New Acyclic Nucleoside Analogues. Stereospecific Synthesis of Purines and Pyrimidines Substituted with Chiral Chains by Sugar-ring Opening of β-D-Galactopyranosyl Nucleosides[1]

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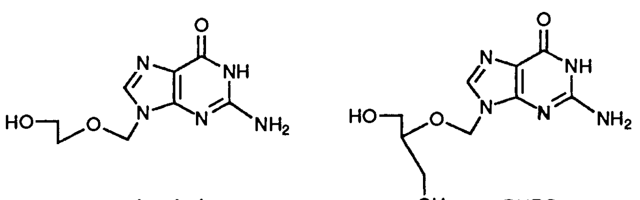
2',3'- and 3',4'-Seco-nucleosides, retaining the carbon framework of β-D-ribofuranosyl nucleosides but having a hydroxymethyl substituent on the 4' or 5' position, have been synthesized and their antiviral properties examined. These hitherto unknown chiral acyclic nucleosides were stereospecifically prepared by ring opening of β-D-galactopyranosyl nucleosides by means of periodate oxidation followed by borohydride reduction. None of the prepared compounds showed marked antiviral effect against a variety of DNA and RNA viruses.

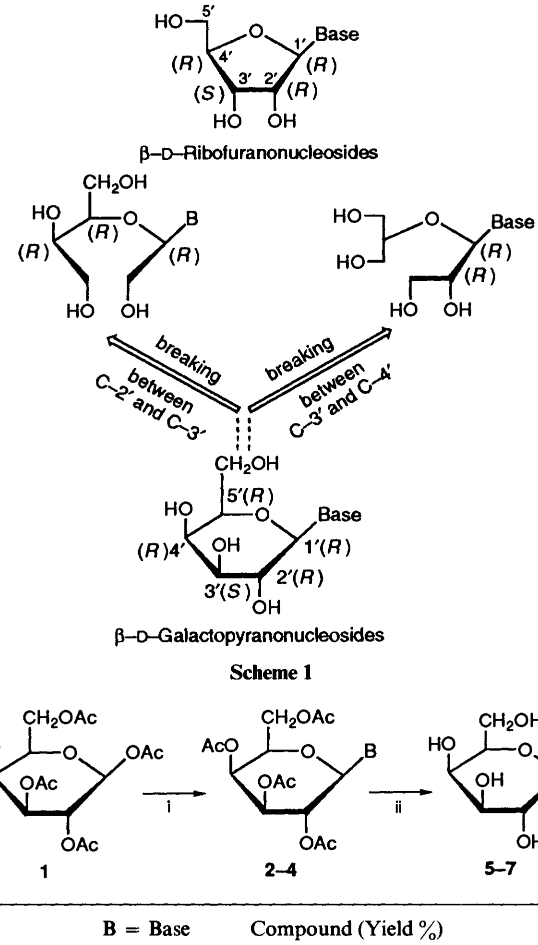
There has been considerable interest in nucleosides modified on the sugar moiety as potential antiviral agents.[2] Among these, two acyclic analogues, 9-[(2-hydroxyethoxy)methyl]guanine (Acyclovir)[3] and 9-[(1,3-dihydroxypropan-2-yloxy)methyl]-guanine (DHPG)[4] have been approved for clinical use against herpes simplex virus type 1 and human cytomegalovirus infection, respectively.



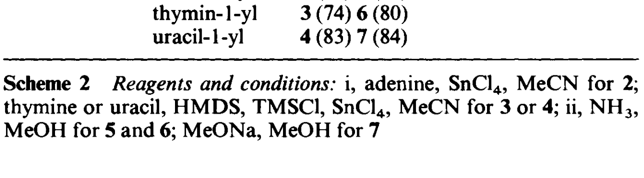
Acyclovir DHPG

The search for new antiviral drugs has led to the synthesis of a large number of acyclic nucleosides.[5] Among them are the 1',2'-,[6] 2',3'-[7] and 3',4'-seco-nucleosides[8] which retain the carbon framework and chirality of the β-D-ribofuranosyl moiety of the natural nucleosides at their asymmetrical carbon atoms.

We have now extended these studies to the stereospecific synthesis and biological evaluation of two kinds of *C*-branched-hydroxymethyl open-ring β-D-ribofuranonucleoside derivatives lacking the C-2'–C-3' or the C-3'–C-4' bond (Scheme 1). The synthetic route chosen to obtain these chiral acyclic nucleosides consisted of periodate oxidation of pre-formed β-D-galactopyranosyl nucleosides (which possess the requisite *R* configuration at their 1'-, 2'- and 5'-carbon) and reduction of the resulting dialdehydes with sodium borohydride.



Scheme 1



1 2–4 5–7

B = Base	Compound (Yield %)
adenin-9-yl	**2** (61) **5** (81)
thymin-1-yl	**3** (74) **6** (80)
uracil-1-yl	**4** (83) **7** (84)

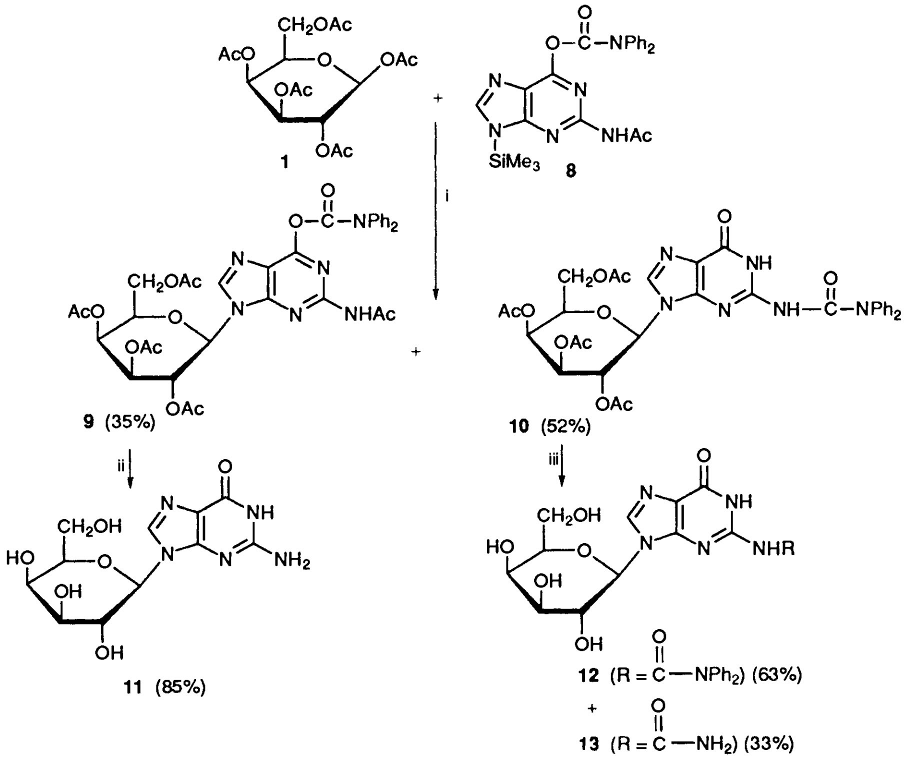
Scheme 2 *Reagents and conditions:* i, adenine, $SnCl_4$, MeCN for **2**; thymine or uracil, HMDS, TMSCl, $SnCl_4$, MeCN for **3** or **4**; ii, NH_3, MeOH for **5** and **6**; MeONa, MeOH for **7**

Results and Discussion

Condensation reactions of commercial 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose **1** and purine or pyrimidine bases were employed to prepare the starting hexopyranonucleosides. In accord with Baker's rule,[9] owing to 2-*O*-acetyl participation during the condensations, only the desired β (*trans*-1',2') anomers were obtained.

Thus, the method of Saneyoshi[10] was successful with adenine, while the β-D-1-*N* nucleosides of thymine and uracil were obtained by Vorbruggen procedures.[11] Removal of the acetyl sugar-protecting groups from compounds **2–4** with methanolic ammonia or sodium methoxide afforded the desired β-D-galactopyranosyl nucleosides **5–7** (Scheme 2).

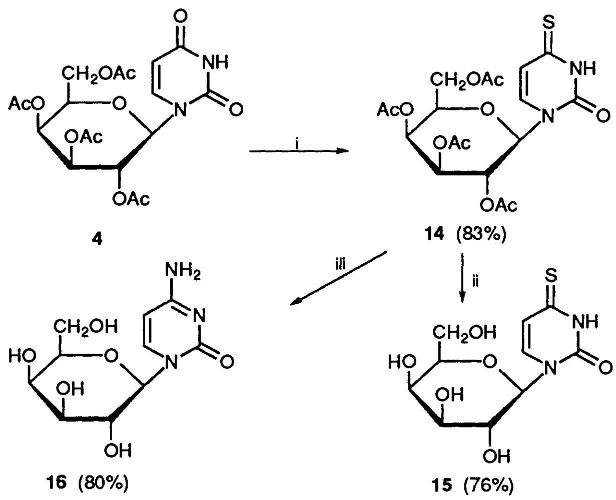
In the guanine series, the sugar **1** was condensed with silylated 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine **8** in anhydrous toluene in the presence of trimethylsilyl triflate (TMSTf) as catalyst, following a procedure previously used in the pentofuranosyl series.[12] After reaction, two compounds were



Scheme 3 *Reagents and conditions:* i, TMSTf, toluene; ii, NH_3, MeOH; iii, NH_4OH, MeOH

