mmol), and a magnetic stir bar was added 16 (40 mg, 0.147 mmol). The reaction mixture was then heated to 70 °C for 5 h, at which point the reduction was complete according to TLC. The reaction mixture was cooled to room temperature, and H_2O (0.15 mL) was added. The resulting slurry was filtered off and the filtrate evaporated to give a residue that upon silica gel chromatography with $EtOAc/Et_3N$ (90:10) as eluent afforded 35 mg (92 %) of (±)-α-lycorane (1a).[23a] The spectral data are in agreement with those reported in the literature:[3a] ^1H NMR δ 6.70 (s, 1 H, H-12), 6.59 (s, 1 H, H-8), 5.89 (s, 2 H, H-10), 4.10 (d, J = 15.1 Hz, 1 H, one of H-7), 3.76 (d, J = 15.1 Hz, one of H-7), 3.12 (app dt, J = 7.9, 9.4 Hz, 1 H, one of H-5), 2.82 (app dt, J = 3.4, 9.4 Hz, 1 H, one of H-5), 2.50–2.32 (m, 3 H), 2.22 (app dq, J = 3.5, 13.0 Hz, 1 H, one of H-1), 1.94–1.55 (m, 6 H), 1.17 (m, 1 H, one of H-1); ^{13}C δ 146.0, 145.2, 134.9, 128.8, 106.8, 104.4, 100.6, 64.4, 54.6, 54.1, 36.9, 33.8, 27.8, 26.1, 24.8, 20.8; IR (CCl_4) 2933, 1503, 1482, 1456, 1364, 1261, 1242 cm^{-1}.

(±)-γ-Lycorane (2). To a flame-dried, nitrogen-purged reaction flask containing dry THF (5 mL), $LiAlH_4$ (70 mg, 1.84 mmol), and a magnetic stir bar was added 18 (100 mg, 0.369 mmol). The reaction mixture was then heated to 65 °C for 3 h, at which point the reduction was complete according to TLC. Workup as above afforded 80 mg (84 %) of (±)-γ-lycorane (2).[23b] The spectral data are in agreement with those reported in the literature:[3b] ^1H NMR δ 6.61 (s, 1 H, H-12), 6.49 (s, 1 H, H-8), 5.88 (two d, J = 1.4 Hz, 2 H, OCH_2O), 4.00 (d, J = 14.2 Hz, 1 H, one of H-7), 3.37 (ddd, J = 9.0, 9.0, 3.5 Hz, 1 H, one of H-5), 3.20 (d, J = 14.2 Hz, 1 H, one of H-7), 2.73 (ddd, J = 11.5, 5.0 Hz, 1 H, H-12b), 2.36 (dd, J = 5.0, 4.0 Hz, 1 H, H-12c), 2.23–2.08 (m, 2 H), 2.07–1.94 (m, 1 H), 1.80–1.58 (m, 3 H), 1.54–1.23 (m, 4 H); ^{13}C NMR δ 146.0, 145.6, 133.1, 127.3, 108.3, 106.2, 100.6, 62.8, 57.1, 53.7, 39.4, 37.3, 31.7, 30.4, 29.2, 25.2; IR (CCl_4) 2929, 1505, 1482, 1319, 1244, 1231, 1044 cm^{-1}; MS m/z 257 (M^+, 60.2%), 256 (100), 162 (9.1), 128 (7.5), 115 (6.3), 77 (8.2).

Acknowledgment. Financial support from the Swedish Board of Technical Development and the Swedish Natural Science Research Council is gratefully acknowledged. We thank Prof. L. Kenne (University of Stockholm) for running high-resolution MS.

Registry No. (±)-1a, 63814-02-8; (±)-2, 63814-03-9; (±)-7, 132541-04-9; (±)-8, 132541-05-0; (±)-9, 132541-06-1; (±)-10, 132541-07-2; (±)-11, 132541-08-3; (±)-12, 132541-09-4; (±)-13, 132541-10-7; (±)-14, 132541-11-8; (±)-15, 132541-12-9; (±)-16, 66816-53-3; (±)-17, 132618-67-8; (±)-18, 132619-48-8; 4-bromo-1,2-(methylenedioxy)benzene, 2635-13-4.

(23) (a) Nothing of the isomeric γ-lycorane (2)[3b] could be detected in the ^1H NMR spectrum (<0.2%). (b) Nothing of the isomeric α-lycorane (1a)[3a] could be detected in the ^1H NMR spectrum (<0.2%).

Synthesis of 2′,3′-Dideoxy-3′-*C*-hydroxymethyl Nucleosides as Potential Inhibitors of HIV

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A novel synthesis of 2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides is described. (2*S*,3*R*)-3-[[(4-Bromobenzyl)oxy]methyl]oxirane-2-methanol (1) was regioselectively alkylated using allylmagnesium bromide. The allyl double bond was oxidatively cleaved, and the product was treated with acidic methanol to give the requisite methyl furanoside derivative 5, which was subsequently condensed with purine and pyrimidine bases. Deblocking and separation of the anomers by chromatography afforded the α- and β-nucleoside analogues.

