Pyrrolidine Analogues of 2′,3′-Dideoxynucleosides: Synthesis *via* 9-Aminopurines and 1-Aminopyrimidines

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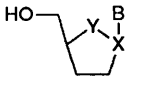
Analogues of 2′,3′-dideoxynucleosides in which the tetrahydrofuran ring is replaced by a pyrrolidine ring linked to the base through an N–N bond have been prepared. The adenine **26**, guanine **25** and hypoxanthine **27** compounds were synthesised *via* 9-aminopurines. Corresponding derivatives of 5-iodouracil **31**, 5-chlorouracil **33** and 5-chlorocytosine **35** were prepared by substitution at the 5-position of hydroxy protected uracil derivatives. Enantiomers, **40a** and **40b**, of the pyrrolidine analogue of dideoxycytidine were prepared from 1-aminocytosine. The novel *N*-aminobases 9-aminoadenine **10**, 1-aminocytosine **13** and 1-aminothymine **15** are described.

The antiviral activity of 2′,3′-dideoxynucleosides (such as 2′,3′-dideoxycytidine **1**)[1,2] against HIV (human immunodeficiency virus), the causative agent of AIDS, has lead to a burgeoning of interest in novel nucleoside analogues with alternative 5-membered ring systems in place of the 2,5-substituted tetrahydrofuran.[3–8] We recently described the synthesis and antiviral activity of compounds **2**–**4**, pyrrolidinyl analogues of the pyrimidine dideoxynucleosides.[9] These compounds are



1; X = CH, Y = O, B = cytosine
2; X = N, Y = CH_2, B = cytosine
3; X = N, Y = CH_2, B = uracil
4; X = N, Y = CH_2, B = thymine

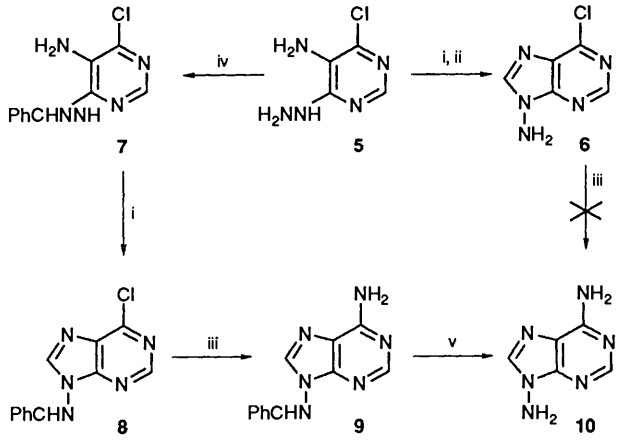
unique in that the 1′-carbon is exchanged for a nitrogen atom, the glycosidic linkage being replaced by an N–N bond. We have previously shown that for acyclonucleosides, antiviral activity against the herpes family is frequently retained or enhanced by substitution of a heteroatom (oxygen[10–13] or nitrogen[14]) at the position adjacent to the guanine base. The pyrimidine nucleoside analogues were prepared by construction of the pyrimidine base on a 1-aminopyrrolidine. Here we describe the synthesis of pyrrolidinyl analogues of purine nucleosides and of 5-substituted pyrimidines using a novel synthetic procedure in which the pyrrolidine ring is constructed on a 1-aminopyrimidine or a 9-aminopurine. This route has also been modified to prepare enantiomers of one pyrrolidinyl nucleoside analogue.

Both the purines and 5-substituted pyrimidines in the 2′,3′-dideoxynucleoside series are of interest for their anti-HIV activity. 2′,3′-Dideoxyinosine appears to show the most clinical promise in terms of its activity and side-effect profile.[15] This compound, however, is converted intracellularly into the triphosphate of 2′,3′-dideoxyadenosine.[16] In the 5-substituted pyrimidine series, large substituents tend to diminish activity, but 5-chloro compounds are of interest because of their improved selectivity index *in vitro*.[17–19]

Surprisingly, although 1-aminouracil[20] and 9-aminohypoxanthine[21] have been known for many years, none of the corresponding amino derivatives of the DNA bases have been reported previously, with the exception of our recent description of 9-aminoguanine.[14]

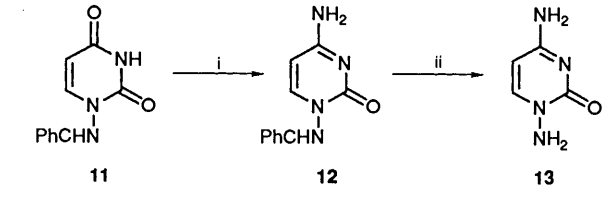
Results and Discussion

Synthesis of 9-Aminopurines and 1-Aminopyrimidines.—Heating of the hydrazinopyrimidine **5**[21] in diethoxymethyl acetate followed by hydrolysis of the intermediate with 50% acetic acid at room temperature afforded 9-amino-6-chloropurine **6** in 29% yield. However, attempted displacement of the 6-chloro substituent with ethanolic ammonia gave rise to a number of products, none of which corresponded to 9-aminoadenine. In order to protect the hydrazino-NH_2 group, **5** was converted into its benzylidene derivative **7** in 93% yield, using a modification of a literature procedure.[21] Heating of **7** in diethoxymethyl acetate afforded the purine **8** in 75% yield, which was successfully treated with ammonia to give the adenine derivative **9** in 93% yield. The benzylidene group was removed from **9** with methylhydrazine in refluxing chloroform–methanol to give 9-aminoadenine **10** in 91% yield. Although compound **9** has been obtained in 4.6% yield by amination of adenine followed by treatment with benzaldehyde prior to isolation,[22] the present route provides a practical synthesis of **9** and a very high yielding route to 9-aminoadenine.



Scheme 1 *Reagents and conditions:* i, $MeCO_2CH(OEt)_2$, heat; ii, 50% AcOH; iii, NH_3–EtOH, heat; iv, PhCHO–AcOH–EtOH, heat; v, $MeNHNH_2$–MeOH–$CHCl_3$, heat

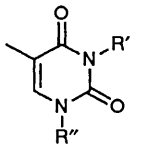
The benzylidene derivative of 1-aminouracil **11**[20] was converted into the corresponding cytosine derivative **12** in 25% yield by reaction with chlorophenyl phosphorodichloridate–triazole followed by ammonia. The benzylidene group was



Scheme 2 *Reagents and conditions:* i, $ClC_6H_4OPOCl_2$–1,2,4-triazole–C_5H_5N, then NH_3–MeOH; ii, $MeNHNH_2$–MeOH–$CHCl_3$, heat

again removed with methylhydrazine and 1-aminocytosine **13** was obtained in 70% yield.