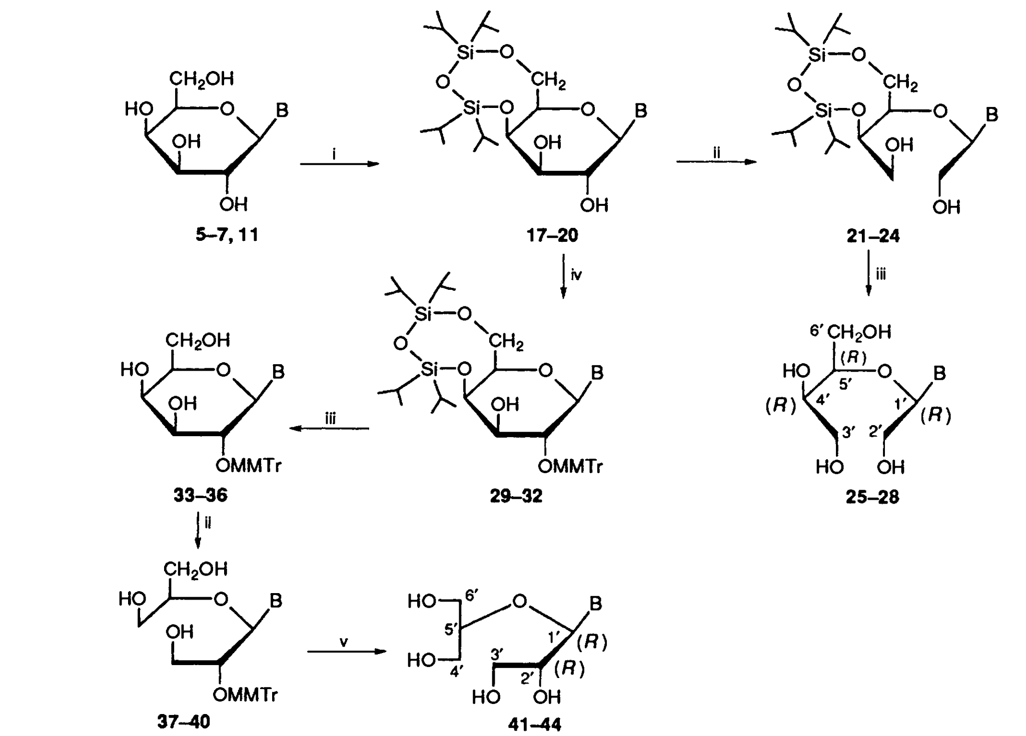
observed by TLC. The less polar compound was isolated by silica gel column chromatography and identified as the desired fully protected nucleoside **9** (35% yield). The other compound could not be isolated because it was transformed on the column into another derivative, which was characterized from its physical properties as the 9-β-D-nucleoside **10** (52% yield) of 2-*N*-(diphenylcarbamoyl)guanine (Scheme 3). This side-reaction seems peculiar to the pyranose series since under the same experimental conditions peracylated ribo- or xylo-furanose gave only the corresponding expected fully protected nucleosides (data not shown). Removal of the protecting groups from pentaacetyl compound **9** with methanolic ammonia afforded 9-β-D-galactopyranosylguanine **11**. On the other hand, treatment of tetraacetate **10** with an ammonium hydroxide–methanol mixture at 50 °C gave a separable mixture of the 2-*N*-diphenylcarbamoyl **12** and 2-*N*-carbamoyl **13** derivatives.

In the cytosine series, instead of condensing[8] the corresponding aglycone or its 4-*N*-benzoyl derivative with the sugar **1**, we preferred to introduce the amine functionality at C-4 of the uracil nucleoside **4** by activating that position and then displacing the activating group with ammonia. This conversion was not attempted by the triazole method of Sung[13] but by ammonolysis of the corresponding thioamide nucleoside **14**, which was prepared in good yield by treatment of the uracil derivative **4** with Lawesson's reagent[14–16] in refluxing dichloroethane, following an approach previously developed for the synthesis of 2′,3′-didehydro-2′,3′-dideoxycytidine[17] (Scheme 4). Compound **14** was treated either with methanolic sodium methoxide at room temperature or with methanolic ammonia at 100 °C to afford the deprotected thioamide **15** and 4-amino derivative **16**, respectively.



Scheme 4 *Reagents and conditions:* i, Lawesson's reagent, $ClCH_2CH_2Cl$; ii, MeONa, MeOH; iii, NH_3, MeOH, 100 °C

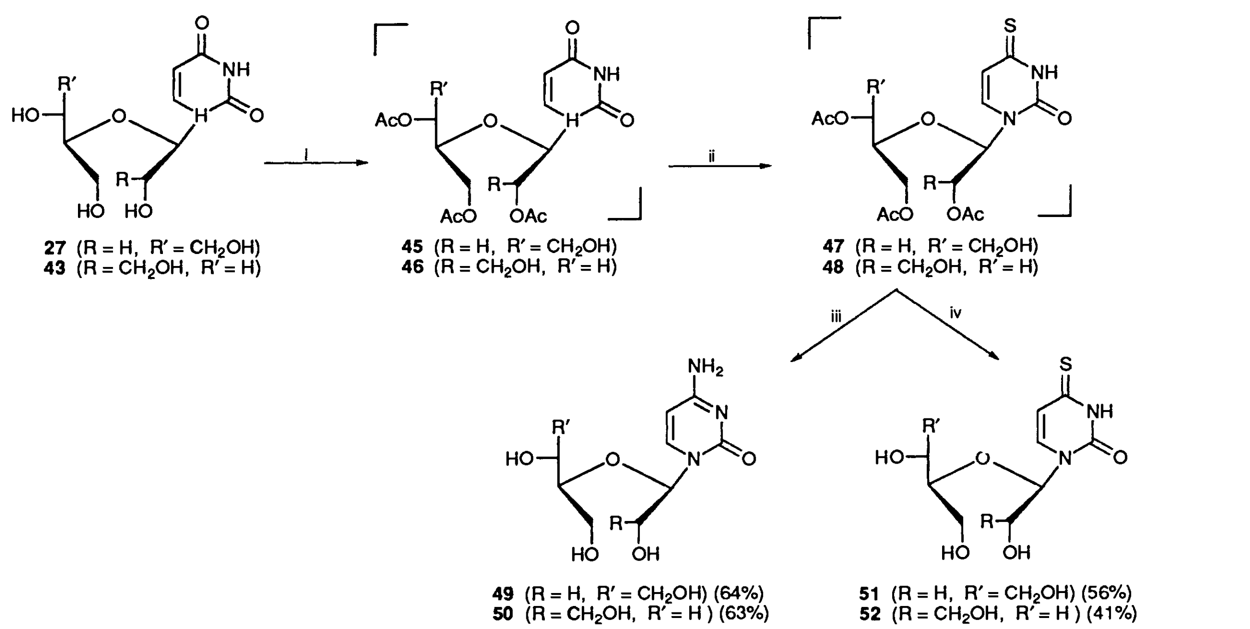
Treatment of the β-D-galactopyranosyl nucleosides **5–7** and **11** with Markiewicz's reagent[18] resulted in their 4′,6′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) derivatives **17–20** which are the key intermediates in our synthetic approach (Scheme 5). On the one hand, scission of their 2′,3′-bond by periodate oxidation[19,20] followed by sodium borohydride reduction of the intermediate dialdehyde resulted in the formation of compounds **21–24**, which were desilylated to give the hitherto unknown chiral (1′*R*,4′*R*,5′*R*) 2′,3′-seco derivatives **25–28** of the β-D-galactopyranosyl nucleosides. On the other hand, reaction of compounds **17–20** with monomethoxytrityl chloride (MMTrCl) gave the intermediates **29–32** with a free 3′-hydroxy function. Purification at this stage was not attempted and compounds **29–32** were directly desilylated to afford the 2′-*O*-monomethoxytritylated compounds **33–36**. When these latter compounds were treated with sodium metaperiodate and then with sodium borohydride, scission of the 3′,4′ bonds followed by reduction of the intermediate dialdehydes resulted in the formation of compounds **37–40**. On subsequent treatment with trifluoroacetic acid (TFA) in dichloromethane, the monomethoxytrityl groups were removed and the hitherto unknown



B = Base	Compound (Yield/%)
adenin-9-yl	**17** (70), **21**, **25** (57), **41** (68)
6-*N*-(4-methoxytrityl)-adenin-9-yl	**29**, **33** (31), **37**
thymin-1-yl	**18** (66), **22**, **26**, (49), **30**, **34** (49), **38**, **42** (62)
uracil-1-yl	**19** (69), **23**, **27** (49), **31**, **35** (50), **39**, **43** (59)
guanin-9-yl	**20** (63), **24**, **28** (46), **44** (34)
2-*N*-(4-methoxytrityl)-guanin-9-yl	**32**, **36** (31), **40**

Scheme 5 *Reagents and conditions:* i, $Pr^i_2Si(Cl)OSi(Cl)Pr^i_2$, pyridine; ii, $NaIO_4$, then $NaBH_4$, aq. 1,4-dioxane; iii, Bu_4NF, THF; iv, MMTrCl, pyridine; v, 2% TFA, CH_2Cl_2 *

* For convenience (mainly during the ^1H NMR spectrum interpretation) we adopted a 'pyranose-like' numbering of the acyclic nucleosides.



Scheme 6 *Reagents and conditions:* i, Ac_2O, pyridine; ii, Lawesson's reagent, $ClCH_2CH_2Cl$; iii, NH_3, MeOH 100 °C; iv, NH_3, MeOH, 25 °C

chiral acyclic nucleosides **41–44** were isolated in satisfactory yields after work-up and purification.

Finally, acetylation of compounds **27** and **43** and then conversion of the uracil moiety of the products **45** and **46** into thioamides **47** and **48** with Lawesson's reagent, followed by amination and deprotection with methanolic ammonia at 100 °C, afforded the desired acyclic cytosine nucleosides **49** and **50** (Scheme 6). When the intermediate compounds **47** and **48** were treated with methanolic ammonia at room temperature, the unprotected thioamide acyclic nucleosides **51** and **52** were obtained.

Structural assignments for the reported compounds are based on elemental analysis and on their physical properties.

Biological Evaluation.—All the prepared β-D-galactopyranosyl nucleosides **5–7**, **11–13** and **15** and **16** and chiral acyclic nucleosides **25–28**, **41–44** and **49–52** were tested for their *in vitro* inhibitory effects on the replication of a number of DNA viruses (*i.e.*, human cytomegalovirus, herpes simplex virus type 1 and type 2, vaccinia virus) and RNA viruses (parainfluenza virus type III, respiratory syncytial virus, Sindbis virus, Coxsackie virus B3 and polio virus-1) in three cell systems (MRC-5, Vero and KB cells). None of these compounds showed marked antiviral effects or detectable alteration of host-cell morphology at the highest concentration tested (generally 0.1 or 1 mmol dm^{-3}). When evaluated in two anti-human immunodeficiency virus (anti-HIV) assays, none of the tested compounds showed marked antiviral effect at a concentration less than 10-fold lower than the minimal concentration causing a detectable alteration of MT-4 or CEM host cell viability.

Experimental

Chemistry.—General procedures and instrumentation used are described in ref. 8.