Introduction

In the early 1980s a new disease, termed acquired immuno deficiency syndrome (AIDS) was discovered which since then has spread so that it now has become a serious epidemic. The causative agent of AIDS is a retrovirus referred to as HIV (human immunodeficiency virus). AIDS is characterized by a profound immunodeficiency which is due to low numbers of a subset of lymphocyte-T-helper cells, which are targeted for the HIV infection, and which makes AIDS patients highly susceptible to a variety of opportunistic infections of bacterial, fungal, protozoal, and viral origin.[1,2] 3′-Azido-3′-deoxythymidine (AZT, zidovudine)[3] is the first and thus far the only drug that has been approved for the treatment of AIDS. The widespread use of zidovudine has raised some concern that viral resistance towards the drug might develop. Recently it was shown that long term use of zidovudine resulted in reduced sensitivity to the drug in isolates of many patients examined,[4] and although the clinical consequences of these findings are unclear, the use of other drugs alone or in combination therapy would considerably reduce this risk. The mechanism for anti-HIV activity of zidovudine is believed to involve activation by cellular kinases to give the corresponding triphosphate which acts as a substrate/inhibitor for viral reversed transcriptase (RT) causing premature termination of chain elongation. There are many other nucleoside analogues in preclinical and clinical development such as 2′,3′-dideoxycytidine,[5] 2′,3′-

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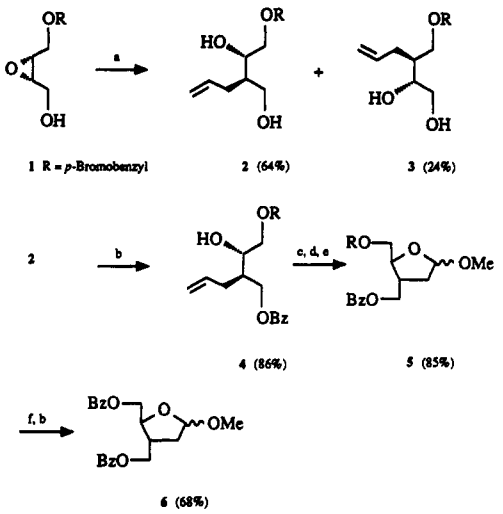
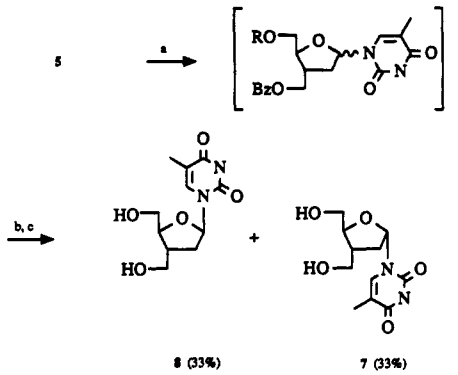
Scheme I[a]



[a] (a) AllylMgBr, diethyl ether, −50 °C; (b) BzCl, pyridine; (c) OsO_4, *N*-methylmorpholine *N*-oxide, THF–H_2O; (d) $NaIO_4$, THF–H_2O; (e) HCl, MeOH; (f) Na, NH_3.

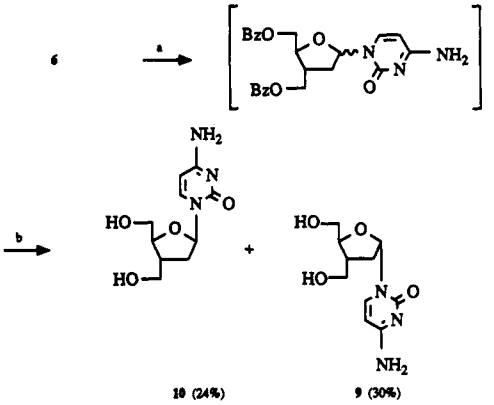
dideoxyinosine,[6] and 3′-azido-2′,3′-dideoxyuridine.[7,8] Since the first report[9] on the synthesis of 2′- and 3′-*C*-methyladenosines, there has been an increasing interest in nucleosides having branched-chain sugars as these compounds have shown interesting biological activities.[10,11] Recently a number of 2′,3′-dideoxy-3′-alkyl-substituted nucleoside analogues have been synthesized.[12-17] The principal methods used for introducing an alkyl side chain have involved free-radical couplings of protected nucleosides, suitably derivatized in the 3′-position, i.e. 3′-iodo,[13] 3′-*O*-(phenyloxythiocarbonyl),[12,15] or through the addition of cyanide to 3′-keto nucleosides.[16] Other methods for the construction of the sugar portion have started from (*S*)-(+)-γ-(hydroxymethyl)-γ-butyrolactone.[14,17] or cyclohexenecarboxylic acid derivatives.[18] In this paper we describe the synthesis of 2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides,[11,18-21] which are close structural analogues to the natural 2′-deoxy nucleosides. The furanose part was constructed using de novo sugar synthesis involving Sharpless epoxidation,[22] regioselective alkylation of a

Scheme II[a]



[a] (a) Silylated thymine, TBDMSOTf, CH_2Cl_2; (b) Pd/H_2; (c) NH_3, MeOH.

Scheme III[a]



[a] (a) Silylated cytosine, TBDMSOTf, CH_2Cl_2; (b) NH_3, MeOH.

2,3-epoxy alcohol using allylmagnesium bromide, followed by oxidative cleavage of the double bond. The resulting protected furanose derivative was condensed with silylated bases[17,23-25] according to the Vorbrüggen method,[24] which after deprotection and separation of α- and β-isomers provided the nucleoside analogues.

Results and Discussion

In our synthetic procedure the chiral epoxy alcohol **1**, readily prepared using Sharpless epoxidation,[26] was regioselectively alkylated at C-3 using allylmagnesium bromide in diethyl ether at −50 °C. The isolated yield after silica gel column chromatography was 64% of the desired 2,4-diol **2** and 24% of the 3,4-diol **3** (Scheme I). Compounds **2** and **3** were differentiated from each other by reacting the mixture of **2** and **3** with sodium periodate,[27] which cleaves the vicinal hydroxyls in **3**. This procedure simplifies the isomeric separation on a larger scale. Attempts to improve the regioselectivity by using cuprous iodide[28] and varying the temperature and solvents or by using higher order cyanocuprates in tetrahydrofuran–tetramethylethylenediamine mixtures[29] were not successful. The primary hydroxyl group in **2** was then selectively benzoylated using benzoyl chloride in pyridine at 0 °C to give **4** in 86% yield. Cis-hydroxylation of the olefinic bond

