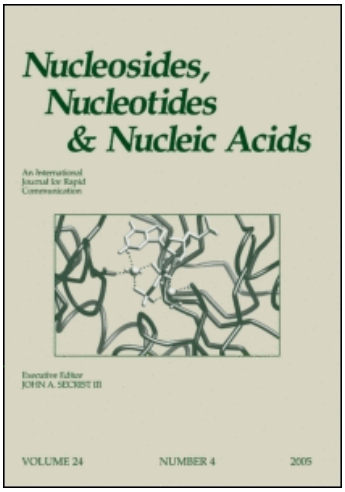


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 3',4'-C-Bishydroxymethyl-2',3',4'-trideoxy-β-L-threo-pentopyranosyl Nucleosides as Potential Inhibitors of HIV

Åsa Lundquist[a]; Ingemar Kvarnström[a]; Stefan C. T. Svensson[a]; Björn Classon[b]; Bertil Samuelsson[bc]
[a] Department of Chemistry, Linköping University, Linköping, Sweden [b] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden [c] Astra Hässle AB, Mölndal, Sweden

To cite this Article Lundquist, Åsa , Kvarnström, Ingemar , Svensson, Stefan C. T. , Classon, Björn and Samuelsson, Bertil(1995) 'Synthesis of 3',4'-C-Bishydroxymethyl-2',3',4'-trideoxy-β-L-threo-pentopyranosyl Nucleosides as Potential Inhibitors of HIV', Nucleosides, Nucleotides and Nucleic Acids, 14: 7, 1493 — 1502
To link to this Article: DOI: 10.1080/15257779508009487
URL: http://dx.doi.org/10.1080/15257779508009487

NUCLEOSIDES & NUCLEOTIDES, 14(7), 1493-1502 (1995)

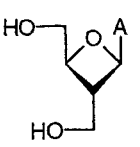
SYNTHESIS OF 3',4'-C-BISHYDROXYMETHYL-2',3',4'-TRIDEOXY-β-L-THREO- PENTOPYRANOSYL NUCLEOSIDES AS POTENTIAL INHIBITORS OF HIV

Åsa Lundquist, Ingemar Kvarnström, and Stefan C. T. Svensson
Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden
Björn Classon and Bertil Samuelsson*,†
Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden
†*Additional Address: Astra Hässle AB, S-431 83 Mölndal, Sweden*

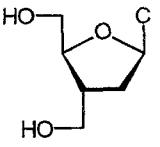
Abstract
The synthesis of 3',4'-bishydroxymethyl-2',3',4'-trideoxy pentopyranosyl derivatives of thymine, uracil, cytosine, and adenine is described. *trans*-(*3S,4S*)-Bis(methoxycarbonyl)cyclopentanone (**3**) was converted to 1-O-acetyl-3,4-C-bis[(*tert*-butyldiphenylsiloxy)methyl]-2,3,4-trideoxy-α,β-L-*threo*-pentopyranose (**6**), which was subsequently condensed with the silylated purine and pyrimidine bases.

Introduction

Nucleoside analogues have been extensively evaluated in the search for agents effective in the treatment of human immunodeficiency virus (HIV) infections. As of today four nucleoside analogues 3'-azido-3'-deoxythymidine (AZT)[1], 2',3'-dideoxyinosine (DDI)[2], 2',3'-dideoxycytidine (DDC)[3], and 2',3'-didehydro-2',3'-dideoxythymidine (D4T)[4] are approved for clinical use against HIV infections. The mechanism for the anti-HIV activity is believed to involve activation by cellular kinases to give the corresponding triphosphates which acts as inhibitors of the viral reverse transcriptase and/or chain terminators of the viral DNA synthesis.[5] Recently hydroxymethyl-branched nucleosides have been reported to show potent anti-HIV activity *in vitro*. Two such compounds are oxetanocin A[6] (**1**) and 1-(2',3'-dideoxy-3'-C-hydroxymethyl-β-D-*erytro*-pentofyranosyl)-cytosine[7] (**2**).