9-(2,3,4,6-*Tetra-O-acetyl-β-D-galactopyranosyl)adenine* **2**.—This compound was prepared by treatment of adenine (10.10 g, 74.74 mmol) with the sugar **1** (30.10 g, 77.11 mmol) and tin(IV) chloride (18.05 cm^3, 153.62 mmol) in anhydrous acetonitrile (500 cm^3) as described for other adenine nucleoside analogue series,[21,22] except that the reaction mixture was heated under reflux for 2 h instead of being stirred overnight at room temperature. After the usual work-up, direct crystallization of the product from methanol afforded the title compound **2** (21.3 g, 61%) (Found: C, 49.3; H, 5.0; N, 15.0. Calc. for $C_{19}H_{23}N_5O_9$: C, 49.0; H, 5.0; N, 15.05%), m.p. 217–218 °C (lit.,[23] 212–213.5 °C); $[\alpha]_D^{20}$ +3.2 (*c* 1.0, Me_2SO) {lit.,[23] $[\alpha]_D^{24}$ +7.3 (*c* 2.6, $CHCl_3$)}; λ_{max}(water)/nm 258 (ε 15 900); λ_{min}/nm 224 (2500); δ_H 8.28 and 8.17 (1 H each, 2 s, 2- and 8-H), 7.32 (2 H, s, NH_2), 6.10 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 5.67 (1 H, t, *J* 9.5, 2'-H), 5.52 (1 H, dd, *J* 3.4 and 10.0, 3'-H), 5.40 (1 H, d, *J* 3.2, 4'-H), 4.61 (1 H, t, *J* 6.2, 5'-H), 4.15–3.95 (2 H, m, 6'-H_2), and 2.21, 1.96, 1.94 and 1.70 (3 H each, 4 s, 4 × OAc); *m/z* (FAB > 0, G-T) 466 $(M + H)^+$ and 136 $(BH_2)^+$.

1-(2,3,4,6-*Tetra-O-acetyl-β-D-galactopyranosyl)-thymine* **3** *and -uracil* **4**.—These compounds were prepared by treatment of thymine (9.60 g, 76.12 mmol) or uracil (8.51 g, 75.92 mmol) with the sugar **1** (30.00 g, 76.85 mmol), hexamethyldisilazane (HMDS) (12.67 cm^3, 60.76 mmol), chlorotrimethylsilane (TMSCl) (7.70 cm^3, 60.88 mmol) and tin(IV) chloride (10.70 cm^3, 91.06 mmol) as described for other thymine and uracil nucleoside analogue series.[21,22,24] After the usual work-up, the residues were directly crystallized to afford the title compounds **3** and **4**.

Compound **3** (25.6 g, 74%, after crystallization from water) (Found: C, 49.1; H, 5.4; N, 6.0. Calc. for $C_{19}H_{24}N_2O_{11}$·$0.5H_2O$: C, 49.0; H, 5.4; N, 6.0%), m.p. 186–188 °C (lit.,[25] 184–186 °C); $[\alpha]_D^{20}$ +7.0 (*c* 0.9, Me_2SO) {lit.,[25] $[\alpha]_D^{20}$ +4.9 (*c* 2.65, $CHCl_3$)}; λ_{max}(95% EtOH)/nm 260 (8700); λ_{min}/nm 230 (1100); δ_H 11.4 (1 H, br s, 3-H), 7.37 (1 H, s, 6-H), 5.99 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 5.45 (1 H, dd, *J* 3.4 and 9.9, 3'-H), 5.32 (1 H, d, *J* 3.4, 4'-H), 5.23 (1 H, t, *J* 9.6, 2'-H), 4.51 (1 H, t, *J* 6.2, 5'-H), 4.15–3.95 (2 H, m, 6'-H_2) and 2.19, 1.99, 1.94, 1.93 and 1.81 (3 H each, 5 s, 5-Me and 4 × OAc); *m/z* (FAB > 0, G-T) 457 $(M + H)^+$, 331 $(s)^+$ and 127 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 455 $(M - H)^-$ and 125 $(B)^-$.

Compound **4** (28.0 g, 83%, after crystallization from propan-2-ol) (Found: C, 48.5; H, 5.1; N, 6.0. Calc. for $C_{18}H_{22}N_2O_{11}$: C, 48.9; H, 5.0; N, 6.3%), m.p. 115–118 °C (lit.,[26] 167 °C; lit.,[27] 106–108 °C); $[\alpha]_D^{20}$ +25.0 (*c* 1.1, Me_2SO) {lit.,[26] $[\alpha]_D^{22}$ +32 (*c* 1, MeOH); lit.,[27] +30 (*c* 0.58, MeOH)}; λ_{max}(95% EtOH)/nm 257 (8800); λ_{min}/nm 225 (170); δ_H 11.5 (1 H, br s, 3-H), 7.56 (1 H, d, $J_{5,6}$ 8.1, 6-H), 6.02 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 5.72 (1 H, d, $J_{5,6}$ 8.1, 5-H), 5.46 (1 H, dd, *J* 3.4 and 10.1, 3'-H), 5.32 (1 H, d, *J* 3.2, 4'-H), 5.18 (1 H, t, *J* 9.5, 2'-H), 4.53 (1 H, t, *J* 6.2, 5'-H), 4.15–3.95 (2 H, m, 6'-H_2) and 2.16, 1.99, 1.95 and 1.93 (3 H each, 4 s, 4 × OAc); *m/z* (FAB > 0, G-T) 885 $(2M + H)^+$, 443 $(M + H)^+$, 331 $(s)^+$ and 113 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 883 $(2 M - H)^-$, 441 $(M - H)^-$ and 111 $(B)^-$.

9-(*β-D-Galactopyranosyl)adenine* **5**.—A solution of protected nucleoside **2** (5.00 g, 10.74 mmol) in methanolic ammonia (previously saturated at −10 °C and tightly stoppered; 100 cm^3) was stirred overnight at room temperature. The solution was evaporated to dryness under reduced pressure and the residue was co-evaporated under reduced pressure several times with methanol. Crystallization of the product from methanol afforded the title compound **5** (2.6 g, 81%) (Found: C, 39.9; H, 5.8; N, 20.8. Calc. for $C_{11}H_{15}N_5O_5$·$2H_2O$: C, 39.5; H, 5.75; N, 21.0%), m.p. 192–193 °C (lit.,[23] 198–200 °C; lit.,[28] 198–201 °C); $[\alpha]_D^{20}$ +22.5 (*c* 0.9, Me_2SO) {lit.,[23] $[\alpha]_D^{20}$ +95.5 (*c* 0.5, water); lit.,[28] +31.6 (*c* 0.6, water)}; λ_{max}(95% EtOH)/nm 260 (15 400); λ_{min}/nm 225 (2700); δ_H 8.25 and 8.13 (1 H each, 2 s, 2- and 8-H), 7.19 (2 H, s, NH_2), 5.37 (1 H, d, $J_{1',2'}$ 9.3, 1'-H), 5.17 (1 H, d, *J* 5.4, 2'-OH), 4.96 (1 H, d, *J* 5.4, 3'-OH), 4.63 (1 H, t, *J* 5.6, 6'-OH), 4.52 (1 H, d, *J* 5.7, 4'-OH), 4.20–4.15 (1 H, m; 4.16 ppm, t well resolved after D_2O exchange, 2'-H), 3.76 (1 H, m; d well resolved after D_2O exchange, 4'-H), 3.66 (1 H, t, *J* 6.0, 5'-H) and 3.55–3.44 (3 H, m, 3'-H and 6'-H_2); *m/z* (FAB > 0, G-T) 298 $(M + H)^+$ and 136 $(BH_2)^+$.

1-(*β-D-Galactopyranosyl)thymine* **6**.—This compound was synthesized from the protected nucleoside **3** (7.20 g, 15.78 mmol) with methanolic ammonia (160 cm^3) as described above for the synthesis of compound **5**. Crystallization of the product from water afforded the title compound **6** (3.62 g, 80%) (Found: C, 41.7; H, 6.0; N, 8.9. Calc. for $C_{11}H_{16}N_2O_7$·$\frac{5}{3}H_2O$: C, 41.5; H, 6.1; N, 8.6%), m.p. 146–148 °C (lit.,[25] amorph); $[\alpha]_D^{20}$ +49.0 (*c* 1.0, Me_2SO) {lit.,[25] $[\alpha]_D^{25}$ +47.2 (*c* 1.0, water); lit.,[29] $[\alpha]_D$ + 46.1 (*c* 0.74, MeOH)}; λ_{max}(water)/nm 264 (9400); λ_{min}/nm 233 (2400); δ_H 11.2 (1 H, br s, 3-H), 7.47 (1 H, s, 6-H), 5.29 (1 H, d, $J_{1',2'}$ 9.1, 1'-H), 5.1, 4.9, 4.6 and 4.4 (1 H each, 4 br s, 4 × OH), 3.7–3.6 (2 H, m; 3.70 ppm, 1 H, d, *J* 2.9, 4'-H and 3.65 ppm, 1 H, t, *J* 9.3, 2'-H after D_2O exchange), 3.6–3.4 (4 H, m, 3'-, 5'-H and 6'-H_2) and 1.76 (3 H, s, Me); *m/z* (FAB > 0, G-T) 289 $(M + H)^+$ and 127 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 575 $(2 M - H)^-$, 287 $(M - H)^-$ and 125 $(B)^-$.

