Synthesis of 2′,3′-Dideoxy-3′-*C*-(hydroxymethyl)-4′-thionucleosides as Potential Inhibitors of HIV

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Received July 12, 1993 (Revised Manuscript Received January 21, 1994•)

The synthesis of 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)-4′-thionucleosides is described. For the synthesis of the carbohydrate part, the configuration of the secondary hydroxyl group in (2*S*,3*R*)-1-*O*-(*p*-bromobenzyl)-3-(2′-propenyl)-1,2,4-butanetriol (**1**) was inverted using Mitsunobu reaction conditions, after which the primary hydroxyl group in product **2** was regioselectively benzoylated using phase-transfer catalysis. Oxidative cleavage of the allylic double bond, followed by ring closure and exchange of the *p*-bromobenzyl protecting group gave the methyl furanoside derivative **5**, which was further converted to the corresponding dibenzyl dithioacetal **6**. Ring closure of **6** involving an intramolecular nucleophilic substitution by sulfur with inversion of configuration at C-4 was effected using chlorodiphenylphosphine (CDP), iodine, and imidazole to give thiofuranoside **9**, which was subsequently condensed with silylated thymine, cytosine, and 6-chloropurine. The latter was converted to adenine after the coupling. Deblocking and separation of the anomers gave the α and β-nucleoside analogues. Compounds **14**, **15**, and **18–21** were found to be inactive when tested for anti HIV-1 activity *in vitro*.

Introduction

As of today, the only drugs approved for the treatment of AIDS are the 2′,3′-dideoxynucleosides 3′-azido-2′,3′-dideoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI), and 2′,3′-dideoxycytidine (ddC).[1–3] A wide variety of sugar-modified nucleoside analogues have been prepared and tested for anti HIV-1 activity. Nucleosides where the furanoside ring oxygen is replaced by sulfur were first described in the 1960's and were shown to have interesting biological activities.[4–7] Recently, the synthesis of a number of thionucleosides have been reported. Among these are the 4′-thio analogues of AZT, ddI, ddC, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) and the 4′-thio analogues of the naturally occuring 2′-deoxynucleosides of which some have antiviral activity.[8–11] The principal method for the synthesis of thionucleosides has been by condensation of 4-thiofuranosyl derivatives with purine and pyrimidine bases. 4-Thiofuranosides have been prepared by displacement of a leaving group with a sulfur-containing nucleophile, followed by ring closure or ring contraction,[9,12] acetolysis of an γ,γ-diethoxy episulfide,[13] or ring closure of a dialkyl dithioacetal.[14–16] Triiodoimidazole–triphenylphosphine and chlorodiphenylphosphine–iodine–imidazole have also been reported to effect ring closure of dialkyl dithioacetals to give the corresponding 4-thiofuranoside derivatives.[17–20] 2′,3′-Dideoxy-3′-*C*-(hydroxymethyl)cytidine (**I**) has been reported to be a potent inhibitor of HIV-1 activity *in vitro* and represents a lead structure of a new type.[21,22] In order to investigate the structure–activity relationship (SAR) for this type of compound we have synthesized 4′-thio analogues **II** of 2′,3′-dideoxy-3′-*C*-(hydroxymethyl) purine and pyrimidine nucleosides. To prepare the thiofuranoside part both triiodoimidazole–triphenylphosphine and chlorodiphenylphosphine–iodine–imidazole reagent systems[23,24] were reacted with the appropriate dialkyl dithioacetals. The stereospecificity in this reaction was also investigated. The resulting protected 4-thiofuranoside derivative was condensed with silylated bases according to the Vorbrüggen method[25] to give the protected 4′-thionucleoside analogues.

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• Abstract published in *Advance ACS Abstracts*, March 1, 1994.

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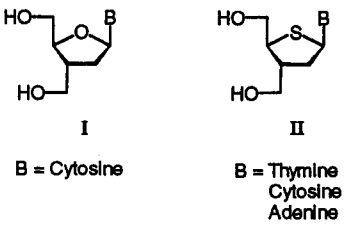
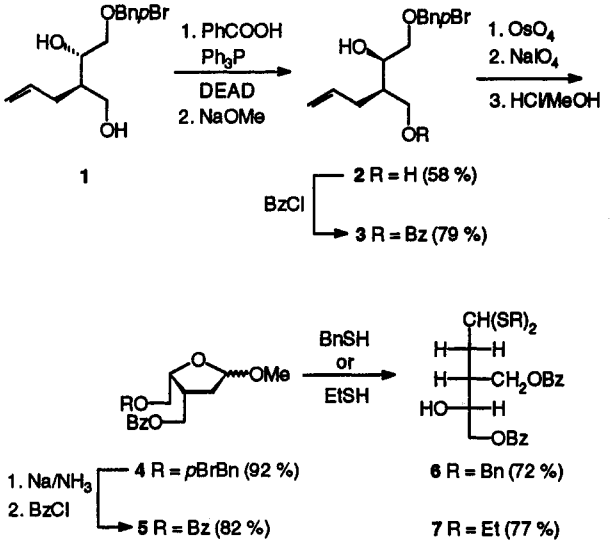


Figure 1.

