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Synthesis of Some 2',3'-Dideoxy-3'-C-Fluoromethyl and 3'-C-Azidomethyl Nucleosides

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SYNTHESIS OF SOME 2',3'-DIDEOXY-3'-C-FLUOROMETHYL AND 3'-C-AZIDOMETHYL NUCLEOSIDES

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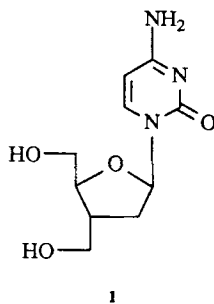
Abstract

The synthesis of 3'-C-fluoromethyl and 3'-C-azidomethyl nucleosides is reported. The 3'-C-fluoromethyl furanoside **4** was synthesized via fluoride ion induced displacement of the corresponding trifluoromethanesulfonate. The 3'-C-hydroxymethyl furanoside **3** was converted to the corresponding 3'-C-azidomethyl furanoside **6** using triphenylphosphine-carbon tetrabromide-lithium azide. The 3'-C-fluoromethyl furanoside derivative **5** and the 3'-C-azidomethyl furanoside derivative **7** were subsequently condensed with silylated purine and pyrimidine bases. Deblocking and separation of the anomers by chromatography afforded the α - and β -nucleoside analogues. The nucleosides were tested for inhibition of HIV multiplication *in vitro* and were found to be inactive in the assay.

Introduction

Since the approval of 3'-azido-3'-deoxythymidine (AZT, zidovudine)¹ for the treatment of AIDS, there has been an intense focus on the synthesis of new nucleoside derivatives as potential candidates for drugs having improved therapeutic properties over AZT. We have recently reported on the synthesis of 2',3'-dideoxy-3'-hydroxymethyl nucleosides, where the cytidine derivative **1** was shown to be a potent inhibitor of HIV *in vitro*.² In view of this result we decided to synthesize and evaluate the corresponding 3'-C-fluoromethyl- and 3'-C-azidomethyl-2',3'-dideoxynucleosides **8** - **19**. The similarity of the fluorine atom to the hydroxyl group in size, electronegativity, and ability to participate in hydrogen bonding³ makes fluorine an excellent substitute for a hydroxyl group and provides a way to introduce a distinctive modification with minimal steric perturbations. One of the most potent anti HIV agents *in vitro* is 1-

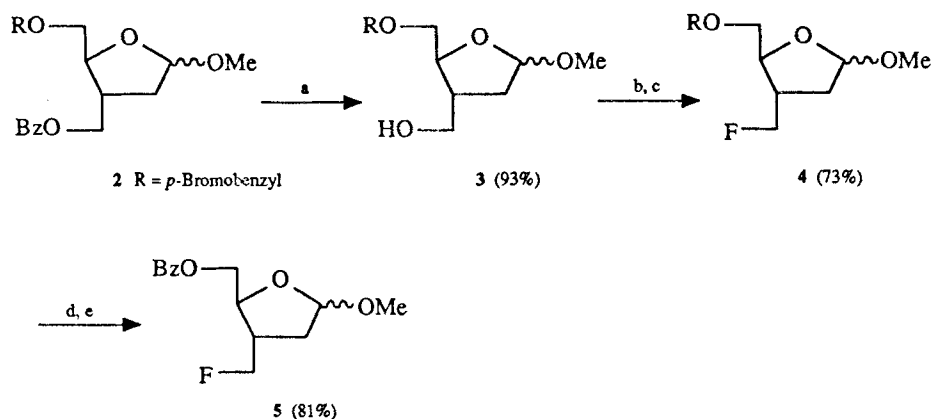
(2',3'-dideoxy-3'-fluoro- β -D-*erythro*-pentofuranosyl)thymine (FddT).⁴ Several other nucleosides with a fluoro substituted sugar moiety have also shown antiviral activity.⁵ Azido substituted nucleosides have also been in focus since the approval of 3'-azido-3'-deoxythymidine for the treatment of AIDS.



Since the completion of the present work the synthesis and anti-HIV activity of 3'-C-hydroxymethyl-, 3'-C-fluoromethyl- and 3'-C-azidomethyl-2',3'-dideoxy-nucleosides have appeared in the patent literature.⁶

Results and discussion.

The now readily available methyl 3-C-[(benzoyloxy)methyl]-5-O-(*p*-bromobenzyl)-2,3-dideoxy-D-*erythro*-pentofuranoside² **2** was partially deblocked using methanolic ammonia to give methyl 5-O-(*p*-bromobenzyl)-3-C-(hydroxymethyl)-2,3-dideoxy-D-*erythro*-pentofuranoside **3** in 93% yield (Scheme I). In the first approach to synthesize the fluoro derivatives, direct displacement of the hydroxyl group in **3** by use of diethylaminosulfur trifluoride (DAST)⁷ was attempted. Compound **3** was treated with either neat DAST,⁸ or by DAST in dichloromethane,⁹ which in both reactions only gave decomposition products. Adding 4-dimethylaminopyridine (DMAP)¹⁰ to the reaction mixture, prevented decomposition but slowed down the reaction rate so that even after several days only about 10% of the desired compound **4** had formed. Binkley¹¹ has reported that trifluoromethanesulfonates readily reacts with tetrabutylammonium halides. Adapting this procedure, compound **3** was treated with trifluoromethanesulfonic anhydride, followed by tetrabutylammonium fluoride (TBAF) in anhydrous tetrahydrofuran at room temperature for 15 min, which gave the desired product **4** in 73% yield (Scheme I).