1-(*β-D-Galactopyranosyl)uracil* **7**.—The protected nucleoside **4** (12.00 g, 27.13 mmol) was dissolved in a freshly prepared, stirred methanolic solution of 0.3 mol dm^{-3} sodium methoxide (600 cm^3), and the reaction mixture was stirred for 2 h at room temperature. Water (300 cm^3) was added and the solution was neutralized to pH 6–7 (pH paper) by the addition of Dowex 50

Wx2 (pyridinium form) ion-exchange resin. The resin was filtered off and washed successively with warm MeOH and water, and the combined filtrates were evaporated to dryness. Crystallization of the product from methanol afforded the title compound **7** (6.28 g, 84%) (Found: C, 43.7; H, 5.0; N, 10.1. Calc. for $C_{10}H_{14}N_2O_7$: C, 43.8; H, 5.15; N, 10.2%), m.p. 234–235 °C (lit.,[30] 250–251 °C; lit.,[27] 234 °C); $[\alpha]_D^{20}$ +20.7 (*c* 0.8, Me_2SO); λ_{max}(water)/nm 259 (8700); λ_{min}/nm 229 (2300); δ_H 11.4 (1 H, br s, 3-H), 7.61 (1 H, d, $J_{5,6}$ 8.1, 6-H), 5.67 (1 H, d, 5-H), 5.30 (1 H, d, $J_{1',2'}$ 9.1, 1'-H), 5.24 (1 H, d, *J* 5.2, 2'-OH), 4.95 (1 H, br s, 3'-OH), 4.67 (1 H, t, *J* 5.5, 6'-OH), 4.52 (1 H, d, *J* 6.5, 4'-OH), 3.70–3.60 (2 H, m; 3.68 ppm, 1 H, d, *J* 3.1, 4'-H and 3.63 ppm, 1 H, t, *J* 9.3, 2'-H after D_2O exchange) and 3.6–3.4 (4 H, m, 3'-, 5'-H and 6'-H_2); *m/z* (FAB > 0, G-T) 275 $(M + H)^+$ and 113 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 273 $(M - H)^-$ and 111 $(B)^-$.

2-N-*Acetyl*-6-O-*diphenylcarbamoyl*-9-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*galactopyranosyl*)*guanine* **9** *and* 2-N-*Diphenylcarbamoyl*-9-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*galactopyranosyl*)*guanine* **10**.—A suspension of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine[12] (9.00 g, 23.17 mmol) in 1,2-dichloroethane (1790 cm^3) containing *N,O*-bis(trimethylsilyl)acetamide (8.66 cm^3, 35.04 mmol) was stirred at 80 °C for 15 min. After cooling, the resulting clear solution was evaporated to dryness to give the silylated base **8**, which was dissolved in dry toluene (100 cm^3). Trimethylsilyl trifluoromethanesulfonate (TMSTf) (5.71 cm^3, 31.47 mmol) and the sugar **1** (10.77 g, 27.59 mmol) in dry toluene (70 cm^3) was added and the solution was stirred at 80 °C for 1 h, then cooled to room temperature. After dilution with ethyl acetate (900 cm^3), the solution was poured into ice-cold saturated aq. sodium hydrogen carbonate (500 cm^3). The organic phase was separated, thrice washed with water (500 cm^3), dried over sodium sulfate, filtered, and evaporated to dryness. Column chromatography of the residue on silica gel with a stepwise gradient of methanol (0–5%) in dichloromethane led to the isolation of the *title compounds* **9** and **10**.

Compound **9** (5.82 g, 35%), m.p. 142–145 °C (after lyophilization from 1,4-dioxane) (Found: C, 56.8; H, 4.75; N, 11.35. $C_{34}H_{34}N_6O_{12}$ requires C, 56.8; H, 4.8; N, 11.7%); $[\alpha]_D^{20}$ −3.2 (*c* 0.9, Me_2SO); λ_{max}(95% EtOH)/nm 277 (14 900), 250sh (20 800) and 223 (33 300); λ_{min}/nm 268 (14 200); δ_H 10.64 (1 H, s, 2-NH), 8.59 (1 H, s, 8-H), 7.5–7.3 (10 H, m, 2 × Ph), 6.07 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 5.77 (1 H, t, *J* 9.4, 2'-H), 5.53 (1 H, dd, *J* 3.4 and 10.1, 3'-H), 5.41 (1 H, d, *J* 3.4, 4'-H), 4.60 (1 H, t, *J* 6.3, 5'-H), 4.15–3.95 (2 H, m, 6'-H_2) and 2.31, 2.21, 1.96, 1.95 and 1.74 (3 H each, 5 s, 4 × OAc and 1 × NAc); *m/z* (FAB > 0, G-T) 719 $(M + H)^+$, 389 $(BH_2)^+$, 331 $(s)^+$ and 196 $(Ph_2N–C{\equiv}O)^+$; *m/z* (FAB < 0, G-T) 717 $(M - H)^-$ and 387 $(B)^-$.

Compound **10** (8.22 g, 52%), m.p. 144–147 °C (crystallized from 95% EtOH) (Found: C, 55.5; H, 5.1; N, 11.6. $C_{32}H_{32}N_6O_{11}\cdot 1H_2O$ requires C, 55.3; H, 4.9; N, 12.1%); $[\alpha]_D^{20}$ +18.0 (*c* 1.0, Me_2SO); λ_{max}(95% EtOH)/nm 280 (17 100), 260sh (18 900) and 251 (19 500); λ_{min}/nm 269 (16 200) and 228 (11 200); δ_H 12.0 and 9.4 (1 H, each, 2 br s, 1-H and 2-NH), 8.09 (1 H, s, 8-H), 7.45–7.25 (10 H, m, 2 × Ph), 5.79 (1 H, d, $J_{1',2'}$ 9.1, 1'-H), 5.52 (1 H, t, *J* 9.6, 2'-H), 5.42 (1 H, dd, *J* 9.9 and 3.2, 3'-H), 5.34 (1 H, d, $J_{3',4'}$ 3.0, 4'-H), 4.48 (1 H, t, *J* 6.2, 5'-H), 4.10–3.95 (2 H, m, 6'-H_2) and 2.14, 1.96, 1.93 and 1.78 (3 H each, 4 s, 4 × OAc); *m/z* (FAB > 0, G-T) 677 $(M + H)^+$, 347 $(BH_2)^+$, 331 $(s)^+$ and 196 $(Ph_2N–C{\equiv}O)^+$; *m/z* (FAB < 0, G-T) 675 $(M - H)^-$ and 345 $(B)^-$.

9-(β-D-*Galactopyranosyl*)*guanine* **11**.—A solution of the protected nucleoside **9** (5.60 g, 7.79 mmol) in methanolic ammonia (80 cm^3) was stirred overnight at room temperature. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in water. The solution was thrice washed with dichloromethane, and evaporated to dryness. Crystallization of the product from water afforded the *title compound* **11** (2.07 g, 85%), m.p. 222–224 °C (Found: C, 38.8; H, 5.4; N, 20.4. $C_{11}H_{15}N_5O_6\cdot\frac{3}{2}H_2O$ requires C, 38.8; H, 5.3; N, 20.6%); $[\alpha]_D^{20}$ +26.3 (*c* 0.95, Me_2SO); λ_{max}(water)/nm 274sh (9700) and 253 (13 400); λ_{min}/nm 223 (3900); δ_H 9.5 (1 H br s, 1-H), 7.78 (1 H, s, 8-H), 6.48 (2 H, s, NH_2), 5.2, 4.9, 4.7 and 4.5 (1 H each, 4 br s, 4 × OH), 5.11 (1 H, d, $J_{1',2'}$ 9.3, 1'-H), 4.00 (1 H, t, 2'-H), 3.73 (1 H, m, 4'-H) and 3.60–3.40 (4 H, m, 3'-, 5'-H and 6'-H_2); *m/z* (FAB > 0, G-T) 314 $(M + H)^+$ and 152 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 312 $(M - H)^-$ and 150 $(B)^-$.

2-N-*Diphenylcarbamoyl*-9-(β-D-*galactopyranosyl*)*guanine* **12** *and* 2-N-*Carbamoyl*-9-(β-D-*galactopyranosyl*)*guanine* **13**.—A solution of the nucleoside **10** (0.30 g, 0.44 mmol) in an ammonium hydroxide (20% in water)–methanol mixture (4:1; 60 cm^3) was heated at 50 °C for 16 h in a sealed stainless steel bomb. The reaction mixture was cooled and evaporated to dryness. Column chromatography of the residue on silanized silica gel RP2 with a linear gradient of methanol (0–100%) in water led to the isolation of the *title compounds* **13** and **12**.

Compound **12** (0.14 g, 63%), m.p. 248–250 °C (from water) (Found: C, 52.6; H, 5.1; N, 16.0 $C_{24}H_{24}N_6O_7\cdot 2H_2O$ requires C, 52.9; H, 5.2; N, 15.4%); $[\alpha]_D^{20}$ +19.1 (*c* 0.9, Me_2SO); λ_{max}(water)/nm 278sh (17 800) and 259 (20 100); λ_{min}/nm 226 (9700); δ_H 12.0 and 9.8 (1 H each, 2 br s, 1-H and 2-NH), 8.04 (1 H, s, 8-H), 7.90–7.30 (10 H, m, 2 × Ph), 5.25 (1 H, d, *J* 5.3, 2'-OH), 5.16 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 4.92 (1 H, d, *J* 5.2, 3'-OH), 4.63 (1 H, t, *J* 5.0, 6'-OH), 4.50 (1 H, d, *J* 6.2, 4'-OH), 4.00 (1 H, m, 2'-H), 3.71 (1 H, m, 4'-H), 3.55–3.45 (4 H, m, 3'-, 5'-H and 6'-H_2); *m/z* (FAB > 0, G-T) 509 $(M + H)^+$ and 347 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 507 $(M - H)^-$.

Compound **13** (52 mg, 33%), m.p. 279–282 °C (from water) (Found: C, 38.8; H, 4.7; N, 22.1. $C_{12}H_{16}N_6O_7\cdot H_2O$ requires C, 38.5; H, 4.85; N, 22.45%); $[\alpha]_D^{20}$ +15.6 (*c* 0.9, Me_2SO); λ_{max}(water)/nm 278sh (8500) and 256 (14 200); λ_{min}/nm 224 (1300); δ_H 11.9 and 10.0 (1 H each, 2 br s, 1-H and 2-NH), 8.00 (1 H, s, 8-H), 7.2–6.4 (2 H, br s, NH_2), 5.24 (1 H, d, *J* 5.1, 2'-OH), 5.16 (1 H, d, $J_{1',2'}$ 9.3, 1'-H), 4.9 (1 H, br s, 3'-OH), 4.66 (1 H, t, *J* 5.4, 6'-OH), 4.51 (1 H, d, *J* 4.8, 4'-OH), 4.15–4.05 (1 H, m; 4.08 ppm, t well resolved after D_2O exchange, *J* 9.3, 2'-H), 3.76 (1 H, br s; d well resolved after D_2O exchange, *J* 2.8, 4'-H), 3.59 (1 H, t, *J* 5.8, 5'-H) and 3.55–3.40 (3 H, m, 3'-H and 6'-H_2).