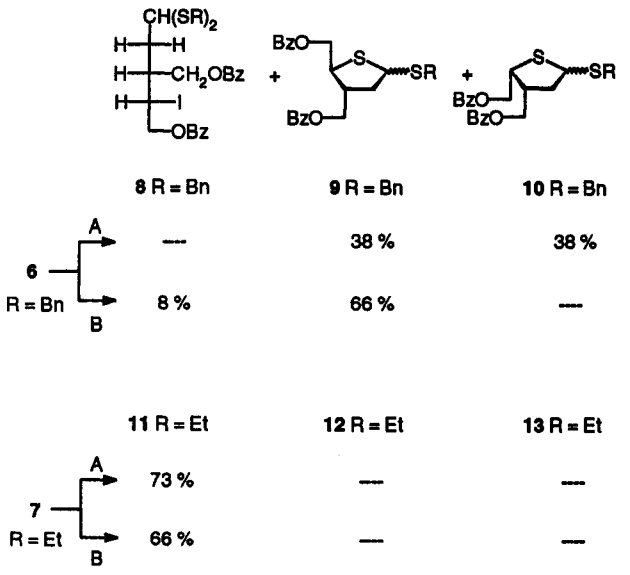
Scheme 1



Results and Discussion

Inversion of configuration of the secondary hydroxyl group in 1[21,26] using Mitsunobu conditions[27] gave the corresponding di-*O*-benzoylated product, which was debenzoylated using sodium methoxide in methanol to give compound **2** in 58% yield from **1** (Scheme 1). A byproduct arising from elimination between C-2 and C-3 was also formed in this reaction. Variations of the reaction conditions failed to improve the yield of **2**. Regioselective benzoylation of the primary hydroxyl group in **2** using benzoyl chloride in pyridine gave **3** in only 45% yield, which was surprising as the epimer **1** previously has been monobenzoylated in 86% yield using the same reaction conditions.[21] However using phase-transfer catalysis[28] with benzoyl chloride and tetrabutylammonium hydrogen sulfate in dichloromethane and aqueous sodium hydroxide gave the desired mono-*O*-benzoylated **3** in 79% yield together with the mono-*O*-benzoylated secondary hydroxyl group in 19% yield. Hydroxylation of the olefinic bond in **3** using a catalytic amount of osmium tetraoxide with *N*-methylmorpholine *N*-oxide as reoxidant gave the corresponding diol, which was cleaved using sodium periodate in aqueous tetrahydrofuran. The resulting furanose was subjected to methanol containing hydrochloric acid (0.05%, w/w) providing the methyl furanoside **4** in 92% yield from **3**. Deblocking of the *p*-bromobenzyl group in **4** using sodium–liquid ammonia, followed by benzoylation, afforded the di-*O*-benzoylated furanoside **5** in 82% yield. Treatment of **5** with ethyl mercaptan in dichloromethane

Scheme 2



A = Triiodoimidazole, Ph_3P, 100°C
B = CDP, I_2, Imidazole, 20°C

containing a catalytic amount of stannic chloride[17] gave the corresponding diethyl dithioacetal **7** in 77% yield. To afford ring closure, two reagent systems were examined *i.e.* triiodoimidazole and triphenylphosphine (reagent system A) and chlorodiphenylphosphine (CDP), iodine, and imidazole (reagent system B). Both single[17] and double[18] inversion of configuration at C-4 have been reported using this methodology for ring closure of thioacetals. Recently, Tiwari *et al.*[19] and Bellon *et al.*[20] have shown that the double inversion at C-4 reported by Huang and Hui[18] using reagent system A proceeds by single inversion of configuration, thus giving the incorrect epimer. In our hands, reagent systems A and B reacted with **7** giving the iodinated product **11** in 73% and 66% yield, respectively, with no trace of thiofuranosides **12** or **13** being formed (Scheme 2). To circumvent this, **5** was converted to the more-reactive dibenzyl dithioacetal **6**, in 72% yield. Reacting **6** with reagent system A produced an unseparable mixture of the thiofuranosides **9** and **10**. Compound **9** arises from the direct intramolecular displacement by sulfur of the activated hydroxyl group at C-4. Compound **10**, which is the C-4 epimer of compound **9**, is formed in two steps from **6**. First the hydroxyl group at C-4 is substituted by iodide with inversion of configuration giving the 4-iodo compound **8**, which then undergoes an intramolecular ring closure where sulfur substitutes the iodide with a second inversion of configuration at C-4. This mechanism was substantiated by a separate experiment where isolated iodide **8** was refluxed in toluene producing thiofuranoside **10**. Reacting **6** with reagent system B gave a separable mixture of iodide **8** in 8% yield and the desired thiofuranoside **9** in 66% yield with no trace of **10** being formed. Under these mild conditions (20 °C), iodide **8** did not cyclize to **10**. The ratio of **8** and **9** formed in the reaction using reagent system B could be controlled by choosing solvent and/or by varying the concentration of starting material **6**. Ring closure was favored in dilute solutions and by use of polar solvents (Table 1). The benzyl dithiofuranoside **9** was subsequently condensed with silylated thymine in the presence of trimethylsilyl triflate and mercuric acetate in dichlo-

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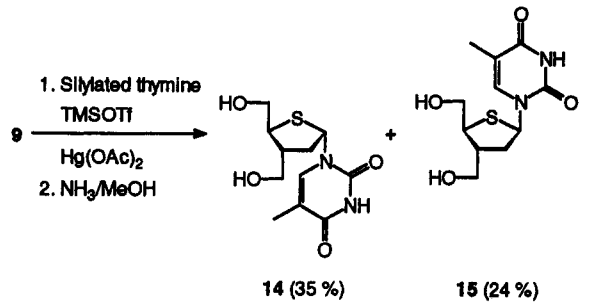
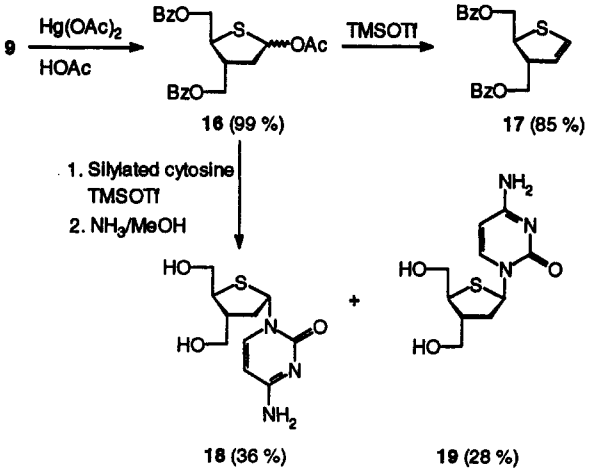
Table 1. Ring Closure of 6 with Reagent System B

concn of 6, mM	solvent	tot. yield, %	ratio 8/9
20	acetonitrile	74	1/8
80	acetonitrile	71	1/4
80	toluene	74	1/1
160	acetonitrile	72	4/1