Scheme I^a

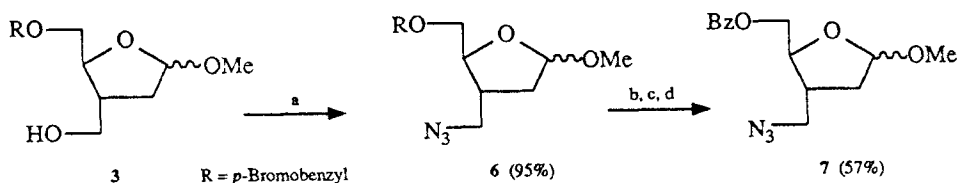
^a (a) NH₃, MeOH; (b) Tf₂O, CH₂Cl₂-pyridine, -15 °C; (c) TBAF, THF; (d) Pd/H₂, EtOH; (e) BzCl, pyridine-CH₂Cl₂

Complete anhydrous conditions was essential to avoid decomposition. Compound **4** was then hydrogenated followed by treatment with benzoyl chloride in pyridine, to afford the 5-*O*-benzoylated furanoside **5** in 81% yield.

To obtain the azido derivative **6**, two reaction routes were attempted. In the first, compound **3** was treated with trifluoromethanesulfonic anhydride, followed by treatment with sodium azide in *N,N*-dimethylformamide, which afforded the 3'-*C*-azidomethyl derivative **6** in 55% yield. The second route, was based on the *in situ* conversion of primary and secondary hydroxyls in nucleosides, to the corresponding azide¹² using triphenylphosphine-carbon tetrabromide-lithium azide. When compound **3** was reacted with this reagent system for 24 h, **6** was isolated in 95% yield (Scheme II). To remove the *p*-bromobenzyl group without affecting the azido group, compound **6** was oxidized with the chromium trioxide-pyridine-acetic anhydride complex^{13,14} in dichloromethane, to afford the corresponding 5-*O*-*p*-bromobenzoyl derivative. Removal of the *p*-bromobenzoyl group by treatment with sodium methoxide in methanol, followed by silica gel column chromatography, and benzoylation gave compound **7** in 57% yield.

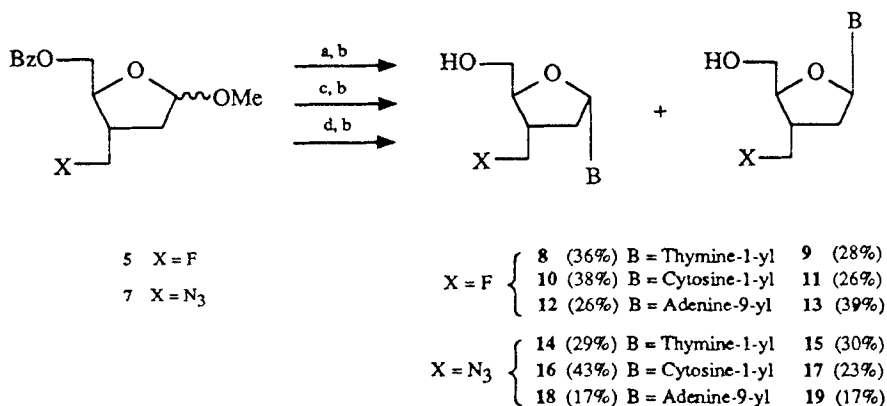
The furanosides **5** and **7** were subsequently condensed with silylated thymine, cytosine and 6-chloropurine¹⁵⁻¹⁹ according to the Vorbrüggen method¹⁹ (Scheme III).

Scheme II^a



^a (a) LiN₃, CBr₄, PPh₃, DMF; (b) CrO₃-pyridine, Ac₂O, CH₂Cl₂; (c) NH₃, MeOH; (d) BzCl, Pyridine.

Scheme III^a



^a(a) Silylated thymine, TBDMSOTf, CH₂Cl₂; (b) NH₃, MeOH; (c) Silylated cytosine, TBDMSOTf, 1,2-dichloroethane; (d) Silylated 6-Cl-purine, TBDMSOTf, CH₂Cl₂.

The anomeric mixtures from the condensations of **5** with silylated thymine were deblocked using methanolic ammonia and separated by silica gel column chromatography to give **8** and **9** in 36% and 28% yields, respectively. The anomeric mixtures from the condensations of **5** with silylated cytosine and silylated 6-chloro-

purine were deblocked using methanolic ammonia and separated by semipreparative HPLC (C-18) to give the nucleosides **10**, **11**, **12**, and **13** in 38%, 26%, 26%, and 39% yields, respectively. The anomeric mixture from the condensations of **7** with silylated thymine was deblocked using methanolic ammonia and treated with *tert*-butyldimethylsilyl chloride in pyridine, and then separated by silica gel column chromatography. Desilylation²⁰ afforded **14** and **15** in 29% and 30% yields, respectively. The anomeric mixture from the condensation of **7** with silylated cytosine was deblocked using methanolic ammonia and separated by semipreparative HPLC (C-18), to give the nucleosides **16** and **17** in 43% and 23% yields, respectively. The anomeric mixture from the condensations of **7** with silylated 6-chloropurine was separated by silica gel column chromatography. The anomers were deblocked using methanolic ammonia to give **18** and **19** in 17% and 17% yields, respectively. Compounds **8-19** were tested for inhibition of HIV replication in H-9 cells but were all found to be inactive.²¹