1-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*galactopyranosyl*)-4-*thiouracil* **14**.—To a solution of the protected nucleoside **4** (1.00 g, 2.26 mmol) in anhydrous 1,2-dichloroethane (15 cm^3) was added Lawesson's reagent (Aldrich, Art. 22, 743-9) (0.54 g, 1.34 mmol). The reaction mixture was refluxed for 1 h under argon, then evaporated to dryness. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (0–2%) in dichloromethane] to afford the *title compound* **14** (0.86 g, 83%) which was crystallized from propan-2-ol; m.p. 186–187 °C (Found: C, 46.9; H, 4.9; N, 6.0; S, 6.6. $C_{18}H_{22}N_2O_{10}S$ requires C, 47.2; H, 4.8; N, 6.1; S, 7.0%); $[\alpha]_D^{20}$ +35.5 (*c* 0.9, Me_2SO); λ_{max}(95% EtOH)/nm 324 (22 500) and 245 (7600); λ_{min}/nm 272 (5700) and 228 (6300); δ_H 12.85 (1 H, s, 3-H), 7.49 (1 H, d, $J_{5,6}$ 7.6, 6-H), 6.38 (1 H, d, *J* 7.6, 5-H), 6.03 (1 H, d, *J* 9.1, 1'-H), 5.48 (1 H, dd, *J* 10.0 and 3.3, 3'-H), 5.32 (1 H, d, *J* 3.3, 4'-H), 5.19 (1 H, t, *J* 9.5, 2'-H), 4.55 (1 H, t, *J* 6.2, 5'-H), 4.15–3.95 (2 H, m, 6'-H_2) and 2.17, 1.99, 1.96 and 1.94 (3 H each, 4 s, 4 × OAc); *m/z* (FAB > 0, G-T) 459 $(M + H)^+$, 331 $(s)^+$ and 129 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 457 $(M - H)^-$ and 127 $(B)^-$.

1-(β-D-*Galactopyranosyl*)-4-*thiouracil* **15**.—This compound was synthesized from the protected nucleoside **14** (0.40 g, 0.87

mmol) with methanolic 0.2 mol dm^{-3} sodium methoxide (15 cm^3) as described above for the synthesis of the compound **7**. Crystallization of the product from ethanol afforded the title compound **15** (0.19 g, 75%), m.p. 141 °C (start of decomposition); $[\alpha]_D^{20}$ −21.5 (*c* 0.9, Me_2SO); λ_{max}(water)/nm 326 (17 800) and 242 (3400); λ_{min}/nm 275 (1800) and 224 (2700); δ_H 12.9 (1 H, br s, 3-H), 7.22 (1 H, d, *J* 7.4, 6-H), 6.21 (1 H, d, *J* 7.4, 5-H), 5.33 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 6.0–4.0 (4 H, br s, 4 OH), 3.75–3.55 (2 H, m; 3.69 ppm, 1 H, d, *J* 2.8, 4'-H and 3.63 ppm, 1 H, t, *J* 9.2, 2'-H after D_2O exchange) and 3.5–3.35 (4 H, m, 3'-, 5'-H and 6'-H_2); *m/z* (FAB > 0, G-T) 291 (M + H)$^+$ and 129 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 289 (M − H)$^-$ and 127 (B)$^-$.

1-(β-D-*Galactopyranosyl*)*cytosine* **16**.—A solution of the nucleoside **14** (0.40 g, 0.87 mmol) in methanolic ammonia (previously saturated at −10 °C; 5 cm^3) was heated at 100 °C for 2 h in a sealed stainless steel bomb. The reaction mixture was cooled and evaporated to dryness. Column chromatography of the residue on Dowex 1 × 2 (OH$^-$) ion-exchange resin[31] (Fluka, Art. 44300) with a linear gradient of methanol (0–100%) in water led to the isolation of the *title compound* **16** (0.22 g, 92%), which was crystallized from propan-2-ol; m.p. 173–175 °C (Found: C, 41.05; H, 5.8; N, 14.25. $C_{10}H_{15}N_3O_6{\cdot}H_2O$ requires C, 41.2; H, 5.9; N, 14.4%); $[\alpha]_D^{20}$ +52.4 (*c* 1.1, Me_2SO); λ_{max}(water)/nm 267 (8500) and 234 (8100); λ_{min}/nm 251 (7200) and 224 (7800); δ_H 7.51 (1 H, d, *J* 7.4, 6-H), 7.2–7.0 (2 H, br s, NH_2), 5.72 (1 H, d, *J* 7.4, 5-H), 5.42 (1 H, d, *J* 9.2, 1'-H), 5.00 (1 H, d, *J* 5.6, 2'-OH), 4.89 (1 H, d, *J* 5.4, 3'-OH), 4.63 (1 H, t, *J* 5.0, 6'-OH), 4.48 (1 H, d, *J* 5.9, 4'-OH), 3.70–3.55 (2 H, m; 3.69 ppm, 1 H, d, *J* 3.0, 4'-H and 3.62 ppm, 1 H, t, *J* 9.3, 2'-H after D_2O exchange) and 3.50–3.40 (4 H, m, 3'-, 5'-H and 6'-H_2); *m/z* (FAB > 0, G-T) 274 (M + H)$^+$ and 112 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 272 (M − H)$^-$.

General Procedure for the Preparation of 4',6'-O-(1,1,3,3-*Tetraisopropyldisiloxane*-1,3-*diyl*)-β-D-*galactopyranosyl Nucleosides* **17–20**.—To a stirred solution of dried β-D-galactopyranosyl nucleoside **5** (1.00 g, 3.36 mmol), **6** (0.70 g, 2.43 mmol), **7** (5.00 g, 18.23 mmol) or **11** (2.22 g, 7.09 mmol) in a pyridine–dimethylformamide (DMF) mixture (8:2, v/v; 10 cm^3/mmol) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.2 mol equiv.). The reaction mixtures were stirred for 16 h at room temperature, and were then poured into saturated aq. sodium hydrogen carbonate. The organic layers were separated, washed with water, dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure, and the residues were co-evaporated under reduced pressure several times with toluene to give an oil. The *title compounds* were purified by either silica gel column chromatography or direct crystallization.

9-[4,6-O-(1,1,3,3-*Tetraisopropyldisiloxane*-1,3-*diyl*)-β-D-*galactopyranosyl*]*adenine* **17** (1.27 g, 70%, after direct crystallization from a methanol–dichloromethane mixture), m.p. 274–276 °C (Found: C, 51.5; H, 7.8; N, 12.8. $C_{23}H_{41}N_5O_6Si_2$ requires C, 51.2; H, 7.7; N, 13.0%); $[\alpha]_D^{20}$ −23.6 (*c* 0.9, Me_2SO); λ_{max}(95% EtOH)/nm 259 (15 200); λ_{min}/nm 227 (2900); δ_H 8.11 and 8.01 (1 H each, 2 s, 2- and 8-H), 7.22 (2 H, s, NH_2), 5.45 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 5.28 (1 H, d, *J* 5.7, 2'-OH), 5.21 (1 H, d, *J* 4.7, 3'-OH), 4.30–4.24 (1 H, m, 2'-H; t well resolved after D_2O exchange), 4.14 (1 H, d, *J* 2.1, 4'-H), 3.92–3.88 (1 H, m, 5'-H), 3.7–3.6 (3 H, m, 3'-H and 6'-H_2) and 1.2–0.9 (28 H, m, 4 × Pr^i); *m/z* (FAB > 0, G-T) 540 (M + H)$^+$ and 135 $(BH_2)^+$.

1-[4,6-O-(1,1,3,3-*Tetraisopropyldisiloxane*-1,3-*diyl*)-β-D-*galactopyranosyl*]*thymine* **18** {0.85 g, 66%, after chromatography [eluent: stepwise gradient of methanol (0–10%) in dichloromethane], and then lyophilization from a 1,4-dioxane–water mixture}, m.p. 136–138 °C (Found: C, 51.8; H, 8.2; N, 5.2. $C_{23}H_{42}N_2O_8Si_2{\cdot}0.25H_2O$ requires C, 51.6; H, 8.0; N, 5.2%); $[\alpha]_D^{20}$ +20.3 (*c* 1.1, Me_2SO); λ_{max}(95% EtOH)/nm 263 (8900); λ_{min}/nm 230 (2300); δ_H 11.27 (1 H, s, 3-H), 7.07 (1 H, s, 6-H), 5.41 (1 H, d, $J_{1',2'}$ 8.6, 1'-H), 5.26 (1 H, d, *J* 4.1, 2'-OH), 5.14 (1 H, d, *J* 4.1, 3'-OH), 4.07 (1 H, d, *J* 1.9, 4'- or 5'-H), 3.82 (1 H, dd, *J* 5.4 and 9.9, 5'- or 4'-H), 3.7–3.55 (4 H, m, 2'-, 3'-H and 6'-H_2), 1.75 (3 H, s, Me) and 1.1–0.9 (28 H, m, 4 × Pr^i); *m/z* (FAB > 0, G-T) 531 (M + H)$^+$; *m/z* (FAB < 0, G-T) 529 (M − H)$^-$ and 125 (B)$^-$.

1-[4,6-O-(1,1,3,3-*Tetraisopropyldisiloxane*-1,3-*diyl*)-β-D-*galactopyranosyl*]*uracil* **19**.—{6.46 g, 69% after chromatography [eluent: stepwise gradient of methanol (0–5%) in dichloromethane], and then crystallization from dichloromethane}, m.p. 175–176 °C (Found: C, 51.2; H, 7.7; N, 5.4. $C_{22}H_{40}N_2O_8Si_2$ requires C, 51.1; H, 7.8; N, 5.4%); $[\alpha]_D^{20}$ +38.0 (*c* 1.0, Me_2SO); λ_{max}(95% EtOH)/nm 258 (10 000); λ_{min}/nm 228 (2200); δ_H 11.33 (1 H, s, 3-H), 7.21 (1 H, d, $J_{5,6}$ 8.0, 6-H), 5.72 (1 H, d, *J* 8.1, 5-H), 5.41 (1 H, d, $J_{1',2'}$ 8.3, 1'-H), 5.36 (1 H, d, *J* 4.6, 3'-OH), 5.21 (1 H, d, *J* 4.2, 2'-OH), 4.06 (1 H, d, *J* 0.9, 4'-H), 3.82 (1 H, dd, *J* 10.1 and 5.4, 5'-H), 3.7–3.55 (4 H, m, 2'-, 3'-H and 6'-H_2) and 1.1–0.95 (28 H, m, 4 × Pr^i); *m/z* (FAB > 0, G-T) 517 (M + H)$^+$; *m/z* (FAB < 0, G-T), 515 (M − H)$^-$ and 111 (B)$^-$.