Scheme 3

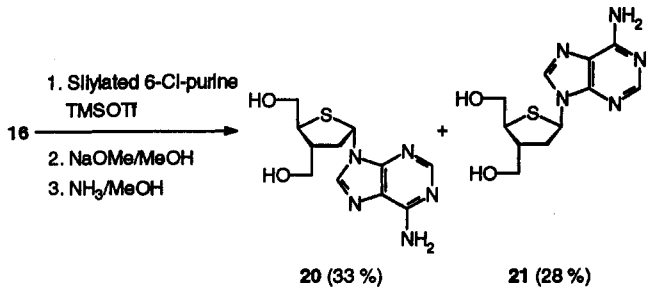


Scheme 4



romethane to give an anomeric mixture of the protected nucleoside (Scheme 3). Deblocking with methanolic ammonia and separation of the anomers by semipreparative HPLC (C-18) gave **14** and **15** in 24 and 35% yield, respectively. Condensation of **9** with silylated cytosine in dichloromethane using the same procedure as for silylated thymine was not successful. Instead, **9** was converted to the corresponding acetate **16** in 99% yield by treatment with mercuric acetate in glacial acetic acid (Scheme 4).[29] Condensation of **16** with silylated cytosine in methylene chloride gave mainly the unsaturated compound **17**, even at −20 °C. In acetonitrile, elimination still occurred, but **18** and **19** could, after deblocking with methanolic ammonia and separation on HPLC (C-18), be isolated in 28 and 36% yield, respectively. Trimethylsilyl triflate-promoted condensation of **16** with 6-chloropurine in dichloromethane gave an anomeric mixture of nucleosides in 90% yield (Scheme 5). Deprotection of the benzoyl groups followed by treatment with saturated methanolic ammonia at 100 °C in a sealed vessel gave, after HPLC (C-18), separation of the anomeric mixture the α-anomer **20** in 33% yield and the β-anomer **21** in 28% yield. Compounds **14**, **15** and **18**–**21** were tested for inhibition of HIV multiplication in a XTT assay in M 4 cells.[30] All compounds were found to be inactive in the assay.

Scheme 5



Structure Assignments. The *erythro* assignment of configuration for compounds **9** and **14**–**21** was based on the X-ray crystallographic structure of compound **17**.[31] Assignment of the α- and β-anomeric configuration for the nucleosides was based on NOE difference spectroscopy and on characteristic ^{1}H NMR features. It is well known that the differences in chemical shift between H-2'a and H-2'b of α-anomers is greater than that of the corresponding β-anomers.[8,21] For the anomeric nucleoside pairs examined, H-2'a and H-2'b were well resolved in **14**, **18**, and **20**, therefore assigned as α-anomers, but unresolved in **15**, **19**, and **21** and thus assigned as β-anomers. It has also been reported that protons syn to the base are more deshielded than those which are anti.[32] The H-4' proton of the β-anomers **15**, **19**, and **21** appeared at a higher field than that of the corresponding α-anomers. The reverse relationship was observed for the H-3' proton. ^{1}H NOE difference spectroscopy was performed on a Bruker AC-P operating at 300.13 MHz on **20** and **21**, which were *p*-nitrobenzoylated at N-6 and at the two hydroxyls. Irradiation of H-1' (6.3 ppm) in the β-anomer gave enhancement of H-2'a (4.3%) and H-4' (1.1%) but no enhancement of H-3'. Irradiation of H-1' (6.4 ppm) in the α-anomer gave enhancement of H-2'b (6.0%) and H-3' (3.3%) but no enhancement of H-4'. By further NOE enhancement studies on the α-anomer it was concluded that H-2'a, H-6' and H-4' were located on one face of the ring plane, whereas H-1', H-2'b, H-3', and H-5' were located on the opposite face. UV-absorption spectra recorded for compounds **20** and **21** had λ_{max} of 261 nm which verified the N-9 regioselectivity of the glycosylation reaction.[21]

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 FX-100 or Bruker AC-250 instrument, using $CDCl_3$ or DMSO solutions with TMS as internal standard. UV absorption spectra were recorded with a Perkin-Elmer Lambda 5 or a HITACHI U-2000 spectrophotometer. TLC was performed on Merck precoated 60 F-254 plates. Spots were visualized by UV light and/or charring with ethanolic sulfuric acid (1:1). Column chromatography was 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.

(2*R*,3*R*)-1-*O*-(*p*-Bromobenzyl)-3-(2'-propenyl)-1,2,4-butanetriol (2). To benzoic acid (12.74 g, 0.104 mol) and diethyl azodicarboxylate (DEAD) (18.18 g, 0.104 mol) dissolved in diethyl ether (200 mL) were added a solution of triphenylphosphine (27.40 g, 0.104 mol) and compound **1** (10.96 g, 34.8 mmol) in diethyl

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ether (200 mL). The reaction mixture was stirred overnight at room temperature. The white precipitate was filtered off, the solution was concentrated and purified by flash column chromatography (toluene–ethyl acetate, 50:1) to give the dibenzoylated compound as a syrup. This compound was dissolved in methanol (225 mL), sodium methoxide (1.1 M, 30 mL) was added, and the solution was stirred overnight at room temperature. The solution was neutralized using Dowex 50W×8 (H^+), filtered, concentrated, and purified by flash column chromatography (toluene–ethyl acetate, 1:1) to give compound **2** (6.30 g, 58%) as a colorless syrup. **2**: $[\alpha]^{22}_D$ −11.6° (*c* 1.0, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.4–1.8 (m, 1H, H-3), 2.15 (dt, 2H, H-1′), 3.0–3.3 (broad, 2H, OH-2 and OH-4), 3.5 (m, 2H, H-1), 3.6–3.4 (m, 3H, H-4 and H-2), 4.50 (s, 2H, CH_2Ph), 4.9–5.2 (m, 2H, H-3′a and H-3′b), 5.5–6.0 (m, 1H, H-2′), 7.15–7.5 (m, 4H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 33.0 (C-1′), 41.6 (C-3), 63.4 (C-4), 72.5, 72.9, 73.1 (CH_2Ph, C-1 and C-2), 116.6 (C-3′), 121.5, 129.1, 131.3, 135.8, 136.4 (C-2′ and aromatic C). Anal. Calcd for $C_{14}H_{19}O_3Br$: C, 53.35; H, 6.08. Found: C, 53.08; H, 6.00.