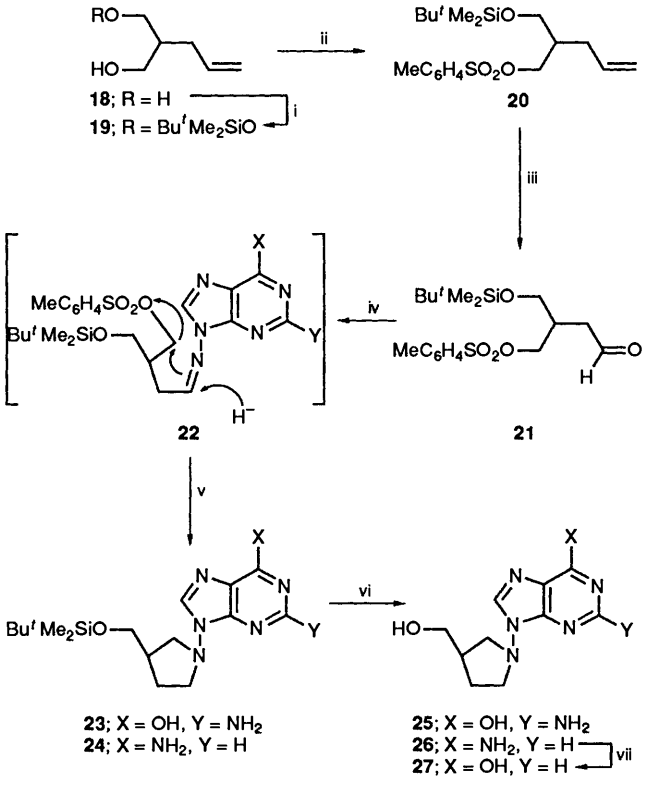
An attempt to prepare 1-aminothymine **15** *via* condensation of benzaldehyde semicarbazone with ethyl diethoxy-2-methylpropionate in an analogous manner to the literature preparation of **11**[20] was not successful. Compound **15** was



14; R′ = R″ = H
15; R′ = H, R″ = NH_2
16; R′ = NH_2, R″ = H
17; R′ = R″ = NH_2

prepared by the direct amination of thymine **14** with hydroxylamine *O*-sulphonic acid; the reaction was, as expected, non-selective and 3-aminothymine **16** and the 1,3-diamino compound **17** were also obtained.

Purine Pyrrolidinyl Nucleosides.—The diol **18** was monoprotected by reaction with sodium hydride followed by *tert*-butyldimethylsilyl chloride to give **19** in 86% yield. Tosylation of **19** with toluene-*p*-sulphonyl chloride and pyridine (2 equiv.) in dichloromethane[23] afforded **20** in 84% yield. Compound **20**



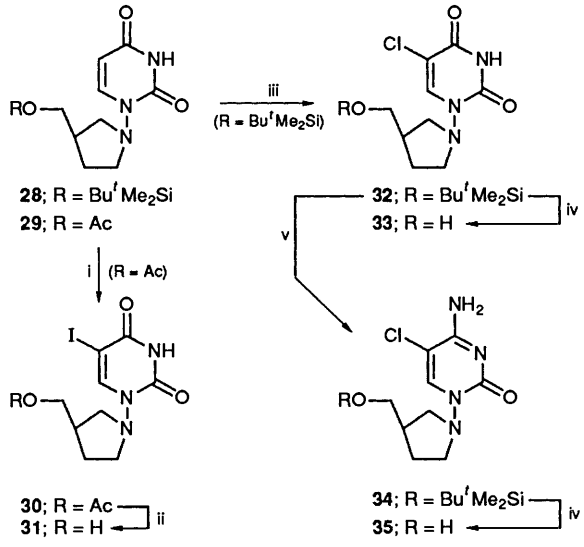
23; X = OH, Y = NH_2
24; X = NH_2, Y = H

25; X = OH, Y = NH_2
26; X = NH_2, Y = H
27; X = OH, Y = H

Scheme 3 *Reagents and conditions:* i, NaH–Bu^tMe_2SiCl–THF; ii, $MeC_6H_4SO_2Cl$–C_5H_5N–CH_2Cl_2; iii, O_3–MeOH–$CHCl_3$, −78 °C then $(MeO)_3P$; iv, 9-aminoguanine–AcOH–DMSO, heat or 9-aminoadenine–AcOH–DMF, heat; v, $NaBH_4$–EtOH; vi, 80% AcOH, heat; vii, $NaNO_2$–HCl_{aq}, heat

was converted into the aldehyde **21** by ozonolysis only when required for subsequent condensation, **21** being determined by the characteristic aldehyde signal in the ^1H NMR spectrum. The aldehyde was condensed with 9-aminoguanine or 9-aminoadenine to afford the respective intermediate imines **22** which were treated with sodium borohydride *in situ*, resulting in reduction and cyclisation to the pyrrolidine ring. From 9-aminoguanine, **23** was obtained in 6% yield, the poor yield probably being due to the very low solubility of 9-aminoguanine. Compound **23** was deprotected with 80% acetic acid at 70 °C to afford the 2′,3′-dideoxyguanosine analogue **25** in 58% yield. The dideoxyadenosine analogue **26** was prepared similarly except that the intermediate **24** was not purified and **26** was obtained in 23% overall yield from 9-aminoadenine. Hydrolytic deamination of **26** with nitrous acid afforded the dideoxyinosine analogue **27** in 53% yield.

5-Substituted Pyrimidine Pyrrolidinyl Nucleosides.—The preparation of **28** and **29** from 1-aminopyrrolidine has already been reported.[9] However, **28** can also be prepared by the route



28; R = Bu^tMe_2Si
29; R = Ac

30; R = Ac
31; R = H

32; R = Bu^tMe_2Si
33; R = H

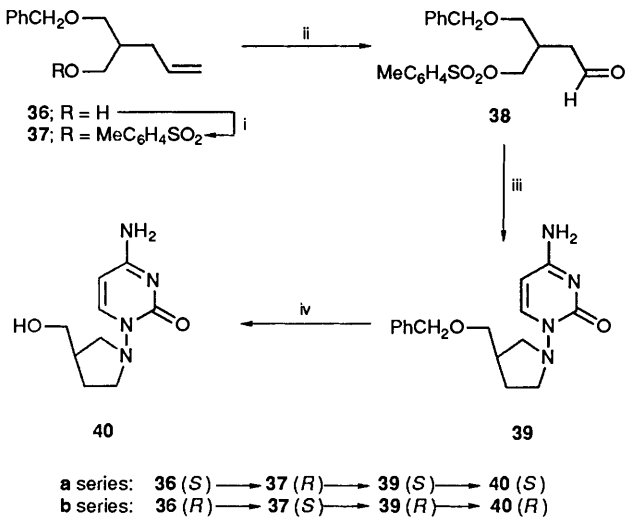
34; R = Bu^tMe_2Si
35; R = H

Scheme 4 *Reagents and conditions:* i, I_2–$Ce(NH_4)_2(NO_3)_6$– MeCN, heat; ii, NH_3–MeOH; iii, *N*-chlorosuccinimide–Ac_2O–AcOH, heat; iv, 80% AcOH, heat; v, $ClC_6H_4OPOCl_2$–1,2,4-triazole–C_5H_5N, then NH_3–MeOH

described above, using 1-aminouracil in place of the 9-aminopurines. Iodination of **29** with iodine in the presence of ceric ammonium nitrate afforded the 5-iodo compound **30** in 28% yield and subsequent deprotection with methanolic ammonia gave the 5-iodouracil derivative **31** in 63% yield. Chlorination of **28** with *N*-chlorosuccinimide in acetic acid afforded the 5-chloro compound **32** in 46% yield. Conversion of **32** into the corresponding cytosine was carried out by the triazolide procedure. Conversion of **32** into the intermediate triazolide was extremely slow even in the presence of a large excess of 1,2,4-triazole, but after 4 days a 42% yield of **34** was obtained (59% on recovered starting material). Deprotection of **32** and **34** with 80% acetic acid at 70 °C afforded the 5-chlorouracil **33** and the 5-chlorocytosine **35** in yields of 80 and 67% respectively.