9-[4,6-O-(1,1,3,3-*Tetraisopropyldisiloxane*-1,3-*diyl*)-β-D-*galactopyranosyl*]*guanine* **20**.—(2.5 g, 63%, after direct crystallization from a methanol–dichloromethane mixture), m.p. 280 °C (start of decomposition) (Found: C, 49.6; H, 7.2; Si, 10.5. $C_{23}H_{41}N_5O_7Si_2$ requires C, 49.7; H, 7.4; Si, 10.1%); $[\alpha]_D^{20}$ +5.8 (*c* 0.6, Me_2SO); λ_{max}(95% EtOH)/nm 271sh (12 800) and 256 (14 100); δ_H 11.0 (1 H, br s, 1-H), 7.50 (1 H, s, 8-H), 6.61 (2 H, s, NH_2), 5.4 (2 H, br s, 2'- and 3'-OH), 5.21 (1 H, d, $J_{1',2'}$ 9.3, 1'-H), 4.13 (1 H, s, 4'- or 5'-H), 4.01 (1 H, t, *J* 9.4, 2'-H), 3.85–3.75 (2 H, m, 5'- or 4'-and 6'-H), 3.70–3.60 (2 H, m, 3'- and 6'-H) and 1.1–0.8 (28 H, m, 4 × Pr^i); *m/z* (FAB > 0; G-T) 556 (M + H)$^+$ and 152 $(BH_2)^+$; *m/z* (FAB < 0, G-T) 554 (M − H)$^-$.

General Procedure for the Preparation of 9- *and* 1-{(1R)-1-[(1R,2R)-2,3-*Dihydroxy*-1-(*hydroxymethyl*)*propoxy*]-2-*hydroxyethyl*}-*purines and -pyrimidines* **25–28**.—To a solution of one of the foregoing silylated nucleosides **17** (0.50 g, 0.93 mmol), **18** (0.16 g, 0.30 mmol), **19** (3.00 g, 5.81 mmol) or **20** (0.50 g, 0.90 mmol) in a 1,4-dioxane–water mixture (8:2; 20 cm^3 by mmol) was added sodium metaperiodate (1.2 mol equiv.). The reaction mixtures were stirred for 6 days at room temperature, filtered, and the insoluble sodium iodate was washed with 1,4-dioxane. The combined filtrates and washings were concentrated to the initial volumes, and sodium borohydride (2.2 mol equiv.) was added in portions. The solutions were stirred for 1 h at room temperature after the additions were complete, then were neutralized to pH 7 (pH paper) by careful addition of acetic acid, and evaporated to dryness under reduced pressure. The residues **21–24** were dissolved in stirred dry tetrahydrofuran (THF) (15 cm^3/mmol) and a 1.1 mol dm^{-3} solution of tetrabutylammonium fluoride (2 mol equiv.) in THF was added. The solutions were stirred overnight at room temperature, then poured into chloroform, and extracted with water. The aqueous layers were combined, evaporated to dryness, and co-evaporated three times with absolute ethanol. The title compounds were purified by chromatography, and then lyophilized.

9-{(1*R*)-1-[(1*R*,2*R*)-2,3-Dihydroxy-1-(hydroxymethyl)propoxy]-2-hydroxyethyl}adenine **25** {0.16 g, 57%, after purification by Dowex 1 × 2 (OH$^-$) ion-exchange resin column chromatography [eluent: linear gradient of methanol (0–100%) in water], and then lyophilization from water}, m.p. 168–170 °C (hygroscopic); $[\alpha]_D^{20}$ +40.3 (*c* 0.7, Me_2SO); λ_{max}(95% EtOH)/nm

260 (14 300); λ_{min}/nm 228 (4400); δ_H 8.22 and 8.12 (1 H each, 2 s, 2- and 8-H), 7.16 (2 H, s, NH_2), 5.84 (1 H, t, *J* 5.7, 1'-H), 5.3, 4.8 and 4.5 (1, 2 and 1 H, respectively, 3 br s, 4 × OH), 3.9–3.8 (2 H, m, 2'-H_2), 3.60 (1 H, m, 4'-H), 3.55–3.50 (2 H, m, 3'-H_2), 3.40 (1 H, m, 5'-H) and 3.3–3.0 (2 H, m, 6'-H_2); *m*/*z* (FAB > 0, G-T) 300 $(M + H)^+$, 165 $(s)^+$ and 136 $(BH_2)^+$.

1-{(1*R*)-1-[(1*R*,2*R*)-2,3-Dihydroxy-1-(hydroxymethyl)propoxy]-2-hydroxyethyl}thymine **26** {0.043 g, 49%, after purification by silica gel column chromatography [eluent: stepwise gradient of methanol (0–15%) in dichloromethane], and then lyophilization from water}, m.p. 140–150 °C (hygroscopic); $[\alpha]_D^{20}$ +42.0 (*c* 1.0, Me_2SO); λ_{max}(95% EtOH)/nm 265 (8500); λ_{min}/nm 228 (2100); δ_H 11.14 (1 H, s, 3-H), 7.46 (1 H, s, 6-H), 5.74 (1 H, t, *J* 5.7, 1'-H), 5.07 (1 H, t, *J* 5.9, 2'-OH), 4.57 (2 H, m, 4'- and 3'- or 6'-OH), 4.50 (1 H, t, *J* 5.2, 6'- or 3'-OH), 3.65–3.20 (8 H, m, 2'-, 3'- and 6'-H_2 and 4'- and 5'-H) and 1.76 (3 H, s, Me); *m*/*z* (FAB > 0, G-T) 291 $(M + H)^+$ and 127 $(BH_2)^+$; *m*/*z* (FAB < 0, G-T) 579 $(2 M - H)^-$ and 125 $(B)^-$.

1-{(1*R*)-1-[(1*R*,2*R*)-2,3-Dihydroxy-1-(hydroxymethyl)propoxy]-2-hydroxyethyl}uracil **27** {0.78 g, 49%, after purification by Dowex 1 × 2 (OH^-) ion-exchange resin column chromatography [eluent: linear gradient of NH_4HCO_3 (0–0.5 mol dm^{-3}) in water], and then lyophilization from water}, m.p. 190–193 °C (hygroscopic); $[\alpha]_D^{20}$ +39.0 (*c* 1.0, Me_2SO); λ_{max}(95% EtOH)/nm 256 (10 100); λ_{min}/nm 228 (2100); δ_H 12.1 (1 H, br s, 3-H), 7.58 (1 H, d, *J* 7.9, 6-H), 5.70 (1 H, t, *J* 5.6, 1'-H), 5.59 (1 H, d, 5-H), 5.2–4.4 (4 H, br s, 4-OH) and 3.7–3.2 (8 H, m, 2'-, 3'- and 6'-H_2 and 4'- and 5'-H); *m*/*z* (FAB < 0, NBA) 275 $(M - H)^-$ and 111 $(B)^-$.

9-{(1*R*)-1-[(1*R*,2*R*)-2,3-Dihydroxy-1-(hydroxymethyl)propoxy]-2-hydroxyethyl}guanine **28** {0.13 g, 46% after purification first by Dowex 1 × 2 (OH^-) ion-exchange resin column chromatography [eluent: linear gradient of methanol (0–100%) in water, followed by a linear gradient of NH_4HCO_3 (0.1–0.4 mol dm^{-3}) in water], then by RP-2 silanized silica gel column chromatography [eluent: linear gradient of methanol (0–100%) in water], and then lyophilization from water}, m.p. 174–177 °C (hygroscopic); $[\alpha]_D^{20}$ +18.8 (*c* 0.9, Me_2SO); λ_{max}(water)/nm 273 sh (10 400) and 253 (14 000); λ_{min}/nm 223 (3200); δ_H 11.0 (1 H, br s, 1-H), 7.71 (1 H, s, 8-H), 6.67 (2 H, s, NH_2), 5.58 (1 H, t, *J* 5.7, 1'-H), 5.3–4.3 (4 H, br s, 4 × OH), 3.85–3.70 (2 H, m, 2'-H_2), 3.65–3.55 (1 H, m, 4'-H), 3.50–3.40 (3 H, m, 5'-H and 3'-H_2) and 3.35–3.05 (2 H, m, 6'-H_2); *m*/*z* (FAB > 0, G-T) 316 $(M + H)^+$ and 152 $(BH_2)^+$; *m*/*z* (FAB < 0, G-T), 314 $(M - H)^-$ and 150 $(B)^-$.

General Procedure for the Preparation of 9- *and* 1-[2-O-(4-*Monomethoxytrityl*)-β-D-*galactopyranosyl*]-*purines and -pyrimidines* **33**–**36**.—To a stirred solution of a silylated nucleoside **17** (0.43 g, 0.80 mmol), **18** (0.60 g, 1.13 mmol), **19** (3.00 g, 5.81 mmol) or **20** (1.00 g, 1.80 mmol) in dry pyridine (10 cm^3/mmol) at room temperature was added over a period of five days chloro-(4-methoxyphenyl)diphenylmethane (4-monomethoxytrityl chloride, MMTrCl) (10 mol equiv.). After the mixtures were cooled, they were quenched with methanol, and then evaporated to dryness under reduced pressure. Dichloromethane and water were added and the organic layers were separated, then washed successively with saturated aq. sodium hydrogen carbonate and water, dried over sodium sulfate, filtered and evaporated to dryness. The residues **29**–**32** were co-evaporated under reduced pressure several times with toluene, then were dissolved in stirred THF (10 cm^3/mmol), and a 1.1 mol dm^{-3} solution of Bu_4NF (2 mol equiv.) in THF was added. The solutions were stirred overnight at room temperature, evaporated to dryness under reduced pressure, and dichloromethane and water were added. The organic layers were separated, thrice washed with water, dried over sodium sulfate, filtered and evaporated to dryness. The *title compounds* were purified by silica gel column chromatography, and then lyophilized.