Structure assignments

The structure assignment of all compounds was mainly based on ¹H NMR data. The introduction of the azido group in compound **6** was evident from the IR spectrum, which showed the characteristic absorption at 2100 cm⁻¹. The ¹H NMR spectrum of the 3'-C-fluoromethyl derivatives displayed a large heteronuclear coupling (²J_{HF} = 47 Hz), and H-3' was shifted downfield (~0.9 ppm) compared to the corresponding hydroxy compounds.² Assignments of the α- and β-anomeric configurations of the nucleosides were based on the same characteristic ¹H NMR features as for the corresponding hydroxy compounds.⁵

Experimental Section

Concentrations were performed under diminished pressure (1-2 kPa) at a bath temperature not exceeding 40 °C. IR spectra were recorded on a PERKIN-ELMER 377 spectrophotometer. NMR spectra were measured with a JEOL GX-270 or FX-100 instrument, using D₂O or CDCl₃ solutions. TMS (for CDCl₃), and TSP or acetone (for D₂O) were used as internal standards. The shifts are reported in ppm (δ scale). UV absorption spectra were recorded with a Perkin-Elmer Lambda 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.

Methyl 5-*O*-(*p*-bromobenzyl)-2,3-dideoxy-3-*C*-(hydroxymethyl)-D-*erythro*-pentofuranoside (3).

Methyl 3-*C*-[(benzyloxy)methyl]-5-*O*-(*p*-bromobenzyl)-2,3-dideoxy-D-*erythro*-pentofuranoside **2** (1.61 g, 3.70 mmol) was treated with methanolic ammonia (30 mL, saturated) for 24 h. The solvent was evaporated, and the residue was purified by flash column chromatography (toluene-ethyl acetate, 1:2) to give compound **3** (1.14 g, 93%) as a colorless syrup. ¹H NMR (100 MHz, CDCl₃): 1.49-2.55 (m, H-2 and H-3), 3.15 (broad, OH-6), 3.27 and 3.33 (2 s, OCH₃), 3.56 (m, H-5 and H-3'), 4.05 (m, H-4), 4.52 (s, CH₂Ph), 4.93 and 5.02 (2 d, *J* = 4.6 and 3.7 Hz, H-1), 7.16-7.5 (m, arom). Anal. Calcd for C₁₄H₁₉O₄Br: C, 50.8; H, 5.8. Found: C, 50.7; H, 5.7.

Methyl 5-*O*-(*p*-bromobenzyl)-2,3-dideoxy-3-*C*-(fluoromethyl)-D-*erythro*-pentofuranoside (4).

To a cold solution (-15 °C) of compound **3** (637 mg, 1.92 mmol) in dichloromethane (15 mL) and pyridine (0.31 mL, 3.85 mmol) under nitrogen, a solution of trifluoromethanesulfonic anhydride (0.38 mL, 2.26 mmol) in dichloromethane (5 mL) was added dropwise. After stirring for 10 min at -15 °C, the mixture was diluted with dichloromethane (100 mL), washed with 1 M hydrogen chloride, saturated aqueous sodium hydrogen carbonate, dried, and concentrated at a bath temperature not exceeding 20 °C. The residue was treated with a solution of anhydrous tetrabutylammonium fluoride in tetrahydrofuran (6 mL, 1 M) for 15 min. The mixture was concentrated and the residue was subjected to flash column chromatography (toluene-ethyl acetate, 9:1) to give compound **4** (466 mg, 73%) as a colorless syrup. ¹H NMR (100 MHz, CDCl₃): 1.54-2.70 (m, H-2 and H-3), 3.30 and 3.34 (2 s, OCH₃), 3.56 (m, H-5), 4.1 (m, H-4), 4.41 and 4.45 (2 dd, *J* = 47 Hz, *J* = 7.1 Hz, *J* = 5.7 Hz, CH₂F), 4.53 (s, CH₂Ph), 5.0 (m, H-1), 7.18-7.30 (m, arom). Anal. Calcd for C₁₄H₁₈O₃BrF: C, 50.5; H, 5.5. Found: C, 50.3; H, 5.4.

Methyl 5-*O*-benzoyl-2,3-dideoxy-3-*C*-(fluoromethyl)-D-*erythro*-pentofuranoside (5).

A mixture of compound **4** (572 mg, 1.72 mmol) in ethanol (40 mL) containing sodium hydrogen carbonate (excess) and 10% Pd on charcoal (50 mg) was treated with

hydrogen for 5 h at ambient pressure. The solids were filtered off and the filtrate was concentrated. The crude residue was dissolved in a mixture of dichloromethane (3 mL) and pyridine (0.3 mL, 3.7 mmol), followed by the addition of benzoyl chloride (0.24 mL, 2.07 mmol). The reaction mixture was stirred for 15 min. Water (2 mL) was added, and the mixture was stirred for 10 min, diluted with dichloromethane, washed with 1 M hydrogen chloride, saturated aqueous hydrogen carbonate, dried, and concentrated. The residue was purified by flash column chromatography (toluene-ethyl acetate, 4:1) to give compound **5** (372 mg, 81%) as a colorless syrup. ^1H NMR (100 MHz, CDCl_3): 1.61-2.95 (m, H-2 and H-3), 3.32 and 3.35 (2 s, OCH_3), 4.25, 4.39 and 4.70 (3 m, H-4, H-5 and CH_2F), 5.03 (m, H-1), 7.42-8.01 (2 m, arom). Anal.Calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4\text{F}$: C, 62.7; H, 6.4. Found: C, 62.6; H, 6.3.

Methyl 3-*C*-(azidomethyl)-5-*O*-(*p*-bromobenzyl)-2,3-dideoxy-D-erythro-pentofuranoside (6).