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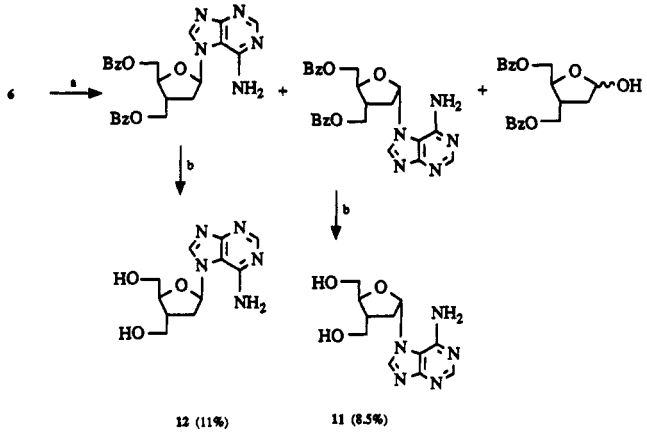
Scheme IV[a]



[a] (a) Silylated adenine, TBDMSOTf, CH_2Cl_2; (b) NH_3, MeOH.

in **4** using a catalytic amount of osmium tetraoxide and *N*-methylmorpholine *N*-oxide as reoxidant[30] gave the corresponding diol which was cleaved using sodium periodate in aqueous tetrahydrofuran to produce an unstable furanose. Treatment of this furanose with methanol containing hydrochloric acid (0.05%, w/w) readily provided the furanoside **5** in 85% yield from **4**. Deblocking of **5**, using sodium–liquid followed by benzoylation, afforded the di-O-benzoylated furanoside **6** in 68% yield. A small sample of this α- and β-anomeric mixture was separated by silica gel column chromatography. The ^1H NMR and mp of the resulting β-anomer were in agreement with those previously reported.[11] The furanoside **5** was condensed with silylated thymine in the presence of *tert*-butyldimethylsilyl triflate to give an anomeric mixture of nucleosides, which was not separated at this stage. Deblocking was carried out by hydrogenation[26] followed by reaction with methanolic ammonia to give a mixture of **7** and **8** (Scheme II). Separation of the anomers by semipreparative HPLC (C-18) gave **7** and **8** in 33% and 33% yield, respectively. Silylated cytosine was condensed with **5** following the same protocol (cf. vide supra). For the deblocking, however, all attempts to remove the *p*-bromobenzyl group by hydrogenolysis were unsuccessful, even with the cytosine amino group acetylated. To circumvent these problems, the di-O-benzoylated derivative **6** was used instead of **5** for the coupling reactions. Silylated cytosine was thus coupled with **6** to give, after deblocking using methanolic ammonia and HPLC (C-18) separation, **9** and **10** in 30% and 24% yields, respectively (Scheme III). Silylated adenine was condensed with compound **6** by following the same procedure as above. The anomers were separated by silica gel column chromatography, deprotected, and purified on HPLC to give the N^7-anomers **11** and **12** in 8.5% and 11% yield, respectively (see Scheme IV). To obtain the N^9-regioisomer, silylated 6-chloropurine[31] was condensed with **6** to give an anomeric mixture, which was converted to **13** and **14** (Scheme V) in 10% and 20% yields, respectively, after HPLC (C-18) separation. The compounds synthesized were evaluated for antiviral effect in vitro, and especially compound **10** was found to be a very potent inhibitor of HIV, inhibiting 50% of HIV multiplication in H9 cells at a concentration of about 0.01 μM. The full results from the biological evaluations will be published shortly.

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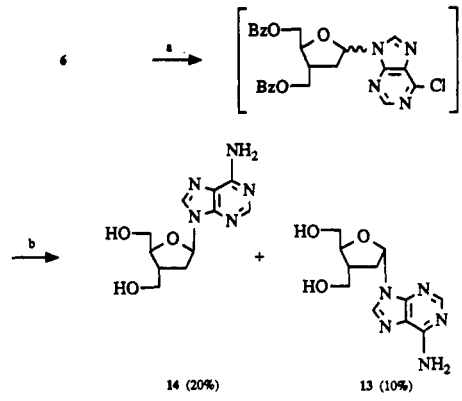
Scheme V[a]



[a] (a) Silylated 6-Cl-purine, TBDMSOTf, CH_2Cl_2; (b) NH_3, MeOH, 100 °C.

Structure Assignments. Assignments of the α- and β-anomeric configurations of the nucleosides were based on NOE difference spectroscopy and on characteristic ^1H NMR features. It has been reported that protons syn to the base are more deshielded than those which are anti.[17,18,32] In the anomeric nucleoside pairs examined, the anomer which had a downfield shift for H-4′ was assigned as the α-anomer. This anisotropic effect of the base was also apparent in the chemical shifts of both H-2′ and H-2″, where the signals for the α-anomers were well resolved but where the β-anomers were unresolved.[33] ^1H NOE difference spectroscopy was performed on a Bruker AC-P operating at 300.13 MHz on **9** and **10**, which were benzoylated at N-4 and at the two hydroxyls. Irradiation of H-1′ (6.17 ppm) gave enhancement of H-4′ (4.41 ppm) in the β-anomer. Irradiation of H-1′ (6.15 ppm) in the α-anomer resulted in a small enhancement of H-3′ but no enhancement of H-4′ (4.51 ppm). By further NOE enhancement studies it was concluded that H-1′, H-3′, and H-5′ were all on the same face of the ring plane in what was assigned as the α-anomer. The N^7- and N^9-isomers of the adenosine nucleoside analogues were identified by UV[34] and NMR spectroscopy.[35,36] In N-alkylated purines, the proton signals of H-8 and H-1 and the carbon signals of C-4, C-8, and C-1′ for the N^7-isomers are shifted downfield relative to the signal of the N^9-isomer, while the signal for C-5 of the N^7-isomer is shifted upfield relative to the N^9-isomer.