Enantiomers of 1-[3-(*Hydroxymethyl*)*pyrrolidin*-1-*yl*]*cytosine.*—The enantiomers **36a** and **36b** were prepared by the literature method.[24] Tosylation of **36a** afforded **37a** in 82% yield. Ozonolysis of **37a** gave the aldehyde **38a** which was not purified but treated directly with 1-aminocytosine **13**, the resulting imine being directly reduced with cyclisation to give the pyrrolidine **39a** in 34% yield. Deprotection of **39a** by catalytic hydrogenolysis afforded a 77% yield of the *S* enantiomer **40a** of the pyrrolidinyl dideoxycytidine analogue. The *R* enantiomer **40b** was prepared similarly. The optical rotations of compounds **37**–**40** were very small, and not a useful guide to purity. The enantiomeric purity of compounds **40a** and **40b** was assayed by analytical HPLC on an α-glycoprotein column; it was found that **40a** contained 7% of the *R* enantiomer and **40b** contained 2% of the *S* enantiomer.

The 2′,3′-dideoxyadenosine analogue **26** was assessed as a



Scheme 5 *Reagents and conditions:* i, $MeC_6H_4SO_2Cl$–C_5H_5N–CH_2Cl_2; ii, O_3–MeOH–$CHCl_3$, −78 °C then $(MeO)_3P$; iii, **13**–AcOH–DMF, heat then $NaBH_4$–EtOH; iv, 5% Pd-C–HCl–MeOH

substrate for adenosine deaminase (calf intestinal mucosa) which is known to deaminate rapidly 2′,3′-dideoxyadenosine. Compound **26** was an extremely poor substrate of adenosine deaminase, being deaminated at roughly 10^{-3} of the rate of 2′,3′-dideoxyadenosine at the single concentration tested.

The antiviral activity of these compounds will be reported elsewhere.

Experimental

M.p.s were determined using a Reichert Kofler apparatus and are uncorrected. ^1H NMR spectra were recorded with a JEOL GX-270 270 MHz spectrometer, *J* values are given in Hz. IR spectra were recorded with a Perkin-Elmer 580 or a Bio-Rad FTS-7 spectrometer and UV spectra with a Uvikon 810 spectrometer. Mass spectra were recorded on a VG 70-70 instrument and accurate masses were measured on a VG ZAB spectrometer. Microanalyses were performed on a Carlo Erba model 1106 analyser. Column chromatography was carried out on Merck 7736 silica gel. All compounds were homogeneous by TLC on silica gel $60F_{254}$ coated aluminium sheets.

9-*Amino*-6-*chloropurine* **6**.—A solution of the hydrazinopyrimidine **5** (6.38 g, 40 mmol) in diethoxymethyl acetate (50 cm^3) was stirred at 120 °C for 1 h and the solvent was removed to afford 6-chloro-9-(ethoxymethylideneamino)purine; δ_H [$(CD_3)_2SO$] 1.40 (3 H, t, *J* 7, CH_3), 4.46 (2 H, q, *J* 7, CH_2), 9.08 (1 H, s, CHN), 9.24 (1 H, s, 2/8-H) and 9.50 (1 H, s, 8/2 H). This was taken up in 50% acetic acid (60 cm^3) and after 5 min the solution was filtered to afford the *title compound* **6** (0.78 g). The solution was evaporated and the residue was azeotroped with toluene and purified by column chromatography on silica gel eluting with chloroform–methanol (20:1, 15:1) to give further product **6** (1.22 g; total 2.0 g, 29%), m.p. 160–162 °C (with decomp.); $\lambda_{max}(H_2O)$/nm 271 (8960) and 302 (5560); ν_{max}(KBr)/cm^{-1} 3480, 3310, 3200, 3160, 3070, 1625, 1605, 1550, 1505 and 1345; $\delta_H[(CD_3)_2SO]$ 6.45 (2 H, s, D_2O exchangeable, NH_2), 8.75 (1 H, s, 2/8-H) and 9.36 (1 H, s, 8/2-H) (Found: C, 35.4; H, 2.4; N, 41.55%. $C_5H_4ClN_5$ requires C, 35.44; H, 2.38; N, 41.30%).

9-*Benzylideneamino*-6-*chloropurine* **8**.—A solution of 5-amino-4-benzylidenehydrazino-6-chloropyrimidine (12.4 g, 50 mmol) in diethoxymethyl acetate (50 cm^3) was heated at 120 °C for 1 h. The solution was allowed to cool and after storage at 4 °C was filtered to afford the *title compound* **8** (9.64 g, 75%), m.p. 168–170 °C; λ_{max}(MeOH)/nm 213 (22 400), 265 (24 600), 282 (23 300) and 292 (23 100); ν_{max}(KBr)/cm^{-1} 1585, 1570, 1560, 1480 and 1435; $\delta_H[(CD_3)_2SO]$ 7.61 (3 H, m, C_6H_5), 7.95 (2 H, m, C_6H_5), 8.90 (1 H, s, 2/8-H), 9.17 (1 H, s, 8/2-H) and 9.71 (1 H, s, PhCH) (Found: C, 55.8; H, 3.2; N, 27.0. $C_{12}H_8ClN_5$ requires C, 55.92; H, 3.13; N, 27.1%).

9-*Benzylideneaminoadenine* **9**.—A suspension of 9-benzylideneamino-6-chloropurine **8** (4.12 g, 16 mmol) in ethanol saturated with ammonia (36 cm^3) was heated at 110 °C for 4 h in an autoclave. The solution was allowed to cool and the solid was filtered off. It was washed with ethanol followed by water to afford the title compound **9** (3.53 g, 93%), m.p. 239–241 °C (lit.,[22] 240–241 °C); $\delta_H[(CD_3)_2SO]$ 7.45 (2 H, s, D_2O exchangeable, NH_2), 7.5–7.95 (5 H, m, C_6H_5), 8.26 (1 H, s, 2/8-H), 8.55 (1 H, s, 8/2-H) and 9.87 (1 H, s, PhCH).

9-*Aminoadenine* **10**.—To a suspension of 9-benzylideneaminoadenine **9** (3.51 g, 14.75 mmol) in chloroform–methanol (2:1; 45 cm^3) was added methylhydrazine (1.9 cm^3, 37 mmol) and the mixture was heated under reflux for 17 h. The solution was cooled to 4 °C and the solid was filtered off and washed with chloroform and ether to afford the *title compound* **10** (2.01 g, 91%), m.p. >300 °C (sublimes); $\lambda_{max}(H_2O)$/nm 258 (12 900); ν_{max}(KBr)/cm^{-1} 3290, 3100, 1675, 1630, 1600, 1580, 1485 and 1415; $\delta_H[(CD_3)_2SO]$ 6.03 (2 H, s, D_2O exchangeable, 9-NH_2), 7.22 (2 H, s, D_2O exchangeable, 6-NH_2), 8.02 (1 H, s, 2/8-H) and 8.17 (1 H, s, 8/2-H) (Found: C, 40.2; H, 4.1; N, 56.0. $C_5H_6N_6$ requires C, 40.00; H, 4.03; N, 55.97%).