1



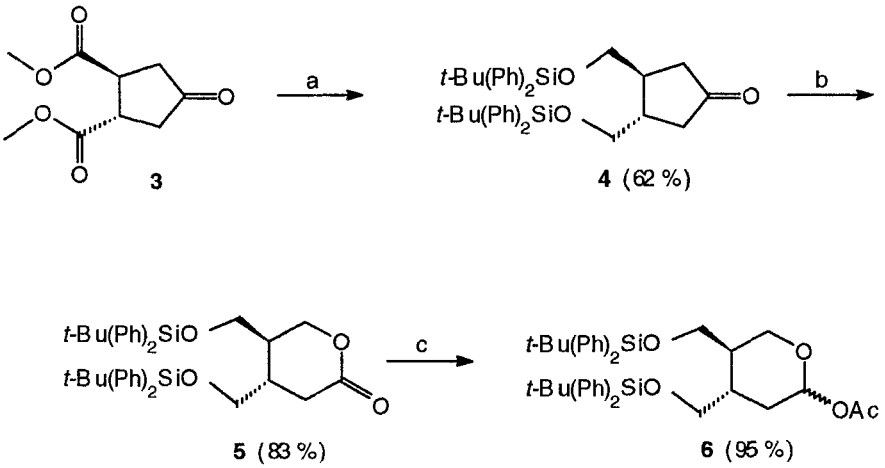
2

In this paper we describe the synthesis of 3',4'-C-bishydroxymethyl-2',3',4'-trideoxy-β-L-threo-pentopyranosyl nucleosides **7-10**. These structures can be viewed as analogues of dihydroxymethyl-branched nucleosides.

Results and Discussion

For starting material enantiomerically pure keto diester **3**, which was prepared by a method developed at our laboratory[8], was used. The keto diester **3** was converted to the ketone **4** via four successive reactions (Scheme I).

Ketalization with ethylene glycol followed by lithium aluminium hydride reduction, silylation with *tert*-butyldiphenylsilyl chloride in pyridine at room temperature, followed by deketalization with 80 % acetic acid afforded **4** in 62 % yield from **3**. Oxidation of the ketone in **4** with *m*-chloroperbenzoic acid[9] gave the lactone **5**, in 83 % yield, which was



3 4 (62 %) 5 (83 %) 6 (95 %)

[a] a. (i) $HOCH_2CH_2OH$,p-TsOH, (ii) LAH, (iii) *t*-Bu(Ph)$_2$SiCl, pyridine, (iv) HOAc 80 %; b. *m*-CPBA, dichloromethane; c. (i) DIBAL-H, (ii) Ac_2O, pyridine

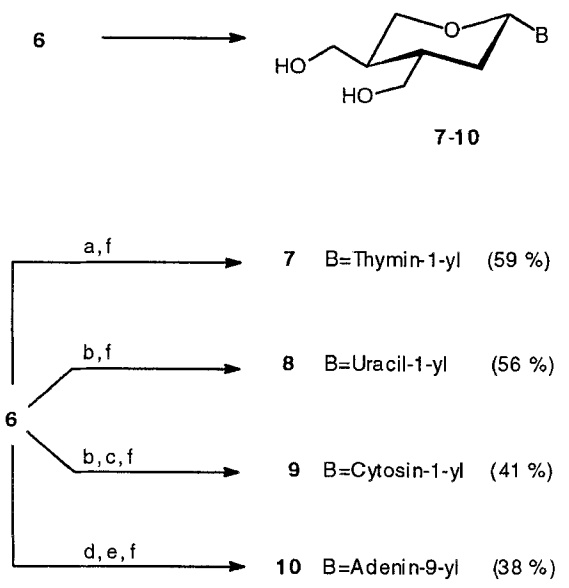
Scheme I[a]

reduced with diisobutyl aluminium hydride and then acetylated with acetic anhydride in pyridine at room temperature giving an anomeric mixture of the pyranose **6** in 95 % yield.

Coupling of **6** with silylated thymine in the presence of trimethylsilyl triflate in dichloromethane[10] followed by deprotection with tetrabutylammonium fluoride gave exclusively the β-anomer **7** having the $^1C_4$ conformation in 59 % yield after silica gel column chromatography (Scheme II).