Experimental Section

Concentrations were performed under diminished pressure (1–2 kPa) at a bath temperature not exceeding 40 °C. NMR spectra were measured with a JEOL GX-270 or FX-100 instrument, using D_2O or $CDCl_3$ solutions. TMS (for $CDCl_3$) and TSP or dioxane (for D_2O) were used as internal standards. The shifts are reported in ppm (δ scale). UV absorption spectra were recorded with a Perkin-Elmer Lamda 5 spectrophotometer. TLC were performed on Merck precoated 60 F-254 plates. Spots were visualized by UV light and/or charring with 8% sulfuric acid. Column chromatography were performed using silica gel 60 (0.040–0.063 mm, Merck). HPLC was performed on a prepacked steel column (250 × 25 mm) using Polygosil 60-7, C-18 (Macherey-Nagel). Organic phases were dried over anhydrous magnesium sulfate. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

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(2*S*,3*R*)-1-*O*-(*p*-Bromobenzyl)-3-(2′-propenyl)-1,2,4-butanetriol (2). To a cold solution (−50 °C) of allylmagnesium bromide (20 mL, M, 20 mmol) in diethyl ether (100 mL) under a nitrogen atmosphere was added a solution of (2*S*,3*R*)-3-[[(4-bromobenzyl)oxy]methyl]oxirane-2-methanol (1) (1.36 g, 5 mmol) in diethyl ether (140 mL) dropwise over 30 min. The mixture was vigorously stirred for 30 min and then quenched using 1 M hydrogen chloride (100 mL). The mixture was warmed to room temperature, and the phases were separated. The aqueous layer was extracted with diethyl ether. The organic layers were combined, and washed with saturated aqueous sodium hydrogen carbonate, dried, and concentrated. The residue was subjected to column chromatography (toluene–ethyl acetate, 1:5) to give 2 (1.00 g, 64%) as a colorless syrup which solidified on standing and 3 (0.40 g, 25%) as a colorless syrup. 2: $[\alpha]^{22}_D$ +1.56° (*c* 1.03, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.8 (m, 1 H, H-3), 2.13 (t, $J_{1',2'} = J_{1',3} = 6.8$ Hz, 2 H, H-1′), 3.3 and 3.0 (broad, 2 H, OH-2 and OH-4), 3.59 (m, 4 H, H-1 and H-4), 4.0 (m, 1 H, H-2), 4.48 (s, 2 H, CH_2Ph), 4.94 and 5.09 (m, 2 H, H-3′a and H-3′b), 5.78 (m, 1 H, H-2′), 7.14-7.5 (m, 4 H, arom.); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 30.6 (C-1′), 42.3 (C-3), 63.3 (C-4), 71.9, 72.3, 72.5 (CH_2Ph, C-1, C-2), 116.4 (C-3′), 121.5, 129.1, 131.3 (aromatic C), 136.4 (C-2′ and aromatic C). Anal. Calcd for 2 ($C_{14}H_{19}O_3Br$): C, 53.34; H, 6.08. Found: C, 53.0; H, 6.1.

(2*S*,3*R*)-4-*O*-Benzoyl-1-*O*-(*p*-bromobenzyl)-3-(2′-propenyl)-1,2,4-butanetriol (4). To an ice-cold mixture of compound 2 (8.54 g, 27 mmol) in pyridine (50 mL) was added dropwise benzoyl chloride (3.21 mL, 27.6 mmol). The reaction mixture was stirred for 15 min. Water (5 mL) was added, and the mixture was heated to room temperature. The solvent was evaporated, and the residue was dissolved in dichloromethane, washed with 1 M hydrogen chloride, saturated aqueous sodium hydrogen carbonate, dried, concentrated, and purified by flash column chromatography (toluene–ethyl acetate, 2:1) to give compound 4 (9.77 g, 86%) as a colorless syrup: $[\alpha]^{22}_D$ +8.5 (*c* 0.71, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.95–2.43 (m, 3 H, H-3 and H-1′), 2.59 (d, $J_{OH\text{-}2,2} = 3.9$ Hz, 1 H, OH-2), 3.54 (m, 2 H, H-1a and H-1b), 3.95 (m, 1 H, H-2), 4.34 (d, $J_{4,3} = 5.1$ Hz, 2 H, H-4), 4.48 (s, 2 H, CH_2Ph), 5.14 and 5.0 (m, 2 H, H-3′a, H-3′b), 5.78 (m, 1 H, H-2′), 7.14-8.1 (m, 9 H arom); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 31.3 (C-1′), 40.4 (C-3), 64.0 (C-4), 70.1 (C-2), 72.3, 72.5 (CH_2Ph, C-1), 116.3 (C-3′), 121.4-135.7 (8 C, arom), 136.4 (C-2′), 166.1 (COPh). Anal. Calcd for $C_{21}H_{23}O_4Br$: C, 60.15; H, 5.53. Found: C, 60.04; H, 5.39.