6-N-(4-*Methoxytrityl*)-9-[2-O-(4-*methoxytrityl*)-β-D-*galactopyranosyl*]*adenine* **33** {0.21 g, 31%, after chromatography [eluent: stepwise gradient of methanol (0–4%) in dichloromethane], and then lyophilization from a 1,4-dioxane–water mixture}, m.p. 170–172 °C (Found: C, 71.6; H, 5.7; N, 8.1. $C_{51}H_{47}N_5O_7 \cdot H_2O$ requires C, 71.2; H, 5.7; N, 8.15%); $[\alpha]_D^{20}$ +18.3 (*c* 1.0, Me_2SO); λ_{max}(95% EtOH)/nm 275 (19 900); λ_{min}/nm 250 (10 200); δ_H 7.61 (1 H, br s, 6-NH), 7.3–6.6 (30 H, m, 2- and 8-H and 28 × ArH), 5.86 (1 H, d, $J_{1',2'}$ 9.0, 1'-H), 4.62 (1 H, t, *J* 5.6, 6'-OH), 4.26 (1 H, br s, 3'- or 4'-OH), 3.9 (1 H, m, 3'- or 4'-H), 3.8 (1 H, m, 2'-H), 3.7 [7 H, m, 5'-H and 2 × OMe (2 s 3.72 and 3.71 ppm)], 3.65–3.60 (2 H, m, 4'- or 3'-OH and 4'-or 3'-H) and 3.45–3.35 (2 H, m, 6'-H_2); *m*/*z* (FAB < 0, NBA) 840 $(M - H)^-$ and 406 $(B)^-$.

1-[2-O-(4-*Methoxytrityl*)-β-D-*galactopyranosyl*]*thymine* **34** {0.31 g, 49%, after chromatography [eluent: stepwise gradient of methanol (0–5%) in dichloromethane], and then lyophilization from water}, m.p. 192–199 °C (Found: C, 65.5; H, 5.8; N, 5.2. $C_{31}H_{32}N_2O_8 \cdot \frac{1}{3}H_2O$ requires C, 65.7; H, 5.8; N, 4.95%); $[\alpha]_D^{20}$ +52.0 (*c* 0.9, Me_2SO); λ_{max}(95% EtOH)/nm 263 (8900); λ_{min}/nm 230 (2300); δ_H 11.30 (1 H, s, 3-H), 7.5–6.3 (14 H, m, 14 × ArH), 6.46 (1 H, s, 6-H), 5.78 (1 H, d, $J_{1',2'}$ 9.0, 1'-H), 4.67 (1 H, t, *J* 5.6, 6'-OH), 4.37 (1 H, d, *J* 6.3, 4'-OH), 3.9–3.8 (1 H, m, 3'-H; 3.82 ppm, dd, *J* 8.9 and 3.1 after D_2O exchange), 3.74 (3 H, s, OMe), 3.62 (1 H, t, 5'-H), 3.6–3.5 (2 H, m, 4'-H and 3'-OH), 3.47 (1 H, t, 2'-H), 3.40–3.35 (2 H, m, 6'-H_2) and 1.56 (3 H, s, Me); *m*/*z* (FAB > 0, G-T) 561 $(M + H)^+$ and 127 $(BH_2)^+$; *m*/*z* (FAB < 0, G-T) 559 $(M - H)^-$ and 125 $(B)^-$.

1-[2-O-(4-*Methoxytrityl*)-β-D-*galactopyranosyl*]*uracil* **35** {1.60 g, 50%, after chromatography [eluent: stepwise gradient of methanol (0–5%) in dichloromethane], and then lyophilization from water}, m.p. 155–156 °C (Found: C, 64.9; H, 5.8; N, 5.2. $C_{30}H_{30}N_2O_8 \cdot 0.5H_2O$ requires C, 64.85; H, 5.6; N, 5.0%); $[\alpha]_D^{20}$ +37.0 (*c* 0.9, Me_2SO); λ_{max}(95% EtOH)/nm 260 (11 000) and 231 (16 600); λ_{min}/nm 250 (10 000); δ_H 11.31 (1 H, d, 3-H), 7.4–6.8 (14 H, m, 14 × ArH), 6.67 (1 H, d, $J_{5,6}$ 8.1, 6-H), 5.79 (1 H, d, $J_{1',2'}$ 8.9, 1'-H), 5.38 (1 H, dd, $J_{3,5}$ 1.9, $J_{5,6}$ 8.0, 5-H), 4.67 (1 H, t, *J* 5.6, 6'-OH), 4.39 (1 H, d, *J* 6.1, 4'-OH), 3.89–3.82 (1 H, m, 3'-H), 3.74 (3 H, s, OMe), 3.64 (1 H, t, *J* 6.0, 5'-H), 3.55 (1 H, m, 4'-H), 3.49 (1 H, d, *J* 6.7, 3'-OH) and 3.45–3.35 (3 H, m, 2'-H and 6'-H_2); *m*/*z* (FAB > 0, NBA) 547 $(M + H)^+$; *m*/*z* (FAB < 0, G-T) 545 $(M - H)^-$ and 111 $(B)^-$.

2-N-(4-*Methoxytrityl*)-9-[2-O-(4-*methoxytrityl*)-β-D-*galactopyranosyl*]*guanine* **36** {0.48 g, 31%, after chromatography [eluent: stepwise gradient of methanol (0–5%) in dichloromethane], and then lyophilization from a 1,4-dioxane–water mixture}, m.p. 204–209 °C (Found: C, 65.6; H, 5.8; N, 7.1. $C_{51}H_{47}N_5O_8 \cdot 4H_2O$ requires C, 65.9; H, 5.95; N, 7.5%); $[\alpha]_D^{20}$ +38.6 (*c* 0.9, Me_2SO); λ_{max}(95% EtOH)/nm 275sh (19 200), 264 (20 600) and 231 (33 500); λ_{min}/nm 250 (18 500); δ_H 10.8 and 7.8 (1 H each, 2 br s, 1-H and 2-NH), 7.5–6.5 (29 H, m, 8-H and 28 × ArH), 4.83 (1 H, d, $J_{1',2'}$ 8.3, 1'-H), 4.71 (1 H, br s, 6'-OH), 4.43 (1 H, br s, 3'-OH), 3.73 (1 H, m, 5'-H), 3.66 (1 H, m, 4'-H), 3.63 (3 H, s, OMe), 3.60 (1 H, m, 4'-OH), 3.56 (3 H, s, OMe), 3.53 (1 H, m, 3'-H) and 3.50–3.35 (3 H, m, 2'-H and 6'-H_2); *m*/*z* (FAB > 0, G-T), 858 $(M + H)^+$ and 424 $(BH_2)^+$.

General Procedure for the Preparation of 9- *and* 1-{(1R,2R)-2,3-*Dihydroxy*-1-[2-*hydroxy*-1-(*hydroxymethylethoxy*]*propyl*}-*purines and -pyrimidines* **41**–**44**.—To a solution of a foregoing tritylated nucleoside **33** (0.50 g, 0.59 mmol), **34** (0.21 g, 0.37 mmol), **35** (1.50 g, 2.74 mmol) or **36** (0.40 g, 0.47 mmol) in a 1,4-dioxane–water mixture (8:2; 20 cm^3/mmol) was added sodium metaperiodate (1.5 mol equiv.). The reaction mixtures were stirred for 1 h at room temperature, filtered, and the precipitates were washed with 1,4-dioxane. The combined filtrates and washings were concentrated to the initial volumes, and sodium borohydride (2.0 mol equiv.) was added in portions. The solutions were stirred for 1 h at room temperature after the additions were complete, then were neutralized to pH 7 (pH paper) by careful addition of acetic acid, and evaporated to dryness under reduced pressure. The residues **37–40** were co-evaporated successively with pyridine and toluene, then were dissolved in a solution of 2% TFA in dichloromethane (30 cm^3/mmol), and the reaction mixtures were stirred for 30 min at room temperature. The reaction mixtures were neutralized by addition of a solution of methanolic ammonia, and water was added. The aqueous layers were washed with dichloromethane and evaporated to dryness. The *title compounds* were purified by chromatography, and then lyophilized.

9-{(1R,2R)-2,3-*Dihydroxy*-1-[2-*hydroxy*-1-(*hydroxymethyl*)-*ethoxy*]*propyl*}*adenine* **41** {0.12 g, 68%, after purification by Dowex 1 × 2 (OH^-) ion-exchange resin column chromatography [eluent: linear gradient of methanol (0–100%) in water], and then lyophilization from water}, m.p. 184–187 °C (Found: C, 41.8; H, 6.0; N, 22.1 $C_{11}H_{17}N_5O_5$·H_2O requires C, 41.6; H, 6.0; N, 22.1%); $[\alpha]_D^{20}$ +41.3 (*c* 0.9, Me_2SO); λ_{max}(95% EtOH)/nm 259 (15 100); λ_{min}/nm 226 (2100); δ_H 8.23 and 8.12 (1 H each, 2 s, 2- and 8-H), 7.14 (2 H, s, NH_2), 5.79 (1 H, d, $J_{1',2'}$ 7.2, 1'-H), 5.06 (1 H, br s, 2'-OH), 4.75 (2 H, br s, 3'- and 4'-OH), 4.33 (1 H, br s, 6'-OH), 4.09 (1 H, m, 2'-H), 3.60–3.50 (3 H, m, 4'-H and 3'-H_2), 3.45 (1 H, m, 4'-H), 3.35 (1 H, m, 5'-H) and 3.20–3.05 (2 H, m, 6'-H_2); *m*/*z* (FAB > 0, G-T) 300 $(M + H)^+$, 165 $(s)^+$ and 136 $(BH_2)^+$; *m*/*z* (FAB < 0, NBA) 298 $(M - H)^-$ and 134 $(B)^-$.

1-{(1*R*,2*R*)-2,3-Dihydroxy-1-[2-hydroxy)-1-(hydroxymethyl)ethoxy]propyl}thymine **42** {0.067 g, 62%, after purification by silica gel column chromatography [eluent: stepwise gradient of methanol (0–15%) in dichloromethane], and then lyophilization from water}, m.p. 215–218 °C (hygroscopic); $[\alpha]_D^{20}$ −48.0 (*c* 1.0, Me_2SO); λ_{max}(water)/nm 266 (9100); λ_{min}/nm 227 (2200); δ_H 11.5 (1 H, s, 3-H), 7.49 (1 H, s, 6-H), 5.69 (1 H, d, $J_{1',2'}$ 7.7, 1'-H), 5.04 (1 H, d, *J* 4.8, 2'-OH), 4.77 (2 H, m, 3'- and 4'-OH), 4.53 (1 H, d, *J* 5.5, 6'-OH), 3.60 (1 H, m, 2'-H), 3.55–3.40 (4 H, m, 3'- and 4'-H_2) and 3.40–3.25 (3 H, m, 5'-H and 6'-H_2, partially obscured by water); *m*/*z* (FAB > 0, G-T) 291 $(M + H)^+$.