The β-anomeric assignment of this nucleoside was based on the 250 MHz ^1H NMR of the corresponding o-nitrobenzoyl protected nucleoside analogue. The hydrogen at C-1' is clearly an axial hydrogen on account of its large coupling constant (J=10.8 Hz) with the axial C-2' hydrogen. This means that thymine is equatorially orientated, as is seemingly normal for pyranosyl nucleosides.[11] Differentiation between α or β is based on the coupling constants of the hydrogens at C-5'. The H-5' axial signal appears as a triplet with a large coupling constant (J=11.6 Hz) to an axial H-4' indicating a $^1C_4$ conformation for the pyranoside. For the synthesis of the uracil nucleoside **8** silylated uracil was condensed with **6** and deprotected following the same protocol as above. The isolated yield of the β-anomeric uracil nucleoside **8** was 56 %. The cytosine nucleoside **9** was synthezised from the protected uracil nucleoside by treatment with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine at room temperature[12] to give the 4-triazolylpyrimidinone derivative. Subsequent treatment of this compound with ammonium hydroxide in dioxane afforded the protected cytosine nucleoside.[11] After deprotection with tetrabutylammonium fluoride the β-anomeric cytosine nucleoside **9** was obtained in 41 % yield. For the synthesis of the adenine nucleoside **10** silylated 6-chloropurine was condensed with **6** following the same protocol as above to give the protected 6-chloropurine nucleoside. The coupling resulted in the exclusive formation of the desired N-9 alkylated isomer, which was assigned by UV[13] and NMR[14] spectroscopy. The 6-chloropurine nucleoside was deprotected with tetrabutylammonium fluoride and reacted with methanolic ammonia giving the β-anomeric adenine nucleoside **10** in 38 % yield. ^1H NMR spectroscopy of the adenine nucleoside **10** showed a small amount (< 5 %) of the α-anomeric adenine nucleoside. Attempts were made to increase the amount of the α-anomer by using acetyl protecting groups, acetonitrile as solvent, and decreasing the reaction time, but only minor changes in the α/β ratio was observed.

The almost exlusive formation of one anomer of the nucleosides **7**, **8** and **10** are in agreement with results obtained in other coupling reactions of pyranosyl nucleosides under thermodynamic conditions.[15] The β-anomeric nucleosides **7**, **8** and **10** are thermodynamically favoured because of the equatorial orientiation of both the base and the hydroxymethyl groups.



[a] a. Silylated thymine, TMSOTf, dichloromethane; b. silylated uracil, TMSOTf, dichloromethane, c. (i) p-$ClC_6H_4OPOCl_2$, 1,2,4-triazole, pyridine; (ii) NH_4OH, dioxane; d. silylated 6-chloropurine, TMSOTf, dichloromethane; e. NH_3, MeOH; f. tetrabutylammonium fluoride, tetrahydrofuran

Scheme II[a]

Compounds **7-10** were tested for inhibition of HIV multiplication in an XTT assay in M4 cells.[16] All compounds were inactive in the assay.

Experimental Section

Removal of solvents was performed under reduced pressure. ^1H and ^{13}C NMR were recorded on a JEOL FX-100 or a Bruker AC 250 instrument using $CDCl_3$ or DMSO-d_6 as solvents with TMS as internal standard. The shifts are reported in ppm (δ scale). TLC analyses were performed on Merck precoated 60 F-254 plates. The spots were visualized by UV light and/or charring with ethanol/ sulfuric acid/ acetic acid/ p-anisaldehyde, 90:3:1:2. Column chromatography was performed using silica gel 60 (0.040-0.063 mm, Merck). Organic phases were dried over anhydrous magnesium sulphate. Optical rotations were measured in $CHCl_3$ or DMSO solutions at room temperature using a Perkin-Elmer 141 instrument.