1-(*Benzylideneamino*)*cytosine* **12**.—To an ice-cooled solution of 1-(benzylideneamino)uracil **11** (8.61 g, 40 mmol) in pyridine (200 cm^3) was added 4-chlorophenyl phosphorodichloridate (8.66 cm^3, 53.2 mmol) and the solution was allowed to warm to room temperature. After 10 min 1,2,4-triazole (7.40 g, 107 mmol) was added and the solution was stirred for 16 h. To this solution were added ammonia (*d* 0.88; 20 cm^3) followed by methanol (40 cm^3) and the mixture was stirred for a further 2 h. The solution was evaporated and the residue was azeotroped with toluene (×2) and purified by column chromatography on silica gel eluting with ethyl acetate–methanol (12:1) to afford the *title compound* **12** (2.11 g, 25%), m.p. 218–221 °C; λ_{max}(MeOH)/nm 256 (13 800) and 312 (16 400); ν_{max}(KBr)/cm^{-1} 3360, 3185, 3090, 1680, 1640, 1605, 1595, 1520 and 1485; $\delta_H[(CD_3)_2SO]$ 5.80 (1 H, d, *J* 7.4, 5-H), 7.31, 7.37 (2 H, 2 × br s, D_2O exchangeable, NH_2), 7.51 (3 H, m, C_6H_5), 7.81 (3 H, m, C_6H_5 and 6-H) and 9.46 (1 H, s, PhCH) (Found: C, 61.5; H, 4.6; N, 26.3. $C_{11}H_{10}N_4O$ requires C, 61.67; H, 4.71; N, 26.15%).

1-*Aminocytosine* **13**.—To a suspension of 1-(benzylideneamino)cytosine **12** (2.0 g, 9.3 mmol) in chloroform–methanol (2:1; 30 cm^3) was added methylhydrazine (1.28 cm^3, 24 mmol) and the mixture was stirred for 6 h. The solid was filtered off and washed with chloroform and further solid was obtained by concentration of the filtrate to afford the *title compound* **13** (0.82 g, 70%), m.p. 252–256 °C; $\lambda_{max}(H_2O)$/nm 274 (7040); ν_{max}(KBr)/cm^{-1} 3365, 3320, 1660, 1620, 1525, 1480 and 1385; $\delta_H[(CD_3)_2SO]$ 5.40 (1 H, s, D_2O exchangeable, 1-NH_2), 5.55 (2 H, d, *J* 7.1, 5-H), 6.91 (2 H, br s, D_2O exchangeable, 4-NH_2) and 7.56 (2 H, d, *J* 7.1, 6-H) (Found: C, 38.0; H, 4.6; N, 44.3. $C_4H_6N_4O$ requires C, 38.09; H, 4.80; N, 44.42%).

Amination of Thymine.—To a solution of thymine **14** (0.76 g, 6 mmol) in aqueous sodium hydroxide (1.2 mol dm^{-3}; 18 cm^3) was added a solution of hydroxylamine *O*-sulphonic acid (1.13 g, 10 mmol) in water (6 cm^3) and the mixture was stirred at

room temperature for 3 h. The solution was neutralised with glacial acetic acid, filtered, and purified by reverse phase HPLC on a C_{18}-silica gel column eluting with 50×10^{-3} mol dm^{-3} aqueous ammonium acetate. The first peak to be eluted was 1,3-*diaminothymine* **17** (100 mg, 11%), m.p. 162–164 °C; $\lambda_{max}(H_2O)$/nm 270 (6550); ν_{max}(KBr)/cm^{-1} 1700, 1654, 1566 and 1445; $\delta_H[(CD_3)_2SO]$ 1.83 (3 H, d, *J* 1.1, CH_3), 5.51 (2 H, s, D_2O exchangeable, NH_2), 5.62 (2 H, s, D_2O exchangeable, NH_2) and 7.56 (1 H, d, *J* 1.1, 6-H) (Found: C, 37.7; H, 5.0; N, 35.8%; M^+, 156.0639. $C_5H_8N_4O_2$ requires C, 38.46; H, 5.16; N, 35.88%; *M*, 156.0647). The second peak to be eluted was 3-*aminothymine* **16** (80 mg, 14%), m.p. 205–207 °C; $\lambda_{max}(H_2O)$/nm 263 (7200), (0.1 mol dm^{-3} NaOH) 286 (8770); ν_{max}(KBr)/cm^{-1} 1720, 1667, 1620 and 1440; $\delta_H[(CD_3)_2SO]$ 1.81 (3 H, d, *J* 1.1, CH_3), 5.41 (2 H, s, D_2O exchangeable, NH_2), 7.27 (1 H, d, *J* 1.2, 6-H) and 11.07 (1 H, br, D_2O exchangeable, 1-H) (Found: C, 42.2; H, 4.9; N, 29.9%; M^+, 141.0546. $C_5H_7N_3O_2$ requires C, 42.55; H, 5.00; N, 29.77%; *M*, 141.0538). The third peak to be eluted was 1-*aminothymine* **15** (54 mg, 6%), m.p. 234–235 °C; $\lambda_{max}(H_2O)$/nm 272 (8380), (0.1 mol dm^{-3} NaOH) 271 (6280); ν_{max}(KBr)/cm^{-1} 1700, 1666, 1610 and 1424; $\delta_H[(CD_3)_2SO]$ 1.73 (3 H, d, *J* 1.1, CH_3), 5.41 (2 H, s, D_2O exchangeable, NH_2), 7.51 (1 H, q, *J* 1.1, 6-H) and 11.24 (1 H, br s, D_2O exchangeable, 3-H) (Found: C, 42.3; H, 5.0; N, 29.9. $C_5H_7N_3O_2$ requires C, 42.55; H, 5.00; N, 29.77%).

2-(tert-*Butyldimethylsilyloxymethyl*)*pent*-4-*en*-1-*ol* **19**.—To a suspension of sodium hydride (60% dispersion-in-oil, hexane washed; 1.92 g, 48 mmol) in tetrahydrofuran (THF) (75 cm^3) was added a solution of 2-hydroxymethylpent-4-en-1-ol (5.6 g, 48 mmol) in THF (25 cm^3). The mixture was stirred for 1 h, after which *tert*-butyldimethylsilyl chloride (7.4 g, 48 mmol) was added and the mixture was stirred for a further 45 min. The solution was diluted with ether (100 cm^3), washed with water (150 cm^3), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel eluting with hexane–ethyl acetate (8:1) to afford the alcohol **19** as a clear colourless liquid (9.5 g, 86%); ν_{max}(film)/cm^{-1} 3370, 2960, 2930, 2890, 2860, 1640 and 1470; $\delta_H[(CD_3)_2SO]$ 0.06 [6 H, s, $Si(CH_3)_2$], 0.90 [9 H, s, $C(CH_3)_3$], 1.63 (1 H, m, CH), 2.07 (2 H, t, *J* 7.0, CCH_2C), 3.38 (2 H, t, *J* 5.1, CH_2OH), 3.57 (2 H, AB of ABX, $J_{AX} = J_{BX}$ 5.5 and J_{AB} 9.8, CH_2OSi), 4.34 (1 H, t, *J* 5.0, D_2O exchangeable, OH), 5.04 (2 H, m, $=CH_2$) and 5.83 (1 H, m, CH=).