To a mixture of compound **3** (1.95 g, 5.89 mmol), triphenylphosphine (1.6 g, 6.1 mmol), and lithium azide (1.5 g, 30.6 mmol) in dry *N,N*-dimethylformamide (25 mL) was added carbon tetrabromide (1.95 g, 5.89 mmol) at room temperature. The mixture was vigorously stirred for 24 h. Methanol (3 mL) was added, and the solvent was evaporated. The mixture was diluted with dichloromethane, washed with water, dried, and concentrated. The residue was purified by flash column chromatography (toluene-ethyl acetate, 4:1) to give compound **4** (1.99 g, 95%) as a colorless syrup. ν_{max} 2100 cm^{-1} ; ^1H NMR (100 MHz, CDCl_3): 1.62-2.55 (m, H-2 and H-3), 3.23 and 3.33 (2 s, OCH_3), 3.39 (m, CH_2N_3), 3.50 (m, H-5), 3.97 (m, H-4), 4.52 (s, CH_2Ph), 5.02 (m, H-1), 7.17-7.53 (m, arom). Anal.Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{BrN}_3$: C, 47.2; H, 5.1; N, 11.8. Found: C, 47.2; H, 5.0; N, 11.9.

Methyl 3-*C*-(azidomethyl)-5-*O*-(benzoyl)-2,3-dideoxy-D-erythro-pentofuranoside (7).

To a stirred solution of dry pyridine (4.7 mL, 58.3 mmol) and dichloromethane (20 mL) was added chromium trioxide (2.8 g, 28.0 mmol). The mixture was stirred for 15 min at room temperature. A solution of **6** (1.68 g, 4.72 mmol) in dichloromethane (20 mL) was added, followed by acetic anhydride (3.2 mL, 32.0 mmol), and the mixture was stirred for 10 min at room temperature. The mixture was passed through a short column of silica gel with ethyl acetate as eluent, to give a crude product, which was treated with methanolic ammonia (30 mL, saturated) for 24 h. The solvent was evaporated, and the residue was purified by flash column chromatography (toluene-ethyl acetate, 1:1) and then dissolved in a mixture of dichloromethane (15 mL)

and pyridine (1 mL, 12.4 mmol), after which benzoyl chloride (0.55 mL, 4.73 mmol) was added. The reaction mixture was stirred for 15 min. Water (2 mL) was added, and the mixture was stirred for 10 min, diluted with dichloromethane, washed with 1 M hydrogen chloride, saturated aqueous hydrogen carbonate, dried, and concentrated. The residue was purified by flash column chromatography (toluene-ethyl acetate, 9:1) to give compound **7** (1.0 g, 57%) as a colorless syrup. ^1H NMR (100 MHz, CDCl_3): 1.66–2.76 (m, H-2 and H-3), 3.29 and 3.33 (2 s, OCH_3) 3.44 (m, CH_2N_3), 4.16 (m, H-4), 4.4 (m, H-5), 5.02 (m, H-1), 7.44–8.05 (2 m, arom). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4\text{N}_3$: C, 57.7; H, 5.9; N, 14.4. Found: C, 57.9; H, 5.7; N, 14.4.

General procedure for the silylations. A suspension consisting of the base (1 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 added xylene.

1-[2',3'-Dideoxy-3'-C-(fluoromethyl)- α - and β -D-*erythro*-pentofuranosyl]-thymine (8** and **9**).**

Thymine (150 mg, 1.19 mmol) was silylated according to the general procedure and dissolved in dichloromethane (5 mL) under nitrogen. To this solution was added compound **5** (200 mg, 0.75 mmol) followed by *tert*-butyldimethylsilyl triflate (0.3 mL, 1.31 mmol). The solution was stirred for 24 hours at room temperature, after which 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 nucleosides. The 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 washed with dichloromethane. The aqueous layer was concentrated to a small volume and the mixture was separated by column chromatography (ethyl acetate-methanol, 20:1). The β -anomer was eluted first followed by the α -anomer. The appropriate fractions were combined and evaporated to give **8** (70 mg, 36%) and **9** (54 mg, 28%). An analytical sample of each of the anomers was obtained by HPLC purification (water-methanol, 80:20, v/v). **8**: $[\alpha]_{\text{D}}^{22}$ -13.1° (*c* 0.82, H_2O); UV (H_2O) λ_{max} 268 nm (ϵ 9268); ^1H NMR (270 MHz, D_2O) δ 1.91 (d, J = 1.1 Hz, 5- CH_3), 2.06 (m, H-2'a), 2.60–2.82 (m, H-2'b and H-3'), 3.68 (dd, $J_{4',5'a}$ = 5.1 Hz, $J_{5'a,5'b}$ = 12.8 Hz, H-5'a), 3.85 (dd, $J_{4',5'b}$ = 2.9 Hz, $J_{5'a,5'b}$ = 12.8 Hz, H-5'b), 4.38 (m, $J_{3',4'}$ = 7.7 Hz, $J_{4',5'a}$ = 5.1 Hz, $J_{4',5'b}$ = 2.9 Hz, H-4), 4.46–4.75 (2 m, $J_{3',3'a}$ = $J_{3',3'b}$ = 9.5 Hz, $J_{3'a,3'b}$