Methyl 3-*C*-[(Benzoyloxy)methyl]-5-*O*-(*p*-bromobenzyl)-2,3-dideoxy-α- and -β-D-*erythro*-pentofuranoside (5). To an ice-cold mixture of compound 4 (7.5 g, 17.9 mmol) and *N*-methylmorpholine *N*-oxide (4.8 g, 35.5 mmol) in tetrahydrofuran–water (3:1, 70 mL) was added osmium tetraoxide (18 mL, 0.36 mmol, 0.02 M in *tert*-butyl alcohol, stabilized with 1% *tert*-butyl hydroxperoxide), and after a few minutes, the ice bath was removed, and the reaction mixture was stirred overnight at room temperature under nitrogen. Sodium hydrogen sulfite (2 g) was added, and the mixture was stirred for 15 min. The mixture was concentrated, and the aqueous residue was partitioned between ethyl acetate and 1 M hydrogen chloride. The organic layer was washed with saturated aqueous sodium hydrogen carbonate, dried, and concentrated. The crude compound was dissolved in tetrahydrofuran–water (3:1, 200 mL) and treated with sodium periodate (7.65 g, 35.8 mmol) at room temperature. The diol was completely cleaved after 30 min. The mixture was concentrated, and the aqueous residue was partitioned between saturated aqueous sodium chloride and diethyl ether. The organic phase was dried, concentrated, and residual solvents were coevaporated with added toluene. The residue was treated with methanolic hydrogen chloride (0.05%, w/w, 50 mL) for 10 min, neutralized using Dowex 2×8 (HCO_3^-), filtered, and concentrated. The residue was purified by flash column chromatography (toluene–ethyl acetate, 3:1) to give compound 5 (6.63 g, 85%) as a colorless syrup: ^1H NMR (100 MHz, $CDCl_3$) δ 1.7–2.9 (3 m, 3 H, H-3, H-2a and H-2b), 3.31, 3.35 (2 s, 3 H, OCH_3), 3.6 (m, 2 H, H-5), 4.1 (m, 1 H, H-4), 4.4 (m, 2 H, H-6), 4.6 (m, 2 H, CH_2Ph), 5.1 (m, 1 H, H-1), 7.1–8.0 (m, 9 H, arom); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 35.6, 36.4 (C-2), 38.7, 39.3 (C-3), 54.3, 54.5 (OCH_3), 65.7, 66.6, (C-6), 71.5, 72.35, 72.37, 73.8 (C-5 and CH_2Ph), 79.9, 81.0 (C-4), 104.8 (C-1), 121.0–136.9 (arom), 165.8 (COPh). Anal. Calcd for $C_{21}H_{23}O_5Br$: C, 57.94; H, 5.33. Found: C, 58.03; H, 5.25.

Methyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α- and -β-D-*erythro*-pentofuranoside (6). A solution of compound 5 (1.0 g, 2,3 mmol) in diethyl ether (3 mL) was dissolved in liquid ammonia (50 mL) in a Dewar bottle. Sodium (300 mg, 13 mmol) was added in portions over 5 min. The solution was stirred for 30 min and then quenched by adding ammonium chloride. The ammonia was evaporated under a stream of nitrogen, and the solid residue was diluted with ethyl acetate. The solids were filtered off and washed several times with ethyl acetate. The filtrate was concentrated, and residual solvents were coevaporated with added toluene. The crude residue was dissolved in pyridine (30 mL), benzoyl chloride (0.8 mL, 6.9 mmol) was added, and the solution was stirred for 40 min at room temperature after which water (5 mL) was added and the mixture concentrated to dryness. The residue was dissolved in dichloromethane, washed with 1 M hydrogen chloride and saturated aqueous sodium hydrogen carbonate, dried, and concentrated. Flash column chromatography (toluene–ethyl acetate, 3:1) gave compound 6 (0.58 g, 68%) as an anomeric mixture. A small sample of this mixture was separated by column chromatography. ^1H NMR and mp of the β-anomer were in agreement with those previously reported.[11]

1-[2′,3′-Dideoxy-3′-*C*-(hydroxymethyl)-α- and -β-D-*erythro*-pentofuranosyl]thymine (7 and 8). A suspension consisting of thymine (150 mg, 1.19 mmol) and a small crystal of ammonium sulfate in a mixture of hexamethyldisilazane (2 mL) and trimethylchlorosilane (0.2 mL) was refluxed until a clean solution was obtained. Volatile matters were evaporated off, and the residue was repeatedly coevaporated with xylene. The resulting syrup was dissolved in dichloromethane (5 mL) under nitrogen. To this solution compound 5 (205 mg, 0.47 mmol) was added followed by the addition of *tert*-butyldimethylsilyl triflate (0.13 mL, 0.56 mmol), and the solution was stirred for 24 h at room temperature. The reaction was quenched by the addition of aqueous sodium hydrogen carbonate, stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, and concentrated to give an anomeric mixture of the protected nucleoside. This mixture was dissolved in ethanol containing sodium hydrogen carbonate (excess) and hydrogenated over 10% palladium on charcoal (50 mg) for 3 h at ambient pressure, and then treated with methanolic ammonia for 24 h. After concentration the residue was dissolved in water and washed with dichloromethane. The aqueous layer was concentrated to a small volume and the mixture was separated by HPLC (water–methanol, 9:1, v/v). The α-anomer was eluted first followed by the β-anomer. The appropriate fractions were combined and evaporated to give 7 (40 mg, 33%) and 8 (41 mg, 33%). 7: $[\alpha]^{26}_D$ −3.6° (*c* 0.36, H_2O); UV (H_2O) λ_{max} 268 nm (ε 13 756); ^1H NMR (270 MHz, D_2O) δ 1.89 (d, $J = 1.1$ Hz, 3 H, 5-CH_3), 1.96 (m, $J_{2'a,2'b} = 13.2$ Hz, $J_{2'a,3'} = 9.9$ Hz, $J_{2'a,1'} = 7.7$ Hz, 1 H, H-2′a), 2.47 (m, 1 H, H-3′), 2.6 (m, $J_{2'a,2'b} = 13.2$ Hz, $J_{2'b,3'} = 8.1$ Hz, $J_{2'b,1'} = 6.2$ Hz, 1 H, H-2′b), 3.64 and 3.68 (dd and d, overlapping, $J_{5'a,4'} = 5.5$ Hz, $J_{5'a,5'b} = 12.1$ Hz, $J_{6',3'} = 6.1$ Hz, 3 H, H-5′a and H-6′), 3.81 (dd, $J_{5'b,4'} = 2.9$ Hz, $J_{5'b,5'a} = 12.1$ Hz, H-5′b), 4.24 (m, $J_{3',4'} = 8.4$ Hz, $J_{4',5'a} = 5.5$ Hz, $J_{4',5'b} = 2.9$ Hz, 1 H, H-4), 6.11 (dd, $J_{1',2'a} = 7.7$ Hz, $J_{1',2'b} = 6.2$ Hz, 1 H, H-1), 7.59 (d, $J = 1.1$ Hz, 1 H, H-6); ^{13}C NMR (25.05 MHz, D_2O) δ 12.5 (5-CH_3), 35.7 (C-2′), 42.2 (C-3′), 62.6, 63.5 (C-5′ and C-6′), 84.2, 87.3 (C-1′ and C-4′), 111.6 (C-5), 138.1 (C-6), 152.4 (C-2), 167.3 (C-4). Anal. Calcd for $C_{11}H_{16}O_5N_2 \cdot 0.5H_2O$: C, 49.8; H, 6.5; N, 10.56. Found: C, 50.0; H, 6.5; N, 10.4. 8: $[\alpha]^{26}_D$ +17.8° (*c* 0.41, H_2O); UV (H_2O) λ_{max} 268 nm (ε 8516); ^1H NMR (270 MHz, D_2O) δ 1.91 (s, 3 H, 5-CH_3), 2.3 (m, 2 H, H-2′), 2.5 (m, 1 H, H-3′), 3.69 (d, $J_{3',6'} = 5.9$ Hz, 2 H, H-6′), 3.76 (dd, $J_{5'b,5'a} = 12.4$ Hz, $J_{5'b,4'} = 5.1$ Hz, 1 H, H-5′b), 3.9 (dd, $J_{5'a,5'b} = 12.4$ Hz, $J_{5'a,4'} = 2.9$ Hz, 1 H, H-5′a), 3.99 (m, $J_{4',5'a} = 2.9$ Hz, $J_{4',5'b} = 5.1$ Hz, $J_{4',3'} = 8.1$ Hz, 1 H, H-4), 6.14 (dd, $J_{1',2'a} = 4.8$ Hz, $J_{1',2'b} = 6.6$ Hz, 1 H, H-1), 7.73 (d, $J = 1.1$ Hz, 1 H, H-6); ^{13}C NMR (25.05 MHz, D_2O) δ 12.5 (5-CH_3), 35.4 (C-2′), 40.9 (C-3′), 62.8, 62.9 (C-5′ and C-6′), 84.5, 86.1 (C-1′ and C-4′), 111.7 (C-5), 138.3 (C-6), 152.7 (C-2), 167.5 (C-4). Anal. Calcd for $C_{11}H_{16}O_5N_2 \cdot 0.8H_2O$: C, 48.8; H, 6.6; N, 10.4. Found: C, 48.9; H, 6.1; N, 10.2.