(2*R*,3*R*)-4-*O*-Benzoyl-1-*O*-(*p*-bromobenzyl)-3-(2′-propenyl)-1,2,4-butanetriol (3). Compound **2** (3.00 g, 9.53 mmol), tetrabutylammonium hydrogen sulfate (0.65 g, 1.90 mmol), and benzoyl chloride (1.11 mL, 9.53 mmol) were dissolved in dichloromethane (220 mL). The mixture was cooled to −5 °C and aqueous sodium hydroxide (5%, 20 mL) was added. Stirring was continued at −5 °C for 1 h and then the mixture was allowed to attain room temperature. The organic layer was separated, washed with water, dried, filtered, and concentrated. Purification by flash column chromatography (toluene–ethyl acetate 3:1) gave compound **3** (3.19 g, 79%) as a colorless syrup. **3**: $[\alpha]^{22}_D$ −10.7° (*c* 1.0, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 2.2–2.4 (m, 3H, H-3 and H-1′), 2.60 (d, 1H, OH), 3.5 (m, 2H, H-1a and H-1b), 3.8–3.9 (m, 1H, H-2), 4.5 (d and s, 4H, H-4 and CH_2Ph), 4.9–5.2 (m, 2H, H-3′a and H-3′b), 5.5–6.0 (m, 1H, H-2′), 7.1–8.1 (m, 9H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 32.7 (C-1′), 40.4 (C-3), 63.6 (C-4), 70.3 (C-2), 72.5, 72.6 (CH_2Ph and C-1), 117.1 (C-3′), 121.4–136.5 (C-2′ and aromatic C), 166.1 (COPh). Anal. Calcd for $C_{21}H_{23}O_4Br$: C, 60.15; H, 5.53. Found: C, 60.03; H, 5.58.

Methyl 3-*C*-[(Benzoyloxy)methyl]-5-*O*-(*p*-bromobenzyl)-2,3-dideoxy-α-and-β-L-*threo*-pentofuranoside (4). To an ice-cold mixture of compound **3** (3.88 g, 9.26 mmol) and *N*-methylmorpholine *N*-oxide (2.50 g, 18.52 mmol) in tetrahydrofuran–water (3:1, 65 mL) was added osmium tetraoxide (9.25 mL, 0.185 mmol, 0.02 M in *tert*-butyl alcohol stabilized with 1% *tert*-butyl hydroperoxide). After a few minutes, the ice bath was removed and the reaction mixture was stirred overnight at room temperature. Sodium hydrogen sulfite (1.5 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, dired, filtered, and concentrated. The crude compound was dissolved in tetrahydrofuran–water (3:1, 110 mL) and treated with sodium periodate (3.96 g, 18.5 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, filtered, concentrated, and residual solvents were coevaporated with toluene. The residue was treated with methanolic hydrogen chloride (0.05%, w/w, 30 mL) for 1 h, 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 **4** (3.70 g, 92%) as a colorless syrup. **4**: ^1H NMR (100 MHz, $CDCl_3$) δ 1.8–2.9 (m, 3H, H-3, H-2a and H-2b), 3.35, 3.37 (2s, 3H, OCH_3), 3.5–3.7 (m, 2H, H-5), 4.3–4.5 (m, 5H, H-4, H-6 and CH_2Ph), 5.1 (m, 1H, H-1), 7.1–8.0 (m, 9H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 35.9, 36.3 (C-2), 38.2, 39.0 (C-3), 54.8, 55.1 (OCH_3), 64.0, 64.1 (C-6), 69.7, 70.2, 72.7 (C-5 and CH_2Ph), 77.5, 79.4 (C-4), 104.1, 104.9 (C-1), 121.2–136.7 (aromatic C), 165.9 (COPh). Anal. Calcd for $C_{21}H_{23}O_5Br$: C, 57.94; H, 5.32. Found: C, 57.84; H, 5.33.

Methyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α-and-β-L-*threo*-pentofuranoside (5). A solution of compound **4** (1.19 g, 2.74 mmol) in diethyl ether (2 mL) was dissolved in liquid ammonia (50 mL) in a Dewar bottle. Sodium (500 mg, 22 mmol) was added in small portions over 5 min. The solution was stirred for 30 min and then quenched by 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 toluene. The crude residue was dissolved in pyridine (30 mL), benzoyl chloride (1.00 mL, 8.61 mmol) was added, and the solution was stirred overnight at room temperature. Water (5 mL) was added and the mixture was 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, 9:1) gave compound **5** (0.83 g, 82%) as a colorless syrup. **5**: ^1H NMR (100 MHz, $CDCl_3$) δ 2.0–2.3 (m, 2H, H-2), 2.8–3.1 (m, 1H, H-3), 3.36 and 3.38 (2s, 3H, OCH_3), 4.4–4.7 (m, 5H, H-5, H-6 and H-4), 5.0–5.2 (m, 1H, H-1), 7.2–8.1 (m, 10H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) 35.8, 36.2 (C-2), 38.4, 39.3 (C-3), 54.8, 55.1 (OCH_3), 63.7, 63.9, 64.3 (C-5 and C-6), 76.2, 78.1 (C-4), 103.9, 104.9 (C-1), 128.0–132.8 (aromatic C), 165.8 (COPh). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 67.84; H, 5.89.

5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-L-*threo*-pentose Dibenzyl Dithioacetal (6). Compound **5** (0.191 g, 0.516 mmol) was treated at room temperature with benzyl mercaptan (0.24 mL, 2.07 mmol) in dichloromethane (3 mL) containing a catalytic amount of stannic chloride for 24 h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate, dried, filtered, concentrated, and purified by flash column chromatography (toluene–ethyl acetate, 9:1) to give compound **6** (0.266 g, 72%) as a colorless syrup. **6**: $[\alpha]^{22}_D$ −8.1° (*c* 1.0 $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.6–1.85 (m, 2H, H-2), 1.9–2.15 (m, 1H, H-3), 2.7 (d, 1H, OH), 3.6–3.8 (m, 6H, CH_2Ph, H-1 and H-4), 3.9–4.4 (m, 4H, H-5 and H-6), 7.2–8.0 (m, 20H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 34.0, 34.6, 34.9 (C-2 and CH_2Ph), 38.9 (C-3), 47.9 (C-1), 63.2 (C-4), 67.6, 69.8 (C-5 and C-6), 127.1–138.0 (aromatic C), 166.7 (COPh). Anal. Calcd for $C_{34}H_{34}O_5S_2$: C, 69.0; H, 5.84, S, 10.93. Found: C, 69.47; H, 5.82; S, 10.87.