***trans*-(3*S*,4*S*)-Bis[(*tert*-butyldiphenylsiloxy)methyl]cyclopentanone (4).** A solution of *trans*-(3*S*,4*S*)-bis(methoxycarbonyl)cyclopentanone[8] (**3**) (3.0 g, 15.0 mmol), ethylene glycol (20.0 mL, 0.36 mol) and *p*-toluene sulfonic acid monohydrate (80 mg) in toluene (160 mL) was refluxed with a Dean-Stark trap for 6 h. Sodium hydrogen carbonate (60 mg) was added and after additional stirring for 5 min the mixture was washed with saturated aqueous sodium hydrogen carbonate, dried, and concentrated to give the crude ketal. According to ^{1}H NMR the product was almost free from unreacted ketone. The crude ketal diester in dry diethyl ether (50 mL) was added dropwise to a mixture of lithium aluminium hydride (1.14 g, 30.0 mmol) in dry diethyl ether (120 mL) at 0°C. The mixture was stirred at room temperature for 3 h before excess of lithium aluminium hydride was decomposed by successive addition of water (1.6 mL), 3 M aqueous sodium hydroxide (1.6 mL), and water (5.0 mL). After stirring at room temperature for 55 min anhydrous magnesium sulphate (60 g) was added and the stirring was prolonged for 5 min. The precipitate and magnesium sulphate was removed by filtration and washed several times with ethyl acetate. The filtrate was removed to give the corresponding diol. The diol was dissolved in dry pyridine (150 mL) and *tert*-butyldiphenylsilyl chloride (9.6 mL, 36.0 mmol), and the solution was stirred at room temperature for 48 h. Concentration, co-distillation with toluene, and purification by flash column chromatography (toluene-ethyl acetate, 10:1) gave the disilylated ketal. A mixture of the disilylated ketal, acetone (65 mL), methanol (65 mL), and acetic acid (80 %, 330 mL) was stirred at room temperature for 14 h. The reaction mixture was concentrated, co-distilled with toluene, and purified by column chromatography (toluene-ethyl acetate, 12:1) to give compound **4** (5.77 g, 62 %) as a colourless syrup: $[\alpha]^{22}_D$ 17.84° (*c* 0.94, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.00 (s, 18H, 2x[C(C*H*$_3$)$_3$]), 1.64-2.10 (m, 6H, H-2, H-3, H-4, H-5), 3.51-3.84 (m, 4H, 2xC*H*$_2$OSi), 7.32-7.67 (m, 20H, 4xPh); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 19.16 (2x[*C*(CH$_3$)$_3$]), 26.77 (2x[C(*C*H$_3$)$_3$]), 40.17 (C-2, C-5), 41.43 (C-3, C-4), 64.97 (2x*C*H$_2$OSi), 127.86, 129,41, 132.96, 135.20 (4xPh). Anal. Calcd for $C_{39}H_{48}O_3Si_2$: C, 75.43; H, 7.79. Found: C, 75.19; H, 7.74.

***trans*-(3*S*,4*S*)-Bis[(*tert*-butyldiphenylsiloxy)methyl]pentyrolactone (5).** To a solution of compound **4** (1.62 g, 2.61 mmol) in dichloromethane (30 mL) *m*-chloroperoxybenzoic acid (3.87 g, 12.3 mmol) was added, and the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with dichloromethane, and the resulting solution was washed with saturated sodium sulphite followed by saturated sodium hydrogen carbonate, dried, concentrated, and purified by column chromatography (toluene-ethyl acetate, 10:1) to give compound **5** (1.37 g, 83 %) as a colourless syrup: $[\alpha]^{22}_D$ 12.55° (*c* 1.00, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.03

(s, 18H, [C(C*H*$_3$)$_3$]), 1.96-2.14 (m, 2H, H-3, H-4), 2.55 (d, 2H, H-2), 3.52 (m, 4H, 2xC*H*$_2$OSi), 4.31 (d, 2H, H-5), 7.37-7.58 (m, 20H, 4xPh); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 19.16 (2x[*C*(CH$_3$)$_3$]), 26.75 (2x[C(*C*H$_3$)$_3$]), 31.51 (C-2), 34.82, 37.59 (C-3, C-4), 63.22, 65.75 (2x*C*H$_2$OSi), 68.23 (C-5), 127.90, 129.56, 132.62, 135.20 (4xPh), 172.55 (C-1). Anal. Calcd for $C_{39}H_{48}O_4Si_2$: C, 73.54; H, 7.60. Found: C, 73.36; H, 7.74.