= 15.5 Hz, $J_{3'',a,F} = J_{3'',b,F} = 47$ Hz, H-3''a,b), 6.15 (t, $J_{1',2',a,b} = 6.6$ Hz, H-1'), 7.60 (d, $J = 1.1$ Hz, H-6). Anal. Calcd for $C_{11}H_{15}O_4N_2F$: C, 51.2; H, 5.8; N, 10.8. Found: C, 50.9; H, 5.8; N, 10.9. **9**: $[\alpha]^{22}_D +16.3^\circ$ (c 0.6, H₂O); UV (H₂O) λ_{max} 268 nm (ϵ 8880); 1H NMR (270 MHz, D₂O) δ 1.91 (d, $J = 0.7$ Hz, 5-CH₃), 2.32 (m, H-2'), 2.73 (m, H-3'), 3.78 (dd, $J_{4',5'a} = 4.8$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'a), 3.94 (dd, $J_{4',5'b} = 2.9$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'b), 4.1 (m, $J_{3',4'} = 8.5$ Hz, $J_{4',5'a} = 4.8$ Hz, $J_{4',5'b} = 2.9$ Hz, H-4), 4.44-4.73 (2 m, $J_{3',3''a} = J_{3',3''b} = 9.5$ Hz, $J_{3'',a,3''b} = 15.7$ Hz, $J_{3'',a,F} = J_{3'',b,F} = 46.9$ Hz, H-3''a,b), 6.15 (dd, $J_{1',2'a} = 4.4$ Hz, $J_{1',2'b} = 7.3$ Hz, H-1'), 7.77 (d, $J = 1.1$ Hz, H-6). Anal. Calcd for $C_{11}H_{15}O_4N_2F$: C, 51.2; H, 5.8; N, 10.8. Found: C, 51.1; H, 5.8; N, 11.0.

1-[2',3'-Dideoxy-3'-C-(fluoromethyl)- α - and β -D-*erythro*-pentofuranosyl]-cytosine (10 and 11).

Cytosine (200 mg, 1.8 mmol) was silylated according to the general procedure and dissolved in 1,2-dichloroethane (5 mL) under nitrogen. To this solution was added compound **5** (110 mg, 0.41 mmol) followed by *tert*-butyldimethylsilyl triflate (0.4 mL, 1.74 mmol). The solution was stirred for 24 hours at room temperature, after which 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 nucleosides. The 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 washed with dichloromethane. The aqueous layer was concentrated to a small volume and the mixture was separated by HPLC (water-methanol, 94:6, v/v). The α -anomer was eluted first followed by the β -anomer. The appropriate fractions were combined and evaporated to give **10** (38 mg, 38%) and **11** (26 mg, 26%). **10**: $[\alpha]^{22}_D -53.7^\circ$ (c 0.94, H₂O); UV (H₂O) λ_{max} 272 nm (ϵ 7762); 1H NMR (270 MHz, D₂O) δ 1.98 (m, H-2'a), 2.58-2.80 (m, H-2'b and H-3'), 3.68 (dd, $J_{4',5'a} = 5.1$ Hz, $J_{5'a,5'b} = 12.45$ Hz, H-5'a), 3.85 (dd, $J_{4',5'b} = 2.9$ Hz, $J_{5'a,5'b} = 12.45$ Hz, H-5'b), 4.37 (m, $J_{3',4'} = 7.7$ Hz, $J_{4',5'a} = 5.1$ Hz, $J_{4',5'b} = 2.9$ Hz, H-4), 4.39-4.72 (2 m, $J_{3',3''a} = 9.9$ Hz, $J_{3',3''b} = 9.5$ Hz, $J_{3'',a,3''b} = 19.0$ Hz, $J_{3'',a,F} = J_{3'',b,F} = 47$ Hz, H-3''a,b), 6.04 (d, $J_{5,6} = 7.7$ Hz, H-5), 6.12 (t, $J_{1',2'a} = J_{1',2'b} = 6.6$ Hz, H-1'), 7.70 (d, $J_{5,6} = 7.3$ Hz, H-6). Anal. Calcd for $C_{10}H_{14}O_3N_3F \times 1 H_2O$: C, 47.6; H, 6.0; N, 16.6. Found: C, 47.6; H, 5.8; N, 16.6. **11**: $[\alpha]^{22}_D +44.8^\circ$ (c 0.6, H₂O); UV (H₂O) λ_{max} 272 nm (ϵ 8515); 1H NMR (270 MHz, D₂O) δ 2.23 (m, $J_{1',2'a} = 4.0$ Hz, $J_{2'a,3'} = 8.4$ Hz, $J_{2'a,2'b} = 13.0$ Hz, H-2'a), 2.39 (m, $J_{1',2'b} = 7.0$ Hz, $J_{2'b,3'} = 8.5$ Hz, $J_{2'a,2'b} = 13.0$ Hz, H-2'b), 2.65 (m, H-3'), 3.77 (dd, $J_{4',5'a} = 5.1$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'a), 3.93 (dd, $J_{4',5'b} = 2.9$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'b), 4.11 (m, $J_{3',4'} = 8.1$ Hz, $J_{4',5'a} = 5.1$ Hz, $J_{4',5'b} = 2.9$ Hz, H-4), 4.43-4.73 (two m, $J_{3',3''a} = J_{3',3''b} = 9.5$ Hz, $J_{3'',a,3''b} = 19.0$ Hz, $J_{3'',a,F} = J_{3'',b,F} = 47$ Hz, H-3''a,b), 6.03 (d, $J_{5,6} =$

7.3 Hz, H-5), 6.10 (dd, $J_{1',2'a} = 4.0$ Hz, $J_{1',2'b} = 7.0$ Hz, H-1'), 7.93 (d, $J_{5,6} = 7.3$ Hz, H-6). Anal. Calcd for $C_{10}H_{14}O_3N_3F \times 1 H_2O$: C, 47.6; H, 6.0; N, 16.6. Found: C, 47.2; H, 5.8; N, 16.2.

