution of the cyclopropylamine **13** (180.16 mg, 0.61 mmol), 4,6-dichloro-5-formamidopyrimidine (133 mg, 0.69 mmol), and triethylamine (1.4 cm^3, 10.0 mmol) in 1,4-dioxane (10 cm^3) was stirred under reflux for 16 h. The solution was then cooled and evaporated. The residue was purified by column chromatography (SiO_2 30 g, chloroform–ethanol, 50:1) to give the title compound as a colourless oil (248.54 mg, 90.2%) (Found: C, 63.3; H, 5.7; N, 12.2. $C_{24}H_{25}ClN_4O_3$ requires C, 63.64; H, 5.56; N, 12.37%); ν_{max}(film)/cm^{-1} 3250, 1695, 1570 and 1500; δ_H(90 MHz, $CDCl_3$) 0.84 (1 H, m, CH_2), 1.20 (1 H, m, CH_2), 2.98 (1 H, m, CH), 3.23 (1 H, d, *J* 10.1, OCH_2), 3.47 (1 H, d, *J* 10.1, OCH_2), 3.75 (1 H, d, *J* 10.1, OCH_2), 4.02 (1 H, d, *J* 10.1, OCH_2), 4.47 (2 H, s, PhCH_2), 4.53 (2 H, s, PhCH_2), 6.02 (1 H, br s, NH), 7.31 (10 H, complex, 2 × Ph), 7.94 (1 H, d, *J* 1.3, CHO) and 8.29 (1 H, s, 2-H).

9-[2,2-*Bis*(*benzyloxymethyl*)*cyclopropyl*]-6-*chloropurine* **36**.—A mixture of the monoformamide **34** (147.26 mg, 0.33 mmol), triethyl orthoformate (7 cm^3), 12 mol dm^{-3} hydrochloric acid (0.2 cm^3), and DMF (3.2 cm^3) was stirred at room temperature for 3 days. The solution was poured into water (10 cm^3) and extracted with chloroform (20 cm^3 × 2). The combined extracts were washed, dried and evaporated, and the residue was purified by column chromatography (SiO_2 15 g, chloroform–methanol, 30:1) to give the title compound as an oil (81.6 mg, 57.7%) together with starting material (32.0 mg, 21.7%) (Found: C, 66.5; H, 5.1; N, 12.7. $C_{24}H_{23}ClN_4O_2$ requires C, 66.28; H, 5.33; N, 12.88%); ν_{max}(film)/cm^{-1} 1590 and 1555; δ_H(90 MHz, $CDCl_3$) 1.59 (2 H, d, *J* 6.1, CH_2), 3.04 (1 H, d, *J* 10.1, OCH_2), 3.52 (1 H, t, *J* 6.1, CH), 3.53 (1 H, d, *J* 9.7, OCH_2), 3.63 (1 H, d, *J* 10.1, OCH_2), 3.90 (1 H, d, *J* 9.7, OCH_2), 4.25 (2 H, s, PhCH_2), 4.60 (2 H, s, PhCH_2), 7.01–7.44 (10 H, complex, 2 × Ph), 8.25 (1 H, s, 8-H) and 8.72 (1 H, s, 2-H).

9-[2,2-*Bis*(*benzyloxymethyl*)*cyclopropyl*]*adenine* **38**.—A solution of the chloride **36** (89.1 mg, 0.21 mmol) and liquid ammonia (5 cm^3) in methanol (6 cm^3) was heated in a sealed tube at 100 °C for 8 h. The solution was cooled and evaporated, and the residue was purified by column chromatography (SiO_2 10 g, chloroform–methanol, 15:1) to give the title compound as a white solid (8.28 mg, 94.3%); m.p. 197–200 °C (Found: C, 69.1;