5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-L-*threo*-pentose Diethyl Dithioacetal (7). Compound **5** (50 mg, 0.135 mmol) was treated with ethyl mercaptan (0.043 mL, 0.59 mmol), using the same procedure as described for **6**, to give compound **7** (48 mg, 77%) as a colorless syrup. **7**: $[\alpha]^{22}_D$ −2.3° (*c* 1.0, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.22 (dt, 6H, CH_3), 2.3 (m, 2H, H-2), 2.4–2.9 (m, 6H, CH_2, OH and H-3), 3.9–4.3 (m, 2H, H-1 and H-4), 4.5 (m, 4H, H-5 and H-6), 7.2–8.0 (m, 10H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 14.3 ($2CH_3$), 23.7, 24.0 ($2CH_2$), 34.2 (C-2), 39.0 (C-1), 63.2 (C-4), 67.4, 70.0 (C-5 and C-6), 128.1–132.9 (aromatic C), 166.3 (COPh). Anal. Calcd for $C_{24}H_{30}O_5S_2$: C, 62.31; H, 6.54; S, 13.86. Found: C, 62.14; H, 6.38; S, 14.02.

5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-4-iodo-D-*erythro*-pentose Dibenzyl Dithioacetal (8) and Benzyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-1,4-dithio-α-and β-D-*erythro*-pentofuranoside (9). To a solution of compound **6** (0.248 g, 0.423 mmol) in acetonitrile (20 mL) were added chlorodiphenylphosphine (CDP) (0.311 mL, 1.69 mmol), imidazole (0.173 g, 2.54 mmol), and iodine (0.43 g, 1.70 mmol), and the mixture was stirred overnight. After evaporation of the solvent, the crude residue was suspended in toluene and poured into aqueous sodium hydroxide (1 M). Iodine was added until the organic phase remained iodine-colored. The phases were separated and the toluene phase was washed with aqueous sodium thiosulfate (10%), dried, filtered, concentrated, and purified by column chromatography (toluene–ethyl acetate 50:1) to give **8** (0.023 g, 8%) and **9** (0.134 g, 66%) as colorless syrups. **8**: $[\alpha]^{22}_D$ −37.1° (*c* 0.8, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.8–2.0 (m, 2H, H-2), 3.4–3.6 (m, 1H, H-3), 3.73, 3.78 (2s, 4H, CH_2Ph), 4.0 (m, 2H, H-1, H-4), 4.2–4.8 (m, 4H, H-5, H-6), 7.1–8.1 (m, 20H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 33.0 (C-2), 34.6, 35.1 (CH_2Ph), 36.7, 37.9 (C-3, C-4), 47.6 (C-1), 66.0, 66.7 (C-5, C-6), 124.9–137.4 (aromatic C), 165.1, 165.4 (COPh). Anal. Calcd for $C_{34}H_{33}O_4S_2I$: C, 58.62; H, 4.77; S, 9.21. Found: C, 58.77; H, 4.82; S, 9.33. **9**: ^1H NMR (100 MHz, $CDCl_3$) δ 2.0–2.3 (m, 2H, H-2), 2.8 (m, 1H, H-3), 3.8 (m, 3H, CH_2Ph and H-4), 4.5 (m, 5H,

H-1, H-5 and H-6), 7.1–8.1 (m, 15H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 37.2, 37.3 (C-2), 40.4, 40.8 (C-3), 44.2, 45.6 (C-4), 49.0, 49.7, 50.3 and 51.2 (C-1 and CH_2Ph), 65.0, 65.4, 66.6 and 67.5 (C-5 and C-6), 126.8–137.7 (aromatic C), 165.6, 165.7 (COPh). Anal. Calcd for $C_{27}H_{26}O_4S_2$: C, 67.76; H, 5.48; S, 13.40. Found: C, 67.82; H, 5.42; S, 13.30.

Benzyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-1,4-dithio-α- and β-L-*threo*-pentofuranoside (10). Compound **8** (42 mg, 0.060 mmol) and a catalytic amount of sodium iodide was dissolved in toluene (2 mL) and heated at reflux for 24 h. The mixture was allowed to cool to room temperature and washed with aqueous sodium thiosulfate (10%). The phases were separated and the organic phase was dried, filtered, concentrated, and purified by column chromatography (toluene–ethyl acetate 50:1) to give **10** (13 mg, 45%) as a colorless syrup. **10**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.0–2.3 (m, 2H, H-2), 2.8 (m, 1H, H-3), 3.8 (m, 3H, CH_2PH and H-4), 4.5 (m, 5H, H-1, H-5 and H-6), 7.1–8.1 (m, 15H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 37.1, 37.4 (C-2), 38.2, 38.5 (C-3), 43.4, 45.7 (C-4), 47.0, 47.7, 49.8 (C-1 and CH_2Ph), 63.3, 63.7, 64.7, 65.0 (C-5 and C-6), 126.8–137.7 (aromatic C), 165.6, 165.7 (COPh). Anal. Calcd for $C_{27}H_{26}O_4S_2$: C, 67.76; H, 5.48; S, 13.40. Found: C, 67.90; H, 5.43; S, 13.28.