1-O-Acetyl-3,4-C-bis[(*tert*-butyldiphenylsiloxy)methyl]-2,3,3-trideoxy-α/β-L-*threo*-pentopyranose (6). A 100-mL three-necked round bottomed flask was connected to argon, flame dried, and charged with compound **5** (1.24 g, 1.95 mmol) and dry toluene (75 mL). To the mixture was added dropwise diisobutyl aluminium hydride (1 M in toluene, 2.90 mL, 2.90 mmol) at -78°C. The reaction mixture was stirred at -78°C for 1 h before it was allowed to attain room temperature, and methanol (0.48 mL), ethyl acetate (75 mL), and saturated sodium hydrogen carbonate (4.0 mL) were added. After stirring at room temperature for 2 h magnesium sulphate (2 g) was added and the stirring was prolonged for 3 h. The reaction mixture was filtered and concentrated to give the corresponding lactol. The lactol was dissolved in pyridine (15 mL) and acetic anhydride (7.5 mL), and the mixture was stirred at room temperature for 14 h. Concentration, co-distillation with toluene, and purification by column chromatography (toluene-ethyl acetate, 12:1) gave compound **6** (1.25 g, 95 %) as a colorless syrup: $[\alpha]^{22}_D$ -4.82° (*c* 0.84 , $CHCl_3$);. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 1.00 (s, 18H, 2x[C(CH$_3$)$_3$]), 1.77-2.08 (m, 4H, H-2, H-3, H-4), 2.09 (s, 3H, OCOC*H*$_3$), 3.48-3.64 (m, 4H, 2xC*H*$_2$OSi), 3.85 (m, 1H, 5-Ha), 4.07 (m, 1H, H-5e), 5.74 (dd, $J_{1\text{-}2a}$=8.68 Hz, $J_{1\text{-}2e}$=2.91 Hz, 0.67 H,1-Hα), 6.18 (t, 0.33 H, 1-Hβ), 7.15-7.58 (m, 20H, 4xPh); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ: α: 19.21 (2x[*C*(CH$_3$)$_3$]), 21.15 (OCO*C*H$_3$), 26.97 (2x[C(*C*H)$_3$]), 31.37, 36.28, 38.23 (C-2, C-3, C-4), 62.41, 63.66 (2xC*H*$_2$OSi), 65.02 (C-5), 93.86 (C-1), 127.37, 129.37, 133.06, 135.20 (4xPh), 169.49 (O*C*OCH$_3$); β: 19.21 (2x[*C*(CH$_3$)$_3$]), 21.15 (OCO*C*H$_3$), 26.97 (2x[C(*C*H)$_3$]), 32.53, 36.28, 38.43 (C-2, C-3, C-4), 62.41, 63.66 (2xCH$_2$OSi), 65.02 (C-5), 92.01 (C-1), 127.37,129.37, 133.06, 135.20 (4xPh), 169.24 (O*C*OCH$_3$). Anal. Calcd for $C_{41}H_{52}O_5Si_2$: C, 72.31; H, 7.70. Found: C, 72.45; H, 7.83.

1-(3,4-C-Bis(hydroxymethyl)-2,3,4-trideoxy-β-L-*threo*-pentopyranosyl)thymine (7). A suspension of thymine (0.10 g, 0.79 mmol) and a small crystal of ammonium sulphate in trimethylchlorosilane (0.3 mL) and hexamethyldisilazane (4.0 mL) was refluxed under argon until a clear solution was obtained. The mixture was concentrated and co-distilled with toluene. The residue was dissolved in dry dichloromethane (3.3 mL)

under argon, and a solution of compound **6** (0.306 g, 0.45 mmol) in dry dichloromethane (1.65 mL) was added. The mixture was cooled to 0°C and trimethylsilyl triflate (0.10 mL, 0.55 mmol) was added dropwise. After stirring at room temperature for 16 h the reaction was quenched by addition of aqueous sodium hydrogen carbonate, and the resulting mixture was stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, concentrated, and purified by column chromatography (toluene-ethyl acetate, 4:1) to give the protected nucleoside. The nucleoside was deprotected by dissolving in tetrabutylammonium fluoride trihydrate (1 M solution in tetrahydrofuran, 1.2 mL, 1.2 mmol) and tetrahydrofuran (2.8 mL), and subsequent stirring at room temperature for 3 h. Concentration and purification by column chromatography (chloroform-methanol, 3:1) gave compound **7** (0.069 g, 59 %): $[\alpha]^{22}_D$ -3.8° (*c* 1.09, DMSO); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.50-1.79 (m, 4H, H-2', H-3', H-4'), 1.80 (s, 3H, CH_3), 3.14-3.88 (m, 5H, H-5'a, 2xCH_2OH), 4.04-4.11 (dd, $J_{5'e\text{-}5'a}$=11.3 Hz, $J_{5'e\text{-}4'}$=4.2 Hz, 1H, H-5'e), 4.38 (b, 2H, 2xO*H*), 5.45-5.50 (dd, $J_{1'\text{-}2'a}$=10.7 Hz, $J_{1'\text{-}2'e}$=2.0 Hz, 1H, H-1'), 7.48 (d, J=1.2 Hz, 1H, H-6); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 11.7 (CH_3), 32.48 (C-2'), 38.51, 38.75 (C-3', C-4'), 59.81, 62.82 (2xCH_2OH), 69.75 (C-5'), 81.38 (C-1'), 109.34 (C-5), 136.03 (C-6), 150.10 (C-2), 163.55 (C-4). Anal. Calcd for $C_{12}H_{18}O_5N_2$x0.5H_2O: C, 51.61; H, 6.86; N, 10.03. Found: C, 51.85; H, 6.61; N, 9.93.