H, 6.0; N, 17.0. $C_{24}H_{25}N_5O_2$ requires C, 69.38; H, 6.07; N, 16.86%); ν_{max}(Nujol)/cm^{-1} 3300, 1670 and 1590; δ_H(400 MHz, [$^2H_6$]-DMSO) 1.32 (1 H, dd, *J* 1.2, 6.8, CH_2), 1.72 (1 H, dd, *J* 1.2, 4.8, CH_2), 3.16 (1 H, d, *J* 10.2, OCH_2), 3.31 (1 H, d, *J* 10.2, OCH_2), 3.48 (1 H, d, *J* 9.8, OCH_2), 3.58 (1 H, dd, *J* 4.8, 6.8, CH), 3.74 (1 H, d, *J* 9.8, OCH_2), 4.14 (1 H, d, *J* 12.2, PhC*H*$_2$), 4.20 (1 H, d, *J* 12.2, PhC*H*$_2$), 4.57 (1 H, d, *J* 11.7, PhC*H*$_2$), 4.65 (1 H, d, *J* 11.7, PhC*H*$_2$), 6.97–7.37 (12 H, complex, 2 × Ph, NH_2), 8.06 (1 H, s, 8-H) and 8.12 (1 H, s, 2-H).

9-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]*adenine* **39**.—The benzyl ether **38** (10 mg, 0.024 mmol) in 95% formic acid–methanol (1:1; 1 cm^3) was hydrogenolized over palladium-black (4 mg) under atmospheric pressure at room temperature for 8 h. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by column chromatography (SiO_2 3 g, chloroform–methanol, 4:1) to give the title compound as a white solid (4.0 mg, 75.0%); m.p. 228–231 °C (Found: C, 51.3; H, 5.4; N, 29.9. $C_{10}H_{13}N_5O_2$ requires C, 51.05; H, 5.57; N, 29.77%); ν_{max}(Nujol)/cm^{-1} 3400, 1670, 1610 and 1580; δ_H(400 MHz, [$^2H_6$]-DMSO) 1.27 (1 H, m, CH_2), 1.33 (1 H, m, CH_2), 3.08 (1 H, d, *J* 11.5, OCH_2), 3.30 (1 H, d, *J* 11.5, OCH_2), 3.30–3.40 (1 H, m, CH), 3.47 (1 H, d, *J* 11.0, OCH_2), 3.75 (1 H, d, *J* 11.0, OCH_2), 4.65 (1 H, br s, D_2O exchangeable, OH), 4.77 (1 H, br s, D_2O exchangeable, OH), 7.24 (2 H, br s, D_2O exchangeable, NH_2), 8.08 (1 H, s, 8-H) and 8.13 (1 H, s, 2-H).

6-{[2,2-*Bis*(*benzyloxymethyl*)*cyclopropyl*]*amino*}-4-*chloro*-2,5-*diformamidopyrimidine* **35**.—A solution of the cyclopropylamine **13** (24.0 mg, 0.08 mmol), 4,6-dichloro-2,5-diformamidopyrimidine (20.8 mg, 0.088 mmol) and diisopropylethylamine (0.06 cm^3, 0.322 mmol) in dry 1,4-dioxane (4 cm^3) was stirred at room temperature for 7 h, and then at 70 °C for 2 h. The solution was cooled and concentrated and the residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 20:1) to give the title compound as a white solid (36.0 mg, 90.7%); m.p. 124–125 °C (Found: C, 60.7; H, 5.2; N, 13.9. $C_{25}H_{26}ClN_5O_4$ requires C, 60.54; H, 5.28; N, 14.12%); ν_{max}(Nujol)/cm^{-1} 3260, 2880, 1695, 1590, 1520 and 1480; δ_H(400 MHz, $CDCl_3$) 0.84 (1 H, br s, CH_2), 1.12 (1 H, m, CH_2), 2.89 (1 H, br s, CH), 3.23 (1 H, d, *J* 10.1, OCH_2), 3.49 (1 H, d, *J* 10.1, OCH_2), 3.68 (1 H, d, *J* 9.8, OCH_2), 3.96 (1 H, d, *J* 9.8, OCH_2), 4.43–4.53 (4 H, complex, 2 × PhC*H*$_2$), 6.21 (1 H, br s, N*H*CHO), 6.53 (1 H, br s, N*H*CHO), 7.20–7.38 (10 H, complex, 2 × Ph), 7.74 (1 H, br d, *J* 9.8, NHC*H*O), 7.92 (1 H, br s, NH) and 9.38 (1 H, d, *J* 9.8, NHC*H*O).