5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-4-iodo-D-*erythro*-pentose Diethyl Dithioacetal (11). To a solution of compound **7** (28 mg, 0.061 mmol) in acetonitrile (2 mL) were added chlorodiphenylphosphine (CDP) (0.045 mL, 0.24 mmol), imidazole (25 mg, 0.36 mmol), and iodine (61 mg, 0.24 mmol) using the same procedure as described for **8** and **9** to give **11** (23 mg, 66%) as a colorless syrup. **11**: $[\alpha]^{22}_D$ −24.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.1–1.4 (2t, 6H, CH_3), 1.8–2.2 (m, 2H, H-2), 2.4 (m, 1H, H-3), 2.5–2.8 (m, 4H, CH_2), 4.0 (dd, 1H, H-4), 4.3 (dd, 1H, H-1), 4.5–4.8 (m, 4H, H-5 and H-6), 7.2–8.0 (m, 10H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 14.2, 14.4 ($2CH_3$), 23.7, 24.5 ($2CH_2$), 33.3 (C-2), 37.1, 38.2 (C-3 and C-4), 49.0 (C-1), 66.7, 67.2 (C-5 and C-6), 128.4–133.3 (aromatic C), 165.6, 166.1 (COPh). Anal. Calcd for $C_{24}H_{29}O_4S_2I$: C, 50.35; H, 5.11; S, 11.20. Found: C, 50.49; H, 5.10; S, 11.32.

1-[2',3'-Dideoxy-3'-*C*-(hydroxymethyl)-4'-thio-α- and -β-D-*erythro*-pentofuranosyl]thymine (14 and 15). A suspension 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 clear solution was obtained. Volatile matters were evaporated off and the residue was repeatedly coevaporated with toluene. The resulting syrup was dissolved in dichloromethane (5 mL) under nitrogen. To this solution was added compound **9** (153 mg, 0.32 mmol) followed by the addition of trimethylsilyl triflate (0.075 mL, 0.33 mmol) and mercuric acetate (0.102 g, 0.32 mmol), and the solution was stirred for 24 h at room temperature. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate, stirred for 30 min, diluted with dichloromethane, washed with saturated aqueous sodium hydrogen carbonate, dried, filtered, concentrated, and purified by column chromatography (chloroform–ethyl acetate 1:1) to give an anomeric mixture of the protected nucleoside. This mixture was treated with saturated methanolic ammonia (20 mL) for 24 h at room temperature. After concentration to dryness, the residue was dissolved in water and extracted with dichlorcmethane. 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 dryness to give **14** (29.6 mg, 35%) and **15** (20.2 mg, 24%). **14**: $[\alpha]^{22}_D$ +81.6° (*c* 0.59, H_2O); ^{1}H NMR (250 MHz, DMSO) δ 1.83 (d, *J* = 1.1 Hz, 3 H, 5-CH_3), 2.01 (ddd, $J_{2'a,2'b}$ = 11.5 Hz, $J_{2'a,3'}$, = 11.5 Hz, $J_{2'a,1'}$ = 9.5 Hz, 1 H, H-2'a), 2.05–2.20 (m, 1 H, H-3'), 2.40 (ddd, $J_{2'b,2'a}$ = 11.5 Hz, $J_{2'b,1'}$ = 6.5 Hz, $J_{2'b,3'}$ = 4.5 Hz, 1 H, H-2'b), 3.39 (dd, $J_{5'a,5'b}$ = 10.4 Hz, $J_{5'a,4'}$ = 7.1 Hz, 1 H, H-5'a), 3.49 (dd, $J_{6'a,6'b}$ = 10.8 Hz, $J_{6'a,3'}$ = 5.3 Hz, 1 H, H-6'a), 3.57 (dd, $J_{6'b,6'a}$ = 10.8 Hz, $J_{6'b,3'}$ = 5.0 Hz, 1 H, H-6'b), 3.67 (dd, $J_{4',3'}$ = 8.8 Hz, $J_{4',5'a}$ = 7.1 Hz, $J_{4',5'b}$ = 4.7 Hz, 1 H, H-4'), 3.76 (dd, $J_{5'b,5'a}$ = 10.4 Hz, $J_{5'b,4'}$ = 4.7 Hz, 1 H, H-5'b), 6.18 (dd, $J_{1'2'a}$ = 9.5 Hz, $J_{1',2'b}$ = 6.5 Hz, 1 H, H-1'), 7.75 (d, *J* = 1.1 Hz, 1 H, H-6); ^{13}C NMR (63 MHz, DMSO) δ 12.0 (5-CH_3), (C-2' hidden in DMSO), 47.5 (C-3'), 53.9 (C-4'), 59.3, 61.7, 63.5 (C-1', C-5' and C-6'), 110.1 (C-5), 136.5 (C-6), 150.7 (C-2), 163.6 (C-2). Anal. Calcd for $C_{11}H_{16}O_4N_2S$: C, 48.52; H, 5.92; N, 10.29; S, 11.78. Found: C, 48.33; H, 5.74; N, 10.13; S, 11.68. **15**: $[\alpha]^{22}_D$ −34.9° (*c* 0.40, H_2O); ^{1}H NMR (250 MHz, DMSO) δ 1.81 (d, *J* = 1.1 Hz, 3 H, 5-CH_3), 2.16–2.25 (m, 2 H, H-2'), 2.30–2.45 (m, 1 H, H-3'), 3.35 (m, 1 H, H-4'), 3.40 (dd, $J_{6'a,6'b}$ = 10.8 Hz, $J_{6'a,3'}$ = 6.0 Hz, 1 H, H-6'a), 3.48 (dd, $J_{6'b,6'a}$ = 10.8 Hz, $J_{6'b,3'}$ = 5.7 Hz, 1 H, H-6'b), 3.62 (dd, $J_{5'a,5'b}$ = 11.2 Hz, $J_{5'a,4'}$ = 5.4 Hz, 1 H, H-5'a), 3.74 (dd, $J_{5'b,5'a}$ = 11.2 Hz, $J_{5'b,4'}$ = 5.0 Hz, 1 H, H-5'b), 6.05 (dd, $J_{1',2'b}$ = 5.8 Hz, $J_{1',2'a}$ = 5.5 Hz, 1 H, H-1'), 8.03 (d, *J* = 1.1 Hz, 1 H, H-6); ^{13}C NMR (63 MHz, DMSO) δ 12.2 (5-CH_3), (C-2' hidden in DMSO), 45.3 (C-3'), 61.5, 61.6, 63.4 (C-1', C-5' and C-6'), 109.0 (C-5), 137.0 (C-6), 150.7 (C-2), 163.5 (C-4). Anal. Calcd for $C_{11}H_{16}O_4N_2S$: C, 48.52; H, 5.92; N, 10.29; S, 11.78. Found: C, 48.35; H, 5.82; N, 10.13; S, 11.70.