1-(3,4-C-Bis(hydroxymethyl)-2,3,4-trideoxy-β-L-*threo*-pentopyranosyl)uracil (8). Uracil (0.083 g, 0.74 mmol) was silylated following the same procedure as for the preparation of compound **7** and dissolved in dry dichloromethane (3.1 mL) under argon. To this mixture was added compound **6** (0.280 g, 0.41 mmol) in dry dichloromethane (1.5 mL) followed by addition of trimethylsilyl triflate (0.09 mL, 0.50 mmol) at 0°C. The mixture was stirred at room temperature for 16 h. The reaction was quenched by the addition of aqueous sodium hydrogen carbonate, and the resulting mixture was stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, concentrated, and purified by column chromatography (toluene-ethyl acetate, 1:1) to give the protected nucleoside. The nucleoside was deprotected by dissolving in tetrabutylammonium fluoride trihydrate (1 M solution in tetrahydrofuran, 1.14 mL, 1.14 mmol) and tetrahydrofuran (2.8 mL), and subsequent stirring at room temperature for 3 h. Concentration and purification by column chromatography (chloroform-methanol, 5:1) gave compound **8** (0.058 g, 56 %): $[\alpha]^{22}_D$ -16.5° (*c* 1.21, DMSO);^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.49-1.84 (m, 4H, H-2', H-3', H-4'), 3.11-3.59 (m, 5H, H-5'a, 2xCH_2OH), 4.08 (dd, $J_{5'e\text{-}5'a}$=11.4 Hz, $J_{5'e\text{-}4'}$=4.3 Hz, 1H, H-5'e), 4.39 (b, 2H, 2xO*H*), 5.46 (dd, $J_{1'\text{-}2'a}$=10.8 Hz, $J_{1'\text{-}2'e}$=2.3 Hz, 1H, H-1'), 5.60 (d, $J_{5\text{-}}$

$_6$=8.0 Hz, 1H, H-5), 7.62 (d, J_{6-5}=8.1 Hz, 1H, H-6); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 31.93 (C-2'), 37.78, 38.11 (C-3', C-4'), 59.14, 62.09 (2x*C*H_2OH), 69.43 (C-5'), 80.94 (C-1'), 101.06 (C-5), 139.88 (C-6), 149.47 (C-2), 162.26 (C-4). Anal. Calcd for $C_{11}H_{16}O_5N_2$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.43; H, 6.38; N, 10.72.