2-(tert-*Butyldimethylsilyloxymethyl*)*pent*-4-*enyl Toluene*-p-*sulphonate* **20**.—To an ice-cooled solution of the alcohol **19** (4.14 g, 18 mmol) and pyridine (2.91 cm^3, 36 mmol) in dichloromethane (10 cm^3) was added toluene-*p*-sulphonyl chloride (5.15 g, 27 mmol). The solution was stirred for 2.5 h at room temperature and then diluted with ether (40 cm^3). The solution was washed with water (25 cm^3), hydrochloric acid (2 mol dm^{-3}; 25 cm^3) and aqueous sodium hydrogen carbonate (25 cm^3), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel eluting with chloroform–hexane (6:1) followed by ether–hexane (1:1) to afford the sulphonate **20** as a clear liquid (5.8 g, 84%); ν_{max}(film)/cm^{-1} 1365, 1255, 1190, 1180 and 1100; $\delta_H(CDCl_3)$ −0.02 (3 H, s, $SiCH_3$), 0.00 (3 H, s, $SiCH_3$), 0.81 [9 H, s, $C(CH_3)_3$], 1.88 [1 H, m, $CH(CH_2)_3$], 2.05 (2 H, t, *J* 6.8, $CHCH_2CH$), 2.45 (3 H, s, $ArCH_3$), 3.51 (2 H, AB of ABX, J_{AB} 10.5, J_{AX} 6.1, J_{BX} 4.7, CH_2OSi), 4.02 (2 H, d, *J* 5.5, CH_2OS), 4.97 (2 H, m, $=CH_2$), 5.65 (1 H, m, CH=), 7.34 (2 H, d, *J* 8.0, C_6H_4) and 7.97 (2 H, d, *J* 8.2, C_6H_4); CIMS (NH_3) 402 (MNH_4^+) and 385 (MH^+).

Ozonolysis of **20**.—A solution of the alkene **20** (1.9 g, 5 mmol) in methanol (10 cm^3) and dichloromethane (10 cm^3) was cooled to −78 °C and ozonised air was bubbled through until a pale blue colouration was obtained. Nitrogen was bubbled through to remove excess of ozone and trimethyl phosphite (1 cm^3) was added. After 5 min the solution was allowed to warm to room temperature and the solvent was evaporated to afford the aldehyde **21** which was used directly; $\delta_H(CDCl_3)$ 0.00 [6 H, s, $Si(CH_3)_2$], 0.83 [9 H, s, $C(CH_3)_3$], 2.43 (6 H, m, CH_3 and $CHCH_2$), 3.53 (2 H, d, *J* 4, CH_2OSi), 4.04 (2 H, d, *J* 4, CH_2OS), 7.33 (2 H, d, *J* 8, C_6H_4), 7.77 (2 H, d, *J* 8, C_6H_4) and 9.70 (1 H, s, CHO).

9-[3-(tert-*Butyldimethylsilyloxymethyl*)*pyrrolidin*-1-*yl*]*guanine* **23**.—A solution of the aldehyde **21** (from ozonolysis of 5 mmol of alkene **20**) and 9-aminoguanine (0.85 g, 5.0 mmol) in dimethyl sulphoxide (DMSO) (10 cm^3) and acetic acid (0.5 cm^3) was stirred at 50 °C for 1 h. The solution was concentrated by evaporation under reduced pressure and then diluted with THF (10 cm^3) and ethanol (2 cm^3). Sodium borohydride (0.19 g, 5 mmol) was added and the solution was stirred for 16 h at room temperature. The mixture was partitioned between chloroform and water, the organic layer was collected and the solvent was removed. The residue was taken up in THF (8 cm^3) and ethanol (2 cm^3) and more sodium borohydride (0.19 g, 5 mmol) was added. The mixture was stirred at room temperature for 1 h after which it was partitioned between chloroform and water. The aqueous layer was further extracted with ethyl acetate, and the organic layers were combined and evaporated. The residue was purified by column chromatography on silica gel eluting with chloroform–methanol (24:1) to afford the *pyrrolidine* **23** (113 mg, 6%), m.p. >260 °C (decomp.); λ_{max}(MeOH)/nm 255 (13 200) and 270 sh (9720); ν_{max}(KBr)/cm^{-1} 3350, 3150, 1695, 1625 and 1595; $\delta_H[(CD_3)_2SO]$ 0.55 [6 H, s, $Si(CH_3)_2$], 0.87 [9 H, s, $C(CH_3)_3$], 1.59 (1 H, m, 4′-H), 1.98 (1 H, m, 4′-H), 2.44 (1 H, m, 3′-H), 3.10 (1 H, dd, *J* 6.3 and 8.8, 2′-H), 3.41 (3 H, m, 2′-H and 2 × 5′-H), 3.59 (2 H, m, CH_2O), 6.42 (2 H, s, D_2O exchangeable, NH_2), 7.77 (1 H, s, 8-H) and 10.56 (1 H, s, D_2O exchangeable, 1-H); FABMS (thioglycerol) 365 (MH^+) (Found: C, 52.4; H, 7.8; N, 22.3. $C_{16}H_{28}N_6O_2Si$ requires C, 52.72; H, 7.74; N, 23.06%).

9-(3-*Hydroxymethylpyrrolidin*-1-*yl*)*guanine* **25**.—A solution of the silyl ether **23** (106 mg, 0.29 mmol) in 80% acetic acid (3 cm^3) was stirred at 70 °C for 90 min. The solution was diluted with water (1 cm^3), washed with hexane (2 × 4 cm^3) and evaporated. The residue was purified by reverse-phase column chromatography on C_{18}-silica gel eluting with water followed by 5 and 10% methanol in water, to afford the *guanine* **25** (42 mg, 58%), m.p. >300 °C; $\lambda_{max}(H_2O)$/nm 254 (13 100) and 270 (10 100); ν_{max}(KBr)/cm^{-1} 3290, 3150, 2940, 1690, 1645, 1600 and 1575; $\delta_H[(CD_3)_2SO)]$ 1.60 (1 H, m, 4′-H), 1.97 (1 H, m, 4′-H), 2.41 (1 H, septet, *J* 7.4, 3′-H), 3.14 (1 H, dd, *J* 6.3 and 8.5, 2′-H), 3.3–3.45 (5 H, m, 2′-H, 2 × 5′-H and CH_2O), 4.68 (1 H, t, *J* 5.2, D_2O exchangeable, OH), 6.45 (2 H, s, D_2O exchangeable, 2-NH_2), 7.79 (1 H, s, 8-H) and 10.56 (1 H, s, D_2O exchangeable, 1-H) (Found: C, 46.85; H, 5.5; N, 32.9%; M^+, 250.1177. $C_{10}H_{14}N_6O_2 \cdot 0.3H_2O$ requires C, 46.98; H, 5.76; N, 32.92%; *M*, 250.1178).

9-(3-*Hydroxymethylpyrrolidin*-1-*yl*)*adenine* **26**.—A solution of the aldehyde **21** (from ozonolysis of 4 mmol of alkene **20**) and 9-aminoadenine (0.45 g, 3 mmol) in *N*,*N*-dimethylformamide (DMF) (7 cm^3) and acetic acid (0.12 cm^3, 2 mmol) was stirred at 50 °C for 1 h. To this solution were added ethanol (3 cm^3) and sodium borohydride (0.15 g, 4 mmol). The solution was stirred at room temperature for 19 h and then partitioned between chloroform (15 cm^3) and water (15 cm^3). The organic layer was washed with saturated aqueous sodium hydrogen-carbonate (15 cm^3), dried ($MgSO_4$) and evaporated. The

residue was taken up in 80% acetic acid (9 cm^3). The solution was stirred at 70 °C for 2 h. It was then diluted with water (4 cm^3), washed with hexane (2 × 15 cm^3) and the residue azeotroped with toluene and purified by column chromatography on silica gel eluting with chloroform–methanol (15:1, 12:1). The product was triturated with ether to afford the *adenine* **26** (161 mg, 23%), m.p. 164–167 °C; $\lambda_{max}(H_2O)$/nm 259 (13 800); ν_{max}(KBr)/cm^{-1} 3330, 3190, 1665, 1600, 1570, 1475 and 1410; $\delta_H[(CD_3)_2SO]$ 1.67 (1 H, m, 4′-H), 2.02 (1 H, m, 4′-H), 2.48 (1 H, m, 3′-H), 3.30 (1 H, dd, *J* 6.3 and 8.5, 2′-H), 3.42–3.50 (4 H, m, 2 × 5′-H and CH_2O), 3.54 (1 H, t, *J* 8.3, 2′-H), 4.71 (1 H, t, *J* 5.0, D_2O exchangeable, OH), 7.24 (2 H, s, D_2O exchangeable, NH_2), 8.12 (1 H, s, 2/8-H) and 8.16 (1 H, s, 8/2-H) (Found: C, 51.0; H, 6.1; N, 35.8. $C_{10}H_{14}N_6O$ requires, C, 51.27; H, 6.02; N, 35.87%).