1-{(1*R*,2*R*)-2,3-Dihydroxy-1-[(2-hydroxy)-1-(hydroxymethyl)ethoxy]propyl}uracil **43** {0.45 g, 59%, after purification by RP-2 silanized silica gel column chromatography [eluent: linear gradient of methanol (0–100%) in water], and then lyophilization from water}, m.p. 218–220 °C (hygroscopic); $[\alpha]_D^{20}$ +28.0 (*c* 1.0, Me_2SO); λ_{max}(water)/nm 261 (9300); λ_{min} 230 (2200); δ_H 11.17 (1 H, s, 3-H), 7.61 (1 H, d, $J_{5,6}$ 8.0, 6-H), 5.71 (1 H, d, $J_{1',2'}$ 7.5, 1'-H), 5.57 (1 H, d, *J* 8.0, 5-H), 5.08 (1 H, d, *J* 5.4, 2'-OH), 4.78 and 4.73 (1 H each, 2 t, *J* 5.2 and 5.8 respectively, 3'- and 4'-OH), 4.53 (1 H, t, *J* 5.4, 6'-OH), 3.59 (1 H, m, 2'-H), 3.55–3.40 (4 H, m, 3'- and 4'-H_2) and 3.40–3.20 (3 H, m, 5'-H and 6'-H_2, partially obscured by water).

9-{(1*R*,2*R*)-2,3-Dihydroxy-1-[2-hydroxy-1-(hydroxymethyl)ethoxy]propyl}guanine **44** {0.050 g, 34%, after purification first by Dowex 1 × 2 (OH^-) ion-exchange resin column chromatography [eluent: linear gradient of methanol (0–100%) in water, followed by a linear gradient of NH_4HCO_3 (0.1–0.4 mol dm^{-3}) in water], then by RP-2 silanized silica gel column chromatography [eluent: linear gradient of methanol (0–100%) in water], and then lyophilization from water}, m.p. 163–165 °C (hygroscopic); $[\alpha]_D^{20}$ +19.5 (*c* 0.9, Me_2SO); λ_{max}(water)/nm 252 (14 200); λ_{min}/nm 221 (3000); δ_H 9.0 (1 H, br s, 1-H), 7.77 (1 H, s, 8-H), 6.44 (2 H, s, NH_2), 5.55 (1 H, d, $J_{1',2'}$ 7.2, 1'-H), 5.0, 4.7 and 4.4 (1, 2 and 1 H, respectively, 3 br s, 2'-, 3'-, 4'-H and 6'-OH) and 4.1–3.1 [m, other H of the acyclic chain, partially obscured by water; 3.97 ppm (1 H, m, 2'-H), 3.60–3.50 ppm (3 H, m, 4'-H and 3'-H_2), 3.45–3.40 ppm (1 H, m, 4'-H), 3.40–3.30 ppm (1 H, m, 5'-H), 3.20–3.05 ppm (2 H, m, 6'-H_2) after D_2O exchange]; *m*/*z* (FAB > 0, G-T) 316 $(M + H)^+$ and 152 $(BH_2)^+$.

1-{(1R)-1-[(1R,2R)-2,3-*Dihydroxy*-1-(*hydroxymethyl*)*propoxy*]-2-*hydroxyethyl*}*cytosine* **49**.—To a stirred solution of nucleoside **27** (0.50 g, 1.81 mmol) in pyridine (25 cm^3) was added acetic anhydride (0.69 cm^3, 7.24 mmol). The reaction mixture was stirred for 16 h at room temperature, diluted with dichloromethane, and then poured into water. The organic layer was separated, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness to afford crude triacetate **45**, which was dissolved in anhydrous 1,2-dichloroethane (25 cm^3) and treated with Lawesson's reagent (0.44 g, 1.09 mmol) for 1.5 h at reflux under argon. The reaction mixture was evaporated to dryness and the residue was chromatographed on a silica gel column [eluent: stepwise gradient of methanol (0–4%) in dichloromethane]. The appropriate fractions were pooled and evaporated to dryness to afford the thiouracil derivative **47**, which was dissolved in methanolic ammonia (previously saturated at −10 °C; 10 cm^3) and heated at 100 °C for 2 h in a sealed stainless steel bomb. The reaction mixture was cooled and evaporated to dryness. Crystallization from methanol gave the *title compound* **49** (0.32 g, 64%), m.p. 198 °C (start of decomposition) (Found: C, 40.85; H, 6.4; N, 14.2. $C_{10}H_{17}N_3O_6$·$1H_2O$ requires C, 40.95; H, 6.5; N, 14.3%); $[\alpha]_D^{20}$ +46.2 (*c* 1.0, Me_2SO); λ_{max}(water)/nm 269 (8900); λ_{min}/nm 248 (6500); δ_H 7.56 (1 H, d, *J* 7.4, 6-H), 7.15–7.00 (2 H, br s, NH_2), 5.78 (1 H, t, *J* 5.3, 1'-H), 5.66 (1 H, d, 5-H), 5.05 (1 H, br s, 1-OH), 4.6–4.4 (3 H, br s, 3-OH) and 3.7–3.2 (8 H, m, 2'-, 3'- and 6'-H_2, and 4'- and 5'-H, partially obscured by water).

1-{(1R,2R)-2,3-*Dihydroxy*-1-[2-*hydroxy*-1-(*hydroxymethyl*)-*ethoxy*]*propyl*}*cytosine* **50**.—This compound was synthesized from the nucleoside **43** (0.50 g, 1.81 mmol) as described above for the synthesis of compound **49**. Purification by RP-2 silanized silica gel column chromatography [eluent: linear gradient of methanol (0–100%) in water], and then lyophilization from water gave the *title compound* **50** (0.31 g, 63%), m.p. 201–202 °C (Found: C, 40.6; H, 6.3; N, 14.1. $C_{10}H_{17}N_3O_6$·H_2O requires: C, 40.95; H, 6.5; N, 14.3%); $[\alpha]_D^{20}$ +45.0 (*c* 1.0, Me_2SO); λ_{max}(water)/nm 270 (9500); λ_{min}/nm 249 (7000); δ_H 7.52 (1 H, d, *J* 7.5, 6-H), 7.30–7.15 (2 H, br s, NH_2), 5.73 (1 H, d, 5-H), 5.42 (1 H, d, $J_{1',2'}$ 9.3, 1'-H), 5.00 (1 H, d, *J* 5.4, 2'-OH), 4.90 and 4.65 (1 H each, 2 br s, 3'- and 4'-OH), 4.48 (1 H, d, *J* 5.7, 6'-OH), 3.70–3.55 (2 H, m, 2'- and 3'-H) and 3.50–3.30 (6 H, m, 3'- and 5'-H, and 4'- and 6'-H_2, partially obscured by water).

1-{(1R)-1-[(1R,2R)-2,3-*Dihydroxy*-1-(*hydroxymethyl*)*propoxy*]-2-*hydroxyethyl*}-4-*thiouracil* **51**.—A solution of crude triacetate **47** [prepared from compound **27** (0.50 g) as described above for the synthesis of compound **49**] in methanolic ammonia (previously saturated at −10 °C and tightly stoppered; 10 cm^3) was stirred for 2 h at room temperature. The solution was evaporated to dryness under reduced pressure and the residue was co-evaporated under reduced pressure several times with methanol. Crystallization of the product from 95% EtOH afforded the title compound **51** (0.29 g, 56%), m.p. 189–192 °C; $[\alpha]_D^{20}$ −18.3 (*c* 0.9, Me_2SO); λ_{max}(water)/nm 328 (19 500) and 242 (4100); λ_{min}/nm 276 (1900); δ_H 12.5 (1 H, br s, 3-H), 7.48 (1 H, d, *J* 7.4, 6-H), 6.24 (1 H, d, 5-H), 5.76 (1 H, t, $J_{1',2'}$ 5.3, 1'-H), 5.15 (1 H, br s, 1-OH), 4.6 (3 H, br s, 3 × OH) and 3.6–3.2 (8 H, m, 2'-, 3'- and 6'-H_2, and 4'- and 5'-H, partially obscured by water); *m*/*z* (FAB > 0, G-T) 293 $(M + H)^+$ and 129 $(BH_2)^+$; *m*/*z* (FAB < 0, G-T) 291 $(M - H)^-$ and 127 $(B)^-$.

1-{(1R,2R)-2,3-*Dihydroxy*-1-[2-*hydroxy*-1-(*hydroxymethyl*)-*ethoxy*]*propyl*}-4-*thiouracil* **52**.—This compound was synthesized from the nucleoside **43** (0.50 g, 1.81 mmol) as described above for the synthesis of compound **51**. Purification by RP-2 silanized silica gel column chromatography [eluent: linear gradient of methanol (0–100%) in water], and then lyophilization from water gave the title compound **52** (0.22 g, 41%), m.p. 172–175 °C; $[\alpha]_D^{20}$ −22.0 (*c* 0.9, Me_2SO); λ_{max}(water)/nm 328 (20 500) and 242 (4400); λ_{min}/nm 277 (2000); δ_H 12.9 (1 H, br s, 3-H), 7.19 (1 H, d, *J* 7.3, 6-H), 6.19 (1 H, d, 5-H), 5.33 (1 H, d, $J_{1',2'}$ 9.2, 1'-H), 5.8–3.8 (4 H, br s, 4 × OH), 3.70–3.60 (2 H, m, 2'- and 3'-H), 3.55–3.35 (6 H, m, 3'- and 5'-H, and 4'- and 6'-H_2, partially obscured by water); *m*/*z* (FAB > 0, G-T) 293 $(M + H)^+$, 165 $(s)^+$ and 129 $(BH_2)^+$; *m*/*z* (FAB < 0, G-T) 291 $(M - H)^-$ and 127 $(B)^-$.

Biological Methods.—The broad antiviral assays on cell culture and the anti-HIV assays were performed by following previously established procedures as described in refs. 22 and 32.

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