9-[2',3'-Dideoxy-3'-C-(fluoromethyl)- α - and β -D-erythro-pentofuranosyl]-adenine (12 and 13).

6-Chloropurine (120 mg, 0.78 mmol) was silylated according to the general procedure and dissolved in dichloromethane (5 mL) under nitrogen. To this solution was added compound **5** (95 mg, 0.29 mmol) followed by *tert*-butyldimethylsilyl triflate (0.3 mL, 1.31 mmol). The solution was stirred for 24 hours at 40 °C, after which 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 nucleosides. The mixture was treated with methanolic ammonia (5 mL, saturated) at 100 °C in a sealed tube. After 20 h the solvent was evaporated 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, 80:20, v/v). The α -anomer was eluted first followed by the β -anomer. The appropriate fractions were combined and evaporated to give **12** (25 mg, 26%) and **13** (37 mg, 39%). **12**: $[\alpha]^{22}_D$ 35.2° (c 0.71, H_2O); UV (H_2O) λ_{max} 260 nm (ϵ 10239); 1H NMR (270 MHz, D_2O) δ 2.5 (m, H-2'a), 2.70-2.95 (m, H-2'b and H-3'), 3.73 (dd, $J_{4',5'a} = 4.8$ Hz, $J_{5'a,5'b} = 12.5$ Hz, H-5'a), 3.88 (dd, $J_{4',5'b} = 2.9$ Hz, $J_{5'a,5'b} = 12.5$ Hz, H-5'b), 4.40 (m, $J_{3',4'} = 7.7$ Hz, $J_{4',5'a} = 4.8$ Hz, $J_{4',5'b} = 2.9$ Hz, H-4), 4.52-4.78 (2 m, $J_{3',6'a} = 7.0$ Hz, $J_{3',3''b} = 10.0$ Hz, $J_{3'',a,3''b} = 15.5$ Hz, $J_{3'',a,F} = J_{3'',b,F} = 47$ Hz, H-3''a,b), 6.34 (t, $J_{1',2'a} = J_{1',2'b} = 6.6$ Hz, H-1'), 8.15 (s, H-2), 8.29 (s, H-8). Anal. Calcd for $C_{11}H_{14}O_2N_5F \times 0.2 H_2O$: C, 48.8; H, 5.4; N, 25.9. Found: C, 48.9; H, 5.4; N, 25.8. **13**: $[\alpha]^{22}_D$ -24.3° (c 0.9, H_2O); UV (H_2O) λ_{max} 260 nm (ϵ 10364); 1H NMR (270 MHz, D_2O) δ 2.47-2.48 (2 m, $J_{2'a,3'} = 1.8$ Hz, $J_{1',2'a} = 6.8$ Hz, $J_{2'a,2'b} = 13.8$ Hz, $J_{1',2'b} = 4.0$ Hz, $J_{2'b,3'} = 9.8$ Hz, H-2'a,b), 2.85 (m, H-3'), 3.69 (dd, $J_{4',5'a} = 4.6$ Hz, $J_{5'a,5'b} = 12.6$ Hz, H-5'a), 3.87 (dd, $J_{4',5'b} = 2.8$ Hz, $J_{5'a,5'b} = 12.6$ Hz, H-5'b), 4.21 (m, $J_{3',4'} = 7.5$ Hz, $J_{4',5'a} = 4.6$ Hz, $J_{4',5'b} = 2.8$ Hz, H-4), 4.51-4.78 (2 m, $J_{3',3''a} = 9.5$ Hz, $J_{3',3''b} = 8.0$ Hz, $J_{3'',a,3''b} = 15$ Hz, $J_{3'',a,F} = J_{3'',b,F} = 47$ Hz, H-3''a,b), 6.24 (dd, $J_{1',2'a} = 6.8$ Hz, $J_{1',2'b} = 4.0$ Hz, H-1'), 8.04 (s, H-2), 8.25 (s, H-8). Anal. Calcd for $C_{11}H_{14}O_2N_5F \times 0.2 H_2O$: C, 48.8; H, 5.4; N, 25.9. Found: C, 48.9; H, 5.4; N, 26.0.

1-[(3'-C-Azidomethyl)-2',3'-dideoxy- α - and β -D-erythro-pentofuranosyl]-thymine (14 and 15).

Thymine (133 mg, 1.06 mmol) was silylated according to the general procedure and dissolved in dichloromethane (5 mL) under nitrogen. To this solution was added