9-(3-*Hydroxymethylpyrrolidin*-1-*yl*)*hypoxanthine* **27**.—To a solution of the adenine **26** (59 mg, 0.25 mmol) in water (2.5 cm^3) was added concentrated hydrochloric acid (0.2 cm^3) and the solution was warmed to 75 °C. Sodium nitrite (3 portions of 35 mg dissolved in 0.2 cm^3 water) was added over a period of 2 h. The solution was allowed to cool, neutralised with aqueous sodium hydroxide and purified by reverse-phase column chromatography on C_{18}-silica gel eluting with 5–20% methanol in water to afford the *hypoxanthine* **27** (31 mg, 53%), m.p. 197–200 °C (decomp.); $\lambda_{max}(H_2O)$/nm 249 (10 700); ν_{max} (KBr)/cm^{-1} 3370, 1695, 1590, 1550, 1465 and 1410; δ_H $[(CD_3)_2SO]$ 1.66 (1 H, m, 4′-H), 2.01 (1 H, m, 4′-H), 2.46 (1 H, m, 3′-H), 3.26 (1 H, dd, *J* 6.6 and 8.5, 2′-H), 3.35–3.55 (5 H, m, 2′-H, 2 × 5′-H and CH_2O), 8.02 (1 H, s, 2/8-H), and 8.13 (1 H, s, 8/2-H) (Found: C, 49.5; H, 5.6; N, 28.7%; M^+, 235.1068. $C_{10}H_{13}N_5O_2 \cdot 0.4H_2O$ requires C, 49.54; H, 5.74; N, 28.89%; *M*, 235.1069).

1-[3-(*Acetoxymethyl*)*pyrrolidin*-1-*yl*]-5-*iodouracil* **30**.—A solution of the uracil **29** (280 mg, 1.1 mmol), iodine (355 mg, 1.4 mmol) and ceric ammonium nitrate (300 mg, 0.55 mmol) in acetonitrile (12 cm^3) was stirred at 80 °C for 90 min. More iodine (80 mg) was added and the solution was stirred for a further 30 min at 80 °C and evaporated. The residue was taken up in cold ethyl acetate and washed with cold aqueous sodium metabisulphite (5%; 12 cm^3) and brine (12 cm^3), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel eluting with chloroform–methanol (80:1) to afford the 5-*iodouracil* **30** (115 mg, 28%), m.p. commences at 103 °C then recrystallises and melts at 148–151 °C; λ_{max}(MeOH)/nm 216 (9060) and 286 (7910); ν_{max}(KBr)/cm^{-1} 3430, 1720, 1695, 1600 and 1405; $\delta_H(CDCl_3)$ 1.68 (1 H, m, 4′-H), 2.07 (4 H, m, CH_3 and 4′-H), 2.65 (1 H, septet, *J* 7.1, 3′-H), 3.17 (1 H, dd, *J* 6.5 and 8.7, 2′-H), 3.43 (3 H, m, 2′-H and 2 × 5′-H), 4.07 (2 H, AB of ABX, J_{AB} 10.9, J_{AX} 7.8, J_{BX} 6.5, CH_2O), 7.85 (1 H, s, 6-H), and 8.44 (1 H, s, D_2O exchangeable, 3-H) (Found: C, 35.0; H, 3.7; N, 11.1%. $C_{11}H_{14}IN_3O_4$ requires C, 34.85; H, 3.73; N, 11.08%).

1-(3-*Hydroxymethylpyrrolidin*-1-*yl*)-5-*iodouracil* **31**.—A solution of the acetate **30** (87 mg, 0.23 mmol), in methanol (1 cm^3) and ammonia (*d* 0.88; 1 cm^3) was stirred at room temperature for 22 h. The solution was evaporated and the residue was crystallised from acetone to afford the 5-*iodouracil* **31** (49 mg, 63%), m.p. 204–206 °C (decomp.); $\lambda_{max}(H_2O)$/nm 215 (10 100) and 291 (7290); ν_{max}(KBr)/cm^{-1} 3420, 1700, 1670, 1600 and 1405; $\delta_H[(CD_3)_2SO]$ 1.52 (1 H, m, 4′-H), 2.31 (1 H, septet, *J* 7.4, 3′-H), 3.01 (1 H, dd, *J* 6.9 and 8.3, 2′-H), 3.28 (5 H, m, 2′-H, 2 × 5′-H and CH_2O), 4.60 (1 H, t, *J* 5.2, D_2O exchangeable, OH), 8.12 (1 H, s, 6-H) and 11.53 (1 H, br s, D_2O exchangeable 3-H) (Found: C, 32.2; H, 3.8; N, 12.5. $C_9H_{12}IN_3O_3$ requires C, 32.07; H, 3.59; N, 12.46%).

1-[3-(tert-*Butyldimethylsilyloxymethyl*)*pyrrolidin*-1-*yl*]-5-*chlorouracil* **32**.—A solution of the uracil **28** (1.14 g, 3.5 mmol), *N*-chlorosuccinimide (0.67 g, 5 mmol) and acetic anhydride (0.07 cm^3) in acetic acid (3.5 cm^3) was stirred at 50 °C for 50 min and then allowed to cool. The solution was diluted with chloroform (25 cm^3), washed with saturated aqueous sodium hydrogen carbonate (50 cm^3 followed by 25 cm^3), dried ($MgSO_4$), evaporated, and the residue purified by column chromatography on silica gel eluting with hexane–acetone (3:1) to afford the 5-*chlorouracil* **32** (0.58 g, 46%), m.p. 155–159 °C; λ_{max}(EtOH)/nm 278 (8780); ν_{max}(KBr)/cm^{-1} 1738, 1710 and 1685; $\delta_H(CDCl_3)$ 0.05 [6 H, s, $Si(CH_3)_2$], 0.89 [9 H, s, $C(CH_3)_3$], 1.66 (1 H, s, 4′-H), 1.98 (1 H, m, 4′-H), 2.49 (1 H, septet, *J* 7.3, 3′-H), 3.16 (1 H, dd, *J* 6.6 and 8.2, 2′-H), 3.38 (3 H, m, 2′-H and 2 × 5′-H), 3.57 (2 H, AB of ABX, J_{AB} 10.0, J_{AX} 7.4, J_{BX} 6.5, CH_2O), 7.63 (1 H, s, 6-H) and 8.30 (1 H, s, D_2O exchangeable, 3-H) (Found: C, 49.9; H, 7.45; N, 11.7%. $C_{15}H_{26}ClN_3O_3Si$ requires C, 50.06; H, 7.28; N, 11.67%).