9-[2,2-*Bis*(*benzyloxymethyl*)*cyclopropyl*]*guanine* **40**.—A mixture of the diformamido compound **35** (114.3 mg, 0.23 mmol), triethyl orthoformate (6 cm^3), 12 mol dm^{-3} hydrochloric acid (0.2 cm^3) in DMF (1 cm^3) was stirred at 40 °C for 3 days. The solution was diluted with water (20 cm^3) and extracted with chloroform (15 cm^3 × 2). The combined extracts were washed, dried and evaporated, and the residue was purified by column chromatography (SiO_2 8 g, chloroform–methanol, 10:1) to give the crude product **37** (84.64 mg) and starting material (23.42 mg). A solution of the crude product in 80% formic acid (3 cm^3) was stirred at 100 °C for 2.5 h and then cooled and evaporated. The residue was purified by column chromatography (SiO_2 5 g, chloroform–methanol, 5:1) to give the title compound as a white solid (57.2 mg, 57.6%); m.p. 235–238 °C (decomp.) (Found: C, 66.7; H, 6.0; N, 16.2. $C_{24}H_{25}N_5O_3$ requires C, 66.80; H, 5.84; N, 16.23%); ν_{max}(Nujol)/cm^{-1} 3340, 3160, 1690, 1650, 1605, 1570 and 1540; δ_H(400 MHz, [$^2H_6$]-DMSO) 1.25 (1 H, dd, *J* 6.3, 7.8, CH_2), 1.59 (1 H, dd, *J* 4.6, 6.3, CH_2), 3.10 (1 H, d, *J* 10.2, OCH_2), 3.32 (1 H, d, *J* 9.8, OCH_2), 3.40 (1 H, dd, *J* 4.6, 7.8, CH), 3.47 (1 H, d, *J* 10.2, OCH_2), 3.79 (1 H, d, *J* 9.8, OCH_2), 4.17 (1 H, d, *J* 12.2, PhC*H*$_2$), 4.24 (1 H, d, *J* 12.2, PhC*H*$_2$), 4.53 (1 H, d, *J* 12.2, PhC*H*$_2$), 4.57 (1 H, d, *J* 12.2, PhC*H*$_2$), 6.39 (2 H, br s, D_2O exchangeable, NH_2), 7.06–7.35 (10 H, complex, 2 × Ph) and 7.63 (1 H, s, 8-H).

9-[2,2-*Bis*(*hydroxymethyl*)*cyclopropyl*]*guanine* **41**.—A solution of the benzyl ether **40** (75.4 mg, 0.175 mmol) in 95% formic acid–methanol (1:1, 8 cm^3) was hydrogenolized over palladium-black (103 mg) under atmospheric pressure for 5 h. The mixture was filtered and the catalyst was washed with methanol (3 cm^3); the combined filtrate and washings were evaporated and the residue was recrystallized from water to give the title compound as white crystals (33.4 mg, 75.9%); m.p. 278–280 °C (decomp.) (Found: C, 48.0; H, 5.1; N, 28.0. $C_{10}H_{13}N_5O_3$ requires C, 47.80; H, 5.22; N, 27.88%); ν_{max}(Nujol)/cm^{-1} 3340, 3200, 1635, 1610 and 1540; δ_H(400 MHz, [$^2H_6$]-DMSO) 1.19 (1 H, dd, *J* 6.0, 6.1, CH_2), 1.21 (1 H, dd, *J* 6.0, 6.3, CH_2), 3.05 (1 H, dd, *J* 3.9, 11.7, OCH_2), 3.20 (1 H, dd, *J* 6.1, 6.3, CH), 3.30–3.43 (2 H, complex, OCH_2), 3.76 (1 H, dd, *J* 5.9, 11.2, OCH_2), 4.48 (1 H, dd, *J* 3.9, 5.9, D_2O exchangeable, OH), 4.61 (1 H, dd, *J* 3.9, 5.9, D_2O exchangeable, OH), 6.49 (2 H, br s, D_2O exchangeable, NH_2) and 7.63 (1 H, s, 8-H).

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