compound **7** (154 mg, 0.53 mmol) followed by *tert*-butyldimethylsilyl triflate (0.25 mL, 1.09 mmol). The solution was stirred for 24 hours at room temperature, after which 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 nucleosides. The 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 washed with dichloromethane. The aqueous layer was concentrated to a small volume and freeze dried to give 110 mg (0.39 mmol, 74%) of an anomeric mixture of the deblocked nucleosides. The mixture was dissolved in a mixture of *N,N*-dimethylformamid and imidazole (53 mg, 0.78 mmol) followed by the addition of *tert*-butyldimethylsilyl chloride (70 mg, 0.46 mmol), and the solution was stirred for 3 h at room temperature. Water (1 mL) was added, and the mixture was stirred for 10 min, diluted with dichloromethane, washed with 1 M hydrogen chloride, saturated aqueous hydrogen carbonate, dried, and concentrated. The anomers were separated by column chromatography (hexane-ethyl acetate, 1:1), the α -anomer was eluted first followed by the β -anomer. Each of the anomers was separately treated with tetrabutylammonium fluoride (70 mg, 0.22 mmol) in tetrahydrofuran (2 mL) for 24 h, concentrated, the residue dissolved in water, and washed with dichloromethane. The aqueous layer was concentrated to a small volume and purified by HPLC (water-methanol, 80:20, v/v) to give **14** (43 mg, 29%) and **15** (44 mg, 30%). **14**: $[\alpha]_D^{22} +3.1^\circ$ (*c* 1.45, H₂O); UV (H₂O) λ_{\max} 268 nm (ϵ 9155); ¹H NMR (270 MHz, D₂O) δ 1.92 (s, 5-CH₃), 2.02 (m, $J_{1',2'a} = 7.3$ Hz, $J_{2'a,3'} = 9.5$ Hz, $J_{2'a,2'b} = 12.5$ Hz, H-2'a), 2.50-2.74 (2 m, $J_{1',2'b} = 6.2$ Hz, $J_{2'b,3'} = 7.7$ Hz, $J_{2'a,2'b} = 12.5$ Hz, H-2'b and H-3'), 3.54 and 3.58 (2 dd, $J_{3',3''a} = 6.2$ Hz, $J_{3'',a,3''b} = 12.6$ Hz, $J_{3',3''b} = 6.0$ Hz, H-3''a,b), 3.67 (dd, $J_{4',5'a} = 5.1$ Hz, $J_{5'a,5'b} = 12.4$ Hz, H-5'a), 3.85 (dd, $J_{4',5'b} = 2.9$ Hz, $J_{5'b,5'a} = 12.4$ Hz, H-5'b), 4.25 (m, $J_{3',4'} = 8.1$ Hz, $J_{4',5'a} = 5.1$ Hz, $J_{4',5'b} = 2.9$ Hz, H-4'), 6.12 (dd, $J_{1',2'a} = 7.3$ Hz, $J_{1',2'b} = 6.2$ Hz, H-1), 7.60 (d, $J = 1.1$ Hz, H-6). Anal.Calcd for C₁₁H₁₅O₄N₂F: C, 47.0; H, 5.4; N, 24.9. Found: C, 46.8; H, 5.5; N, 24.7. **15**: $[\alpha]_D^{22} 12.5^\circ$ (*c* 0.96, H₂O); UV (H₂O) λ_{\max} 268 nm (ϵ 9434); ¹H NMR (270 MHz, D₂O) δ 1.91 (s, 5-CH₃), 2.34 (dd, $J_{1',2'} = 5.5$ Hz, $J_{2',3'} = 8.8$ Hz, H-2'), 2.59 (m, H-3'), 3.47-3.61 (2 dd, $J_{3',3''a,b} = 6.2$ Hz, $J_{3'',a,3''b} = 12.5$ Hz, H-3''a,b), 3.78 (dd, $J_{4',5'a} = 4.8$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'a), 3.94 (dd, $J_{4',5'b} = 2.6$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'b), 3.98 (m, $J_{4',5'a} = 4.8$ Hz, $J_{4',5'b} = 2.6$ Hz, $J_{3',4'} = 7.3$ Hz, H-4'), 6.1 (t, $J_{1',2'a,b} = 5.5$ Hz, H-1), 7.76 (s, 1H, H-6). Anal.Calcd for C₁₁H₁₅O₄N₅: C, 47.0; H, 5.4; N, 24.9. Found: C, 46.8; H, 5.5; N, 24.7.

1-[3'-C-(Azidomethyl)-2',3'-dideoxy- α - and β -D-*erythro*-pentofuranosyl]-cytosine (16 and 17).

Cytosine (250 mg, 2.25 mmol) was silylated according to the general procedure and dissolved in 1,2-dichloroethane (5 mL) under nitrogen. To this solution was added compound **7** (215 mg, 0.74 mmol) followed by *tert*-butyldimethylsilyl triflate (0.6 mL, 2.61 mmol). The solution was stirred for 24 hours at room temperature, after which 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 nucleosides. The 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 washed with dichloromethane. The aqueous layer was concentrated to a small volume and the mixture was separated by HPLC (water-methanol, 90:10, v/v). The α -anomer was eluted first followed by the β -anomer. The appropriate fractions were combined and evaporated to give **16** (84 mg, 43%) and **17** (45 mg, 23%). **16**: $[\alpha]^{22}_{\text{D}} -46.1^\circ$ (*c* 1.15, H₂O); UV (H₂O) λ_{max} 272 nm (ϵ 8320); ¹H NMR 270 MHz, D₂O) δ 1.96 (m, $J_{1',2'a} = 6.6$ Hz, $J_{2'a,3'} = 9.2$ Hz, $J_{2'a,2'b} = 13.5$ Hz, H-2'a), 2.56 (m, H-3'), 2.74 (m, $J_{1',2'b} = 6$ Hz, $J_{2'b,3'} = 8.0$ Hz, $J_{2'a,2'b} = 14.0$ Hz, H-2'b), 3.46-3.58 (2 dd, $J_{3',3'a,b} = 6.2$ Hz, $J_{3'a,3'b} = 13.0$ Hz, H-3'a,b), 3.68 (dd, $J_{4',5'a} = 5.1$ Hz, $J_{5'a,5'b} = 12.5$ Hz, H-5'a), 3.85 (dd, $J_{4',5'b} = 2.6$ Hz, $J_{5'b,5'a} = 12.5$ Hz, H-5'b), 4.25 (m, $J_{3',4'} = 8.0$ Hz, $J_{4',5'a} = 5.1$ Hz, $J_{4',5'b} = 2.6$ Hz, H-4'), 6.07 (d, $J = 7.7$ Hz, H-5), 6.09 (t, $J_{1',2'a} = J_{1',2'b} = 6.6$ Hz, H-1), 7.79 (d, $J = 7.3$ Hz, H-6). Anal.Calcd for C₁₀H₁₄O₃N₆: C, 45.1; H, 5.3; N, 31.6. Found: C, 44.9; H, 5.1; N, 31.4. **17**: $[\alpha]^{22}_{\text{D}} 55.0^\circ$ (*c* 0.99, H₂O); UV (H₂O) λ_{max} 272 nm (ϵ 8209); ¹H NMR 270 MHz, D₂O) δ 2.22-2.58 (m, H-2' and H-3'), 3.48-3.61 (2 dd, $J_{3',3'a} = 6.2$ Hz, $J_{3'a,3'b} = 12.8$ Hz, $J_{3',3'b} = 6.6$ Hz, H-3'), 3.79 (dd, $J_{4',5'a} = 4.8$ Hz, $J_{5'a,5'b} = 12.4$ Hz, H-5'a), 3.94 (dd, $J_{4',5'b} = 2.9$ Hz, $J_{5'a,5'b} = 12.4$ Hz, H-5'b), 4.0 (m, $J_{3',4'} = 8.1$ Hz, $J_{4',5'a} = 4.8$ Hz, $J_{4',5'b} = 2.9$ Hz, H-4'), 6.04 (d, $J_{5,6} = 6.6$ Hz, H-5), 6.11 (dd, $J_{1',2'a} = 6.6$ Hz, $J_{1',2'b} = 3.7$ Hz, H-1'), 7.93 (d, $J_{5,6} = 7.7$ Hz, H-6). Anal.Calcd for C₁₀H₁₄O₃N₆: C, 45.1; H, 5.3; N, 31.6. Found: C, 45.3; H, 45.2; N, 31.7.