1-(3-*Hydroxymethylpyrrolidin*-1-*yl*)-5-*chlorouracil* **33**.—A solution of the silyl ether **32** (252 mg, 0.7 mmol), in 80% acetic acid (4 cm^3) was stirred at 70 °C for 80 min, water (2 cm^3) was added and the solution was washed with hexane (2 × 6 cm^3). The solution was evaporated and the residue azeotroped with ethanol, and recrystallised from ethyl acetate to afford the 5-*chlorouracil* **33** (138 mg, 80%), m.p. 179–181 °C; λ_{max} (H_2O)/nm 280 (8920); ν_{max}(KBr)/cm^{-1} 1716, 1680, 1616, 1441 and 1413; $\delta_H[(CD_3)_2SO]$ 1.53 (1 H, s, 4′-H), 1.87 (1 H, m, 4′-H), 2.32 (1 H, septet, *J* 7.4, 3′-H), 3.02 (1 H, dd, *J* 6.7 and 8.4, 2′-H), 3.2–3.4 (5 H, m, 2′-H, 2 × 5′-H, and CH_2O), 4.62 (1 H, t, *J* 5, D_2O exchangeable, OH), 8.12 (1 H, s, 6-H) and 11.81 (1 H, br s, D_2O exchangeable, 3-H) (Found: C, 43.95; H, 4.95; N, 17.2. $C_9H_{12}ClN_3O_3$ requires C, 44.00; H, 4.92; N, 17.10%).

1-[3-(tert-*Butyldimethylsilyloxymethyl*)*pyrrolidin*-1-*yl*]-5-*chlorocytosine* **34**.—To a solution of the uracil **32** (0.36 g, 1.0 mmol), in pyridine (5 cm^3) was added 4-chlorophenyl phosphorodichloridate (0.22 cm^3, 1.33 mmol) followed by 1,2,4-triazole (0.36 g, 5.34 mmol and 1-hydroxybenzotriazole (27 mg, 0.2 mmol). The mixture was stirred at room temperature for 24 h after which further 1,2,4-triazole (0.18 g, 2.67 mmol) was added. The mixture was stirred for a further 72 h after which ammonia (*d* 0.88 g cm^{-3}; 0.5 cm^3) and methanol (1.0 cm^3) were added to it and stirring was continued for a further 2.7 h. The solution was evaporated and the residue was azeotroped with toluene (×2) and purified by column chromatography on silica gel eluting with chloroform–methanol (40:1, 25:1) to afford the *cytosine* **34** (0.15 g, 42%), m.p. 172–175 °C; λ_{max}(EtOH)/nm 290 (6250); ν_{max}(KBr)/cm^{-1} 1674, 1645, 1607 and 1492; $\delta_H(CDCl_3)$ 0.04 [6 H, s $Si(CH_3)_2$], 0.88 [9 H, s, $C(CH_3)_3$], 1.65 (1 H. s, 4′-H), 1.99 (1 H, m, 4′-H), 2.51 (1 H, septet, *J* 7.4, 3′-H), 3.16 (1 H, dd, *J* 6.6 and 8.3, 2′-H), 3.35–3.60 (5 H, m, 2′-H, 2 × 5′-H and CH_2O), 5.54 (1 H, br, D_2O exchangeable, NH_2), 7.28 (1 H, br, D_2O exchangeable, NH_2) and 7.62 (1 H, s, 6-H) (Found: C, 50.0; H, 7.7; N, 15.65. $C_{15}H_{27}ClN_4O_2Si$ requires C, 50.19; H, 7.58; N, 15.61%).

1-(3-*Hydroxymethylpyrrolidin*-1-*yl*)-5-*chlorocytosine* **35**.—A solution of the silyl ether **34** (122 mg, 0.34 mmol) in 80% acetic acid (2.8 cm^3) was stirred at 70 °C for 80 min, after which water (1 cm^3) was added and the solution was washed with hexane (2 × 4 cm^3). The solution was evaporated and the residue azeotroped with ethanol and recrystallised from methanol–ethyl acetate to afford the 5-*chlorocytosine* **35** (56 mg, 67%), m.p. 223–227 °C; $\lambda_{max}(H_2O)$/nm 289 (6560); ν_{max}(KBr)/cm^{-1} 1674, 1643, 1612 and 1495; $\delta_H[(CD_3)_2SO]$ 1.53 (1 H, s, 4′-H), 1.86 (1 H, m, 4′-H), 2.33 (1 H, septet, *J* 7.4, 3′-H), 3.06 (1 H, dd, *J* 6.9 and 8.2, 2′-H), 3.2–3.45 (5 H, m, 2′-H, 2 × 5′-H, and

CH_2O), 4.58 (1 H, t, *J* 5.2, D_2O exchangeable, OH), 7.12 (1 H, br, D_2O exchangeable, NH_2), 7.76 (1 H, br, D_2O exchangeable, NH_2) and 7.94 (1 H, s, 6-H) (Found: C, 44.1; H, 5.3; N, 22.4%; M^+, 244.0727. $C_9H_{13}ClN_4O_2$ requires C, 44.18; H, 5.36; N, 22.90%; *M*, 244.0726).

(R)-2-*Benzyloxymethylpent-4-enyl Toluene*-p-*sulphonate* **37a**.—To a solution of the (*S*)-alcohol **36a** (0.43 g, 2.1 mmol) and pyridine (0.15 cm^3, 6 mmol) in dichloromethane (2 cm^3) was added toluene-*p*-sulphonyl chloride (0.76 g, 4 mmol) and the mixture was stirred for 4 h. It was then partitioned between ether (15 cm^3) and water (15 cm^3) and the organic layer was washed with hydrochloric acid (2 mol dm^{-3}; 15 cm^3) and saturated aqueous sodium hydrogen carbonate (15 cm^3) and dried ($MgSO_4$). The solution was evaporated and the residue was purified by column chromatography on silica gel eluting with hexane–ethyl acetate (7:1) to afford the *sulphonate* **37a** as a liquid (0.62 g, 82%); ν_{max}(film)/cm^{-1} 1360, 1190 and 1180; δ_H($CDCl_3$) 2.03 (1 H, m, CH), 2.11 (2 H, m, CH_2CH=), 2.42 (3 H, s, CH_3), 3.39 (2 H, AB of ABX, J_{AB} 9.3, J_{AX} 6.1 and J_{BX} 5.0, CH_2OBn) 4.07 (2 H, d, *J* 5.2, CH_2OS), 4.39 (2 H, s, $PhCH_2$), 4.95 (1 H, m, =CH_2), 5.01 (1 H, s, =CH_2), 5.65 (1 H, m, CH=) 7.28 (7 H, m, C_6H_5 and 2 of C_6H_4) and 7.78 (2 H, d, *J* 8.3, C_6H_4) (Found: C, 66.5; H, 6.8. $C_{20}H_{24}O_4S$ requires C, 66.64; H, 6.71%).

(S)-2-*Benzyloxymethylpent-4-enyl Toluene*-p-*sulphonate* **37b**.—*Compound* **37b** was prepared in a similar way to **37a** but using the (*R*)-alcohol **36b**; ν_{max}(film)/cm^{-1} 1360, 1190 and 1180; δ_H($CDCl_3$) 2.03 (1 H, m, CH), 2.11 (2 H, m, CH_2CH=), 2.41 (3 H, s, CH_3), 3.39 (2 H, AB of ABX, J_{AB} 9.3, J_{AX} 6.1 and J_{BX} 5.0, CH_2OBn), 4.07 (2 H, d, *J* 5.2, CH_2OS), 4.38 (2 H, s, $PhCH_2$), 4.96 (1 H, m, =CH_2), 5.01 (1 H, s, =CH_2), 5.62 (1 H, m, CH=), 7.28 (7 H, m, C_6H_5 and 2 of C_6H_4) and 7.77 (2 H, d, *J* 8.5, C_6H_4) (Found: C, 66.9; H, 6.8. $C_{20}H_{24}O_4S$ requires C, 66.64; H, 6.71%).