1-*O*-Acetyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-4-thio-α- and -β-D-*erythro*-pentofuranose (16). Compound **9** (0.182 g, 0.381 mmol) and mercuric acetate (0.243 g, 0.761 mmol) in glacial acetic acid (5 mL) were stirred at room temperature for 30 min. The solvent was evaporated and coevaporated with toluene. The residue was diluted with dichloromethane, filtered through Celite, and concentrated. Flash chromatography (toluene–ethyl acetate 9:1) gave compound **16** (0.156 g, 99%) as a colorless syrup. **16**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.03, 2.06 (2s, 3H, $COOCH_3$), 2.2–2.6 (m, 2H, H-2), 3.0 (m, 1H, H-3), 3.6–4.0 (m, 1H, H-4), 4.1–4.7 (m, 4H, H-5 and H-6), 6.1–6.2 (m, 1H, H-1), 7.0–7.9 (m, 10H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 21.1 (CH_3), 37.2, 40.8 (C-2), 43.6, 44.2 (C-3), 48.8, 49.0 (C-4), 64.8, 65.4, 66.0, 67.2 (C-5 and C-6), 80.9, 81.9 (C-1), 124.9–132.9 (aromatic C), 165.5, 165.7 (COPh), 169.8 (COOMe). Anal. Calcd for $C_{22}H_{22}O_6S$: C, 63.75; H, 5.35; S, 7.74. Found: C, 63.98; H, 5.52; S, 7.58.

5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-1,2,3-trideoxy-4-thio-D-*erythro*-pent-1-enofuranose (17). Cytosine (25 mg, 0.23 mmol) was silylated following the same procedure as for the preparation of **14** and **15** and dissolved in dichloromethane (2 mL). Compound **16** (24 mg, 0.058 mmol) was added, followed by the addition of trimethylsilyl triflate (0.070 mmol, as a solution in dichloromethane). After 30 min at room temperature, saturated sodium hydrogen carbonate was added. The phases were separated and the organic phase was dried, filtered, concentrated, and purified by column chromatography (toluene–ethyl acetate 20:1) to give compound **17** (18 mg, 85%) as a colorless syrup which solidified on standing. **17**: $[\alpha]^{22}_D$ + 198° (*c* 1.0, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 3.5 (m, 1H, H-3), 4.0–4.6 (m, 5H, H-4, H-5 and H-6), 5.5 (dd, 1H, H-2), 6.3 (dd, 1H, H-1), 7.3–8.1 (m, 10H, aromatic H); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 48.4, 49.8 (C-3 and C-4), 63.4, 65.8 (C-5 and C-6), 119.9, 127.8 (C-1 and C-2), 128.0–132.8 (aromatic C), 165.8, 165.9 (COPh). Anal. Calcd for $C_{20}H_{18}O_4S$: C, 67.78; H, 5.12; S, 9.05. Found: C, 67.85; H, 5.14; S, 8.96.

1-[2',3'-Dideoxy-3'-*C*-(hydroxymethyl)-4'-thio-α- and -β-D-*erythro*-pentofuranosyl]cytosine (18 and 19). Cytosine (100 mg, 0.901 mmol) was silylated following the same procedure as for the preparation of **14** and **15** and dissolved in acetonitrile (5 mL) under nitrogen. Compound **16** (103 mg, 0.249 mmol) was added followed by the addition of trimethylsilyl triflate (0.13 mL, 0.574 mmol) and the reaction mixture was stirred at −20 °C for 1 h. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate, stirred for 30 min, diluted with acetonitrile, washed with saturated aqueous sodium hydrogen carbonate, dried, concentrated, and purified by column chromatography (ethyl acetate–methanol 4:1) to give an anomeric mixture of the protected nucleoside. The mixture was treated with saturated methanolic ammonia (20 mL) 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 **18** (23.3 mg, 36%) and **19** (17.9 mg, 28%). **18**: $[\alpha]^{22}_D$ +99.6° (*c* 0.47, H_2O); ^{1}H NMR (250 MHz, DMSO) δ 1.91 (ddd, $J_{2'a,2'b}$ = 11.9 Hz, $J_{2'a,3'}$ = 11,9 Hz, $J_{2'a,1'}$ = 9.6 Hz, 1 H, H-2'a), 2.10 (m, 1 H, H-3'), 2.39 (ddd, $J_{2'b,2'a}$ = 11.9 Hz, $J_{2'b,1'}$ = 6.5 Hz, $J_{2'b,3'}$ = 5.8 Hz, 1 H, H-2'b), 3.39 (dd, $J_{5'a,5'b}$ = 10.5 Hz, $J_{5'a,4'}$ = 7.2 Hz, 1 H, H-5'a), 3.47 (dd, $J_{6'a,6'b}$ = 10.9 Hz, $J_{6'a,3'}$ = 5.5 Hz, 1 H, H-6'a), 3.54 (dd, $J_{6'b,6'a}$ = 10.9 Hz, $J_{6'b,3'}$ = 5.5 Hz, 1 H, H-6'b), 3.62 (ddd,