9-[3'-C-(Azidomethyl)-2',3'-dideoxy- α - and β -D-*erythro*-pentofuranosyl]-adenine (18 and 19).

6-Chloropurine (360 mg, 2.33 mmol) was silylated according to the general procedure and dissolved in dichloromethane (5 mL) under nitrogen. To this solution was added compound **7** (224 mg, 0.77 mmol), followed by *tert*-butyldimethylsilyl triflate (0.55 mL, 2.4 mmol). The solution was stirred for 24 hours at 40 °C, after which 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 nucleosides. This mixture was separated by column chromatography (toluene-ethyl acetate, 1:2). The α -anomer was eluted first followed by the β -anomer. Each of the anomer 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 evaporated to give **18** (38 mg, 17%) and **19** (39 mg, 17%). An analytical sample of each of the anomers was obtained by HPLC purification (water-methanol, 70:30, v/v). **18**: $[\alpha]_D^{22} +58.3^\circ$ (*c* 1.0, H₂O); UV (H₂O) λ_{\max} 260 nm (ϵ 9353); ¹H NMR 270 MHz, D₂O) δ 2.43 (m, $J_{1',2'a} = 7.0$ Hz, $J_{2'a,3'} = 8.8$ Hz, $J_{2'a,2'b} = 12.8$ Hz, H-2'a), 2.67 (m, H-3'), 2.84 (m, $J_{1',2'b} = 6.2$ Hz, $J_{2'b,3'} = 8.1$ Hz, $J_{2'a,2'b} = 12.8$ Hz, H-2'b), 3.61 (d, $J_{3',3''} = 6.2$ Hz, H-3''), 3.73 (dd, $J_{4',5'b} = 5.1$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'b), 3.88 (dd, $J_{4',5'a} = 2.9$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'a), 4.28 (m, $J_{3',4'} = 8.1$ Hz, $J_{4',5'b} = 5.1$ Hz, $J_{4',5'a} = 2.9$ Hz, H-4'), 6.28 (t, $J_{1',2'a} = J_{1',2'b} = 6.6$ Hz, H-1'), 8.11 (s, H-2), 8.28 (s, H-8). Anal.Calcd for C₁₁H₁₄O₂N₈: C, 45.5; H, 4.9; N, 38.6. Found: C, 45.3; H, 4.8; N, 38.3. **19**: $[\alpha]_D^{22} -27.6^\circ$ (*c* 1.05, H₂O); UV (H₂O) λ_{\max} 260 nm (ϵ 14 102); ¹H NMR 270 MHz, D₂O) δ 2.52 (m, H-2'a), 2.75 (m, H-2'b, H-3'), 3.61 (dd, $J_{3',3''a} = 5.9$ Hz, $J_{3'',a,3'',b} = 12.5$ Hz, H-3''a), 3.64 (dd, $J_{3',3'',b} = 6.2$ Hz, $J_{3'',a,3'',b} = 12.5$ Hz, H-3''b), 3.71 (dd, $J_{4',5'a} = 4.7$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'a), 3.88 (dd, $J_{4',5'b} = 2.9$ Hz, $J_{5'a,5'b} = 12.8$ Hz, H-5'b), 4.12 (m, $J_{3',4'} = 7.3$ Hz, $J_{4',5'a} = 4.7$ Hz, $J_{4',5'b} = 2.9$ Hz, H-4'), 6.36 (dd, $J = 6.6$ Hz, and 3.0 Hz, H-1'), 8.19 (s, H-2), 8.33 (s, H-8). Anal.Calcd for C₁₁H₁₄O₂N₈: C, 45.5; H, 4.9; N, 38.6. Found: C, 45.3; H, 5.0; N, 38.4.

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