1-[2′,3′-Dideoxy-3′-*C*-(hydroxymethyl)-α- and -β-D-*erythro*-pentofuranosyl]cytosine (9 and 10). Cytosine (120 mg, 1.08 mmol) was silylated following the same procedure as for

the preparation of 7 and dissolved in dichloromethane (2 mL) under nitrogen. To this solution was added compound 6 (170 mg, 0.46 mmol) followed by the addition of *tert*-butyldimethylsilyl triflate (0.28 mL, 1.2 mmol). After 24 h at room temperature the reaction was quenched by the addition of aqueous sodium hydrogen carbonate, stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, and concentrated to give an anomeric mixture of the protected nucleoside. This mixture was treated with methanolic ammonia (20 mL, saturated) for 24 h at room temperature. After concentration to dryness, the residue was dissolved in water and extracted with dichloromethane. The aqueous layer was concentrated to a small volume and the mixture was separated by HPLC (water–methanol, 98:2, v/v). The α-anomer was eluted first followed by the β-anomer. The appropriate fractions were combined and evaporated to dryness to give **9** (33 mg, 30%) and **10** (27 mg, 24%). **9**: $[\alpha]^{26}_D$ −54° (*c* 0.3, H_2O); UV (H_2O) λ_{max} 272 nm (ε 10 894); ^{1}H NMR (270 MHz, D_2O) δ 1.92 (m, $J_{2'a,2'b}$ = 13.5 Hz, $J_{2'a,3'}$ = 9 Hz, $J_{2'a,1'}$ = 6.5 Hz, 1 H, H-2'a), 2.5 (m, 1 H, H-3'), 2.7 (m, $J_{2'a,2'b}$ = 13.5 Hz, $J_{2'a,3'}$ = 8 Hz, $J_{2'a,1'}$ = 6 Hz, 1 H, H-2'b), 3.67, 3.69 (d and dd, overlapping, $J_{6',3'}$ = 6.2Hz, $J_{5'a,5'b}$ = 12.5 Hz, $J_{4',5'a}$ = 5.3 Hz, 3 H, H-6' and H-5'a), 3.85 (dd, $J_{5'a,5'b}$ = 12.5 Hz, $J_{4',5'b}$ = 3 Hz, 1 H, H-5'b), 4,28 (m, $J_{3',4'}$ = 8 Hz, $J_{4',5'a}$ = 5.3 Hz, $J_{4',5'b}$ = 3 Hz, 1 H, H-4'), 6.1 (d and t, overlapping, $J_{5,6}$ = 7.3 Hz, $J_{1',2'}$ = 6.5 Hz, 2 H, H-5 and H-1'), 7.8 (d, $J_{5,6}$ = 7.3 Hz, 1 H, H-6); ^{13}C NMR (25.05 MHz, D_2O) δ 36.4 (C-2'), 42.3 (C-3'), 62.7, 63.6 (C-5' and C-6'), 84.4, 88.2 (C-1' and C-4'), 96.6 (C-5), 141.9 (C-6), 158.1 (C-2), 166.8 (C-4). Anal. Calcd for $C_{10}H_{15}O_4N_3 \cdot 0.3H_2O$: C, 48.7; H, 6.4; N, 17.0. Found: C, 49.1; H, 6.3; N, 16.7. **10**: $[\alpha]^{26}_D$ +64° (*c* 0.27, H_2O); UV (H_2O) λ_{max} 272 nm (ε 9208); ^{1}H NMR (270 MHz, D_2O) δ 2.2–2.46 (m, 3 H, H-2' and H-3'), 3.68 (d, $J_{3',6'}$ = 5.5 Hz, 2 H, H-6'), 3.76 (dd, $J_{4',5'a}$ = 5.5 Hz, $J_{5'a,5'b}$ = 12.5 Hz, 1 H, H-5'a), 3.92 (dd, $J_{4',5'b}$ = 2.9 Hz, $J_{5'a,5'b}$ = 12.5 Hz, 1 H, H-5'b), 4.01 (m, $J_{3',4'}$ = 8.1 Hz, $J_{5a',4'}$ = 5.5 Hz, $J_{5'b,4'}$ = 2.9 Hz, 1 H, H-4'), 6.05 (d, $J_{5,6}$ = 7.3 Hz, 1 H, H-5), 6.11 (dd, $J_{1',2'a}$ = 7.0 Hz, $J_{1',2'b}$ = 4,0 Hz, 1 H, H-1'), 7.91 (d, $J_{5,6}$ = 7.3 Hz, 1 H, H-6); ^{13}C NMR (25.05 MHz, D_2O) δ 36.1 (C-2'), 40.8 (C-3'), 62.7, 63.1 (C-5' and C-6'), 84.7, 87.1 (C-1' and C-4'), 96.5 (C-5), 142.2 (C-6), 158.2 (C-2), 166.8 (C-4). Anal. Calcd for $C_{10}H_{15}O_4N_3 \cdot 0.7H_2O$: C, 47.3; H, 6.1; N, 16.6. Found: C, 47.2; H, 5.8; N, 16.4.