$J_{4'3'}$ = 8.9 Hz, $J_{4'5'a}$ = 7.2 Hz, $J_{4',5'b}$ = 4.8 Hz, 1 H, H-4'), 3.74 (dd, $J_{5'b,5'a}$ = 10.5 Hz, $J_{5'b,4'}$ = 4.8 Hz, 1 H, H-5'b), 5.80 (d, $J_{5,6}$ = 7.4 Hz, 1 H, H-5), 6.25 (dd, $J_{1'2'a}$ = 9.6 Hz, $J_{1'2b}$ = 6.5 Hz, 1 H, H-1'), 7.88 (d, $J_{6,5}$ = 7.4 Hz, 1 H, H-6); ^{13}C NMR (63 MHz, DMSO) δ C-2' hidden in DMSO), 47.6 (C-3'), 53.7 (C-4'), 60.2, 61.7, 64.6 (C-1', C-5' and C-6'), 94.8 (C-5), 141.8 (C-6), 155.3 (C-2), 165.2 (C-4). Anal. Calcd for $C_{10}H_{15}O_3N_3S\cdot0.5H_2O$: C, 45.10; H, 6.06; N, 15.78; S, 12.04. Found: C, 45.17; H, 6.11; N, 15.64; S, 12.15. **19**: $[\alpha]^{22}_D$ −53.6° (c 0.36, H_2O); ^{1}H NMR (250 MHz, DMSO) δ 2.05–2.30 (m, 3 H, H-2' and H-3'), 3.32 (dd, $J_{6'a,6'b}$ = 12.1 Hz, $J_{6',3'}$ = 6.0 Hz, 2 H, H-6'), 3.44 (m, 1 H, H-4'), 3.58 (dd, $J_{5'a,5'b}$ = 11.0 Hz, $J_{5'a,4'}$ = 5.8 Hz, 1 H, H-5'a), 3.73 (dd, $J_{5'b,5'a}$ = 11.0 Hz, $J_{5'b,4'}$ = 5.2 Hz, 1 H, H-5'b), 5.76 (d, $J_{5,6}$ = 7.4 Hz, 1 H, H-5), 6.08 (dd, $J_{1',2'a}$ = 4.3 Hz, $J_{1',2'b}$ = 6.0 Hz, 1 H, H-1'), 8.01 (d, $J_{6,5}$ = 7.4 Hz, 1 H, H-6); ^{13}C NMR (63 MHz, DMSO) δ (C-2' hidden in DMSO), 45.5 (C-3'), 53.5 (C-4'), 61.8, 62.1, 63.9 (C-1', C-5', and C-6'), 93.8 (C-5), 142.1 (C-6), 155.4 (C-2), 165.4 (C-4). Anal. Calcd for $C_{10}H_{15}O_3N_3S\cdot0.5H_2O$: C, 45.10; H, 6.06; N, 15.78; S, 12.04. Found: C, 45.05; H, 5.93; N, 15.68; S, 12.22.

9-[2',3'-Dideoxy-3'-*C*-(hydroxymethyl)-4'-thio-α- and -β-D-*erythro*-pentofuranosyl]adenine (20 and 21). 6-Chloropurine (31.6 mg, 0.20 mmol) was silylated following the same procedure as previously described and was dissolved under nitrogen in dichloromethane (1 mL). Compound **16** (50.0 mg, 0.12 mmol) in dichloromethane (0.5 mL) was added followed by the gradual addition of a trimethylsilyl triflate solution in dichloromethane (40.6 μL, 0.22 mmol in 0.5 mL) over a period of 6 h. After stirring for 24 h at room temperature the reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate, stirred for 30 min, and diluted with dichloromethane. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate, dried, filtered, and concentrated. Purification by column chromatography (toluene–ethyl acetate 2:1) gave an anomeric mixture of the protected nucleoside (68.2 mg, 90%). Deprotection of the benzoyl groups in a quantitative yield were performed using diluted sodium methoxide (1 M) in methanol. Conversion of the 6-chloropurine moiety to adenine was accomplished by treating the deprotected anomeric mixture (40.0 mg, 0.13 mmol) with methanolic ammonia (5 mL, saturated at −40 °C for 30 min) in a sealed steel vessel at 100 °C for 24 h. Evaporation of the methanol followed by column chromatography (ethyl acetate–methanol 6:1) gave a mixture of compound **20** and **21** (30.0 mg, 80%). Separation on HPLC (water–methanol 80:20, v/v) gave the α-anomer **20** (10.0 mg, 33%) followed by the β-anomer **21** (8.5 mg, 28%). **20**: $[\alpha]_D$ +69.9° (c 0.50, methanol); UV (H_2O) λ_{max} 261 nm; ^{1}H NMR (250 MHz, DMSO) δ 2.22–2.27 (m, 1H, H-2'a), 2.55–2.70 (m, 2H, H-2'b, H-3'), 3.43 (dd, 1H, H-5'a), 3.52 (dd, 1H, H-6'a), 3.59 (dd, 1H, H-6'b), 3.69–3.81 (m, 2H, H-4' and H-5'b), 6.19 (dd, $J_{1',2'a}$ = 8.8 Hz, $J_{1',2'b}$ = 6.8 Hz, 1H, H-1'), 7.17 (s, 2H, NH_2), 8.14 (s, 1H, H-2), 8.37 (s, 1H, H-8); ^{13}C NMR (63 MHz, DMSO) δ (C-2' hidden in DMSO), 48.1 (C-3'), 54.4 (C-4'), 58.6, 62.1, 64.7 (C-1', C-5', C-6'), 119.2 (C-5), 139.1 (C-8), 149.5 (C-4), 152.6 (C-2), 156.1 (C-6). **21**: $[\alpha]_D$ −24.2° (c 0.40, methanol); UV (H_2O) λ_{max} 261 nm; ^{1}H NMR (250 MHz, DMSO) δ 2.36–2.60 (m, 3H, H-2', H-3'), 3.42–3.57 (m, 3H, H-4' and H-6'), 3.62 (dd, 1H, H-5'a), 3.81 (dd, 1H, H-5'b), 6.10 (dd, $J_{1',2'a}$ = 3.2 Hz, $J_{1',2'b}$ = 5.8 Hz, 1H, H-1'), 7.17 (s, 2H, NH_2), 8.14 (s, 1H, H-2), 8.47 (s, 1H, H-8); ^{13}C NMR (63 MHz, DMSO) δ (C-2' hidden in DMSO), 45.9 (C-3'), 53.9 (C-4'), 59.8, 61.6, 63.9 (C-1', C-5', C-6'), 119.3 (C-5), 139.4 (C-8), 149.3 (C-4), 152.5 (C-2), 156.2 (C-6). Anal. Calcd for a α/β-mixture of **20** and **21** $C_{11}H_{15}O_2N_5S$: C, 47.0; H, 5.4; N, 24.9; S, 11.4. Found: C, 46.7; H, 5.2; N, 24.7; S, 11.6.

Acknowledgment. We thank the National Swedish Board for Technical Development and Medivir AB for financial support, Medivir AB for the biological testings, and Dr. Ingemar Nilsson, Astra Hässle AB, for the NOE-NMR studies.