(S)-1-[3-(*Benzyloxymethyl*)*pyrrolidin*-1-*yl*]*cytosine* **39a**.—Ozonised air was passed through a solution of the (*R*)-sulphonate **37a** (0.58 g, 1.6 mmol) in methanol (3 cm^3) and dichloromethane (3 cm^3) at −78 °C for 40 min. Nitrogen was then passed through for 5 min and triethyl phosphite (0.32 cm^3) was added. After 5 min the solution was allowed to warm to room temperature and evaporated to afford the aldehyde **38a** [δ_H($CDCl_3$) 9.76]. The residue was taken up in DMF (3 cm^3) and to this solution were added 1-aminocytosine (0.19 g, 1.5 mmol) and glacial acetic acid (0.05 cm^3, 0.8 mmol). The mixture was stirred at 50 °C for 1 h and allowed to cool. Sodium borohydride (57 mg, 1.5 mmol) was added and after 1 h further borohydride (57 mg) and ethanol (1.5 cm^3) were added. The solution was stirred for 16 h and partitioned between water (15 cm^3) and chloroform (15 cm^3). The organic layer was washed with brine (15 cm^3), dried ($MgSO_4$), evaporated, and the residue was purified by column chromatography on silica gel eluting with chloroform–methanol (12:1) to afford the (S)-*pyrrolidine* **39a** (153 mg, 34%); ν_{max}(KBr)/cm^{-1} 3330, 3195, 1640, 1515, 1490, 1455 and 1375; δ_H($CDCl_3$) 1.67 (1 H, m, 4′-H), 2.04 (1 H, m, 4′-H), 2.65 (1 H, m, 3′-H), 3.20 (1 H, dd, *J* 6.7 and 8.4, 2′-H), 3.44 (5 H, m, 2′-H, 2 × 5′-H and CH_2O), 4.51 (2 H, s, $PhCH_2$), 5.55 (1 H, d, *J* 7.2, 5-H), 5.85 (2 H, br, D_2O exchangeable, NH_2), 7.32 (5 H, s, C_6H_5) and 7.42 (1 H, d, *J* 7.2, 6-H) (Found: C, 62.4; H, 6.7; N, 17.9; M^+, 300.1590. $C_{16}H_{20}N_4O_2 \cdot 0.5H_2O$ requires C, 62.12; H, 6.84; N, 18.11%; *M*, 300.1586).

(R)-1-[3(*Benzyloxymethyl*)*pyrrolidin*-1-*yl*]*cytosine* **39b**.—*Compound* **39b** was prepared in a similar way to **39a** but using the (*S*)-sulphonate **37b**; ν_{max}(KBr)/cm^{-1} 3385, 3180, 1636, 1608, 1518, 1488 and 1473; δ_H($CDCl_3$) 1.68 (1 H, m, 4′-H), 2.04 (1 H, m, 4′-H), 2.65 (1 H, m, 3′-H), 3.19 (1 H, m, 2′-H), 3.43 (5 H, m, 2′-H, 2 × 5′-H, and CH_2O), 4.52 (2 H, s, $PhCH_2$), 5.84 (1 H, d, *J* 7.2, 5-H), 7.0 (2 H, br, D_2O exchangeable, NH_2), 7.33 (5 H, m, C_6H_5) and 7.44 (1 H, d, *J* 7.4, 6-H) (Found: C, 64.2; H, 6.7; N, 18.5%. $C_{16}H_{20}N_4O_2$ requires C, 63.98; H, 6.71; N, 18.65%).

(S)-1-(3-*Hydroxymethylpyrrolidin*-1-*yl*)*cytosine* **40a**.—To a solution of the (*S*)-benzyl ether **39a** (130 mg, 0.43 mmol) in methanol (7 cm^3) was added methanolic hydrogen chloride (0.3 cm^3) followed by 5% palladium-on-charcoal (30 mg) and the mixture was stirred under hydrogen for 30 min. The solution was filtered, neutralised by addition of ammonia (*d* 0.88), evaporated, and the residue was purified by reverse-phase column chromatography eluting with water followed by 5, 10 and 20% methanol to afford the (S)-*cytosine* **40a** as a white solid (70 mg, 77%) that could be recrystallised from ethyl acetate–methanol, m.p. 181–183 °C; λ_{max}(H_2O)/nm 273 (8100); ν_{max}(KBr)/cm^{-1} 3330, 3180, 2940, 2870, 1640, 1520, 1490 and 1475; δ_H[$(CD_3)_2SO$] 1.53 (1 H, m, 4′-H), 1.86 (1 H, m, 4′-H), 2.32 (1 H, septet, *J* 7.2, 3′-H), 3.04 (1 H, dd, *J* 6.7 and 8.1, 2′-H), 3.2–3.4 (5 H, m, 2′-H, 2 × 5′-H and CH_2O), 4.56 (1 H, t, *J* 5.4, D_2O exchangeable, OH), 5.54 (1 H, d, *J* 7.1, 5-H), 7.02 (2 H, br, D_2O exchangeable, NH_2) and 7.51 (1 H, d, *J* 7.1, 6-H) (Found: C, 51.5; H, 6.75; N, 26.85. $C_9H_{14}N_4O_2$ requires C, 51.42; H, 6.71; N, 26.65%).

(R)-1-(3-*Hydroxymethylpyrrolidine*-1-*yl*)*cytosine* **40b**.—*Compound* **40b** was prepared in a similar way to **40a** but using the (*R*)-benzyl ether **39b**, m.p. 180–182 °C; λ_{max}(H_2O)/nm 273 (8040); ν_{max}(KBr)/cm^{-1} 3330, 3175, 2935, 2870, 1655, 1635, 1515, 1485 and 1470; δ_H[$(CD_3)_2SO$] 1.53 (1 H, m, 4′-H), 1.86 (1 H, m, 4′-H), 2.33 (1 H, septet, *J* 7.5, 3′-H), 3.04 (1 H, dd, *J* 6.7 and 8.3, 2′-H), 3.33 (5 H, m, 2′-H, 2 × 5′-H, and CH_2O), 4.57 (1 H, t, *J* 5.2, D_2O exchangeable, OH), 5.54 (1 H, d, *J* 7.4, 5-H), 7.02, 7.07 (2 H, 2 × br s, D_2O exchangeable, NH_2) and 7.52 (1 H, d, *J* 7.2, 6-H) (Found: C, 51.2; H, 6.7; N, 26.7%. $C_9H_{14}N_4O_2$ requires C, 51.42; H, 6.74; N, 26.65%).

Enantiomeric Purity of **40a** *and* **40b**.—Baseline separation of racemic **40** was achieved by analytical HPLC on a chiral-AGP (α-glycoprotein) column eluting with 0.5% propan-2-ol/99.5% aqueous phosphate buffer (0.01 mol dm^{-3}) pH 7.0. Recrystallised **40a**, the (*S*) enantiomer, consisted of 93.3% slower isomer and 6.7% faster isomer. For **40b**, the (*R*) enantiomer, the first crop contained 87.0% faster isomer and 13.0% slower isomer, but the second crop contained 97.9% faster isomer and 2.1% slower isomer.

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