7-[2',3'-Dideoxy-3'-*C*-(hydroxymethyl)-α- and -β-D-*erythro*-pentofuranosyl]adenine (11 and 12). 6-Aminopurine (200 mg, 1.48 mmol) was silylated following the same procedure as for the preparation of 7 and dissolved in acetonitrile (5 mL) under nitrogen. To this solution was added compound 6 (200 mg, 0.54 mmol) followed by *tert*-butyldimethylsilyl triflate (0.15 mL, 0.65 mmol), and the solution was stirred for 24 h at room temperature. The reaction was quenched by the addition of aqueous sodium hydrogen carbonate, stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, and concentrated to give an anomeric mixture of the protected nucleoside. The anomers were separated by column chromatography (ethyl acetate–methanol–water, 80:15:5), to give the protected α- (40 mg, 16%) and β-anomer (60 mg, 23%). Further eluation gave 5-*O*-benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α- and -β-D-*erythro*-pentofuranose (80 mg, 42%). Each of the anomers was separately treated with methanolic ammonia for 24 h and concentrated, the residue was dissolved in water and washed with dichloromethane. The aqueous layer was concentrated to a small volume and purified by HPLC (water–methanol, 88:12, v/v) to give **11** (12.1 mg, 8.5%) and **12** (15.3 mg, 11%), respectively. **11**: $[\alpha]^{22}_D$ +138° (*c* 0.26, H_2O); UV (H_2O) λ_{max} 270 nm (ε 816); ^{1}H NMR (270 MHz, D_2O) δ 2.41 (m, 1 H, H-2'a), 2.64 (m, 1 H, H-3'), 2.84 (m, $J_{2'b,1'}$ = 6 Hz, $J_{2'b,3'}$ = 8 Hz, $J_{2'b,2'a}$ = 14 Hz, 1 H, H-2'b), 3.74 and 3.79 (dd and q, overlapping, $J_{6',3'}$ = 6.2 Hz, $J_{5'b,4'}$ = 5.5 Hz, $J_{5'b,5'a}$ = 12.5 Hz, 3 H, H-5'b and H-6'), 3.92 (dd, $J_{5'a,4'}$ = 2.9 Hz, $J_{5'a,5'b}$ = 12.5 Hz, 1 H, H-5'a), 4.24 (m, 1 H, H-4'), 6.23 (m, 1 H, H-1'), 8.23 (s, 1 H, H-2), 8.39 (s, 1 H, H-8); ^{13}C NMR (25.05 MHz, D_2O) δ 35.0 (C-2'), 42.1 (C-3'), 62.6, 63.3 (C-5' and C-6'), 83.9, 87.2 (C-1' and C-4'), 111.5 (C-5), 144.4 (C-8), 152.4, 153.1 (C-2 and C-4), 159.2 (C-6). Anal. Calcd for $C_{11}H_{15}O_3N_5 \cdot 0.5H_2O$: C, 48.2; H, 5.9; N, 25.5. Found: C, 48.6; H, 5.6; N, 25.5. **12**: $[\alpha]^{22}_D$ −14° (*c* 0.7, H_2O); UV (H_2O) λ_{max} 270 nm (ε 114); ^{1}H NMR (270 MHz, D_2O) δ 2.48 (m, $J_{2'a,1'}$ = 6 Hz, $J_{2'a,3'}$ = 8.5 Hz, $J_{2'a,2'b}$ = 13 Hz, 1 H, H-2'a), 2.61 (m, 1 H, H-3'), 2.80 (m, $J_{2'b,1'}$ = 3.5 Hz, $J_{2'b,3'}$ = 7.5 Hz, $J_{2'b,2'a}$ = 13 Hz, 1 H, H-2'b), 3.46 (dd, $J_{5'a,4'}$ = 5.5 Hz, $J_{5'a,5'b}$ = 12.5 Hz, 1 H, H-5'a), 3.76 and 3.79 (dd and d, overlapping, $J_{5'b,4'}$ = 3.0 Hz, $J_{5'b,5'a}$ = 12.5 Hz, $J_{6',3'}$ = 5.9 Hz, 3 H, H-5'b and H-6'), 4.22 (m, $J_{4',5'b}$ = 3.0 Hz, $J_{4',5'a}$ = 5.5 Hz, $J_{4',3'}$ = 8.0 Hz, 1 H, H-4'), 6.22 (dd, $J_{1',2'b}$ = 3.5 Hz, $J_{1',2'}$ = 6 Hz, 1 H, H-1'), 8.22 (s, 1 H, H-2), 8.39 (s, 1 H, H-8); ^{13}C NMR (25.05 MHz, D_2O) δ 34.5 (C-2'), 40.9 (C-3'), 62.9, 63.2 (C-5' and C-6'), 85.2, 87.1 (C-1' and C-4'), 111.8 (C-5), 143.6 (C-8), 152.6, 153.1 (C-2 and C-4), 159.0 (C-6). Anal. Calcd for $C_{11}H_{15}O_3N_5 \cdot 0.5H_2O$: C, 48.2; H, 5.9; N, 25.5. Found: C, 48.2; H, 5.7; N, 25.1.

9-[2',3'-Dideoxy-3'-*C*-(hydroxymethyl)-α- and -β-D-*erythro*-pentofuranosyl]adenine (13 and 14). 6-Chloropurine (200 mg, 1.3 mmol) was silylated following the same procedure as for the preparation of 7 and dissolved in acetonitrile (5 mL) under nitrogen. To this solution was added compound 6 (280 mg, 0.76 mmol) followed by *tert*-butyldimethylsilyl triflate (0.33 ml, 1.43 mmol), and the solution was stirred for 24 h at room temperature. The reaction was quenched by the addition of aqueous sodium hydrogen carbonate, stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, and concentrated to give an anomeric mixture of the protected nucleoside. The mixture was treated with methanolic ammonia (5 mL, saturated) at 100 °C in a sealed tube. After 20 h the solvent was removed, and the residue was dissolved in water and washed with dichloromethane. The aqueous layer was concentrated to a small volume and the mixture was separated by HPLC (water–methanol, 92:2, v/v). The α-anomer was eluted first followed by the β-anomer. Appropriate fractions were combined and evaporated to give **13** (20 mg, 10%) and **14** (40 mg, 20%). **13**: $[\alpha]^{26}_D$ +41° (*c* 0.23, H_2O); UV (H_2O) λ_{max} 260 nm (ε 12 864); ^{1}H NMR (270 MHz, D_2O) δ 2.45 (m, 1 H, H-2'a), 2.6 (m, 1 H, H-3'), 2.82 (m, $J_{2'b,1'}$ = 6 Hz, $J_{2'b,3'}$ = 7.8 Hz, $J_{2'b,2'a}$ = 14 Hz, 1 H, H-2'b), 3.72 and 3.74 (dd and d, overlapping, $J_{5'b,4'}$ = 5.5 Hz, $J_{5'b,5'a}$ = 12.5 Hz, $J_{6',3'}$ = 5.9 Hz, 3 H, H-5'b and H-6'), 3.86 (dd, $J_{5'a,4'}$ = 2.9 Hz, $J_{5'a,5'b}$ = 12.5 Hz, 1 H, H-5'a), 4.31 (m, 1 H, H-4'), 6.35 (m, 1 H, H-1'), 8.19 (s, 1 H, H-2), 8.32 (s, 1 H, H-8); ^{13}C NMR (25.05 MHz, D_2O) δ 35.5 (C-2'), 42.3 (C-3'), 62.5, 63.3 (C-5' and C-6'), 83.8, 85.3 (C-1' and C-4'), 119.4 (C-5), 140.3 (C-8), 148.9 (C-4), 153.0 (C-2), 155.9 (C-6). Anal. Calcd for $C_{11}H_{15}O_3N_5 \cdot H_2O$: C, 46.6; H, 6.0; N; 24.7. Found: C, 46.5; H, 5.5; N, 24.3. **14**: $[\alpha]^{26}_D$ −17° (*c* 0.27, H_2O); UV (H_2O) λ_{max} 260 nm (ε 10 744); ^{1}H NMR (270 MHz, D_2O) δ 2.5 (m, 1 H, H-3'), 2.67 (m, 2 H, H-2'), 3.69 (dd, $J_{5'a,4'}$ = 5.1 Hz, $J_{5'a,5'b}$ = 12.5 Hz, 1 H, H-5'a), 3.77 (d, $J_{6',3'}$ = 5.5 Hz, 2 H, H-6'), 3.87 (dd, $J_{5'b,4'}$ = 2.9 Hz, $J_{5'b,5'a}$ = 12.5 Hz, 1 H, H-5'b), 4.13 (m, 1 H, H-4'), 6.34 (m, 1 H, H-1'), 8.18 (s, 1 H, H-2), 8.32 (s, 1 H, H-8); ^{13}C NMR (25.05 MHz, D_2O) δ 35.7 (C-2'), 41.4 (C-3'), 62.8, 63.4 (C-5' and C-6'), 85.0, 85.3 (C-1' and C-4'), 119.2 (C-5), 140.5 (C-8), 148.7 (C-4), 153.0 (C-2), 155.8 (C-6). Anal. Calcd for $C_{11}H_{15}O_3N_5 \cdot 0.8H_2O$: C, 47.2; H, 6.0; N, 25.0. Found: C, 47.3; H, 5.4; N, 24.7.

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Registry No. 1, 108267-97-6; 2, 132235-65-5; 3, 132235-66-6; 4, 132235-67-7; α-5, 132235-67-7; β-5, 132235-69-9; α-6, 132235-81-5; α-6 de-O^1-methyl derivative, 132235-79-1; β-6, 69827-96-9; β-6 de-O^1-methyl derivative, 132235-80-4; 7, 132235-70-2; 8, 132235-71-3; 9, 132235-72-4; 10, 132235-73-5; 11, 132235-74-6; 11 di-*O*-benzoyl derivative, 132235-78-0; 12, 132235-75-7; 12 di-*O*-benzoyl derivative, 132235-77-9; 13, 132235-76-8; 14, 130469-38-4; allylmagnesium bromide, 1730-25-2; thymine, 65-71-4; cytosine, 71-30-7; 6-aminopurine, 73-24-5; 6-chloropurine, 87-42-3.