1-(3,4-C-Bis(hydroxymethyl)-2,3,4-trideoxy-β-L-*threo*-pentopyranosyl)cytosine (9). Uracil (0.089 g, 0.79 mmol) was silylated following the same procedure as for the preparation of compound **7** and dissolved in dry dichloromethane (3.3 mL) under argon. To this mixture was added compound **6** (0.304 g, 0.44 mmol) in dry dichloromethane (1.65 mL) followed by addition of trimethylsilyl triflate (0.10 mL, 0.55 mmol) at 0°C. The mixture was stirred at room temperature for 16 h. The reaction was quenched by the addition of aqueous sodium hydrogen carbonate, and the resulting mixture was stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, concentrated, and purified by column chromatography (toluene-ethyl acetate, 1:1) to give the protected uracil nucleoside. To a solution of the protected uracil nucleoside and 1,2,4-triazole (0.138 g, 2.0 mmol) in anhydrous pyridine (1.8 mL) was added droppwise 4-chlorophenyl phosphorodichloridate (0.11 mL, 0.69 mmol) at 0°C. The reaction was stirred at room temperature for 48 h before it was concentrated to give a syrup which was dissolved in dichloromethane, washed with water, dried, and concentrated to give the 4-triazolylpyrimidinone derivative. A mixture of the 4-triazolylpyrimidinone derivative, dioxane (4.0 mL) and ammonium hydroxide (2.0 mL) was stirred at room temperature for 14 h. Concentration and purification by column chromatography (chloroform-methanol, 10:1) gave the protected cytosine nucleoside. The nucleoside was deprotected by dissolving in tetrabutylammonium fluoride trihydrate (1 M solution in tetrahydrofuran, 0.74 mL, 0.74 mmol) and tetrahydrofuran (1.84 mL), and subsequent stirring at room temperature for 3 h. Concentration and purification by column chromatography (chloroform-methanol, 3:1) gave compound **9** (0.046 g, 41 %): $[\alpha]^{22}_D$ -41.2 (*c* 0.75, DMSO); ^{1}H NMR (250.13 MHz) δ 1.58-1.83 (m, 4 H, H-2', H-3', H-4'), 3.17-3.57 (m, 5H, H-5'a, 2x*C*H_2OH), 4.08 (dd, $J_{5'e-5'a}$=11.3 Hz, $J_{5'e-4'}$=4.2 Hz, 1H, H-5'e), 4.41 (b, 2H, 2xO*H*), 5.54 (dd, $J_{1'-2'a}$=11.3 Hz, $J_{1'-2'e}$=4.2, 1H, H-1'), 5.76 (d, J_{5-6}=7.4 Hz, 1H, H-5), 6.98 (b, 2H, NH_2), 7.56 (d, J_{5-6}=7.4Hz, 1H, H-6); ^{13}C NMR (62.90 MHz) δ 33.37 (C-2'), 38.53, 38.74 (C-3', C-4'), 59.84, 62.81 (2x*C*H_2OH), 70.06 (C-5'), 82.10 (C-1'), 93.91 (C-5), 140.87 (C-6), 154.55 (C-2), 165.50 (C-4). Anal. Calcd for $C_{11}H_{17}O_4N_3$x2.0H_2O: C, 45.36; H, 7.26; N, 14.42. Found: C, 45.59; H, 6.99; N, 14.41.

9-(3,4-C-Bis(hydroxymethyl)-2,3,4-trideoxy-β-L-*threo*-pentopyranosyl)adenine (10). Adenine (0.122 g, 0.79 mmol) was silylated following the same procedure as for the preparation of compound **7** and dissolved in dry dichloromethane (3.3 mL) under argon. To this mixture was added compound **6** (0.305 g, 0.45 mmol) in dry dichloromethane (1.65 mL) followed by addition of trimethylsilyl triflate (0.10 mL, 0.55 mmol) at 0°C. The mixture was stirred at room temperature for 16 h. The reaction was quenched by the addition of aqueous sodium hydrogen carbonate, and the resulting mixture was stirred for 30 min, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, concentrated, and purified by column chromatography (toluene-ethyl acetate, 4:1) to give the protected nucleoside. The nucleoside was deprotected by dissolving in tetrabutylammonium fluoride trihydrate (1 M solution in tetrahydrofuran, 1.28 mL, 1.28 mmol) and tetrahydrofuran (2.9 mL), and subsequent stirring at room temperature for 3 h. Concentration and purification by column chromatography (chloroform-methanol, 3:1) gave the 6-chloropurine nucleoside. A solution of the protected 6-chloropurine nucleoside in dry methanol (6.0 mL) was saturated with ammonia and then heated in a bomb at 100°C for 48 h. The ammonia was evaporated off under a steam of argon, and the resulting solution was concentrated and purified by column chromatography (chloroform-methanol, 3:1) to give compound **10** (0.047 g, 38 %): $[\alpha]^{22}_D$ 16.7 (*c* 0.65, DMSO); UV(H_2O) λ_{max} 259.5 nm; ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 1.50-2.28 (m, 4 H, H-2', H-3', H-4'), 3.06-3.66 (m, 5H, H-5'a, 2xCH_2OH), 4.11 (dd, $J_{5'e\text{-}5'a}$=11.4 Hz, $J_{5'e\text{-}4'}$=4.2 Hz, 1H, H-5'e), 4.45 (b, 2H, 2xO*H*), 5.64 (dd, $J_{1'\text{-}2'a}$=10.4 Hz, $J_{1'\text{-}2'e}$=3.3 Hz, 1H, H-1'), 7.02 (s, 2H, NH_2), 8.18 (s, 1H, H-2), 8.25 (s, 1H, H-8); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.12 (C-2'), 38.62, 38.74 (C-3', C-4'), 59.89, 62.82 (2xCH_2OH), 69.75 (C-5'), 81.29 (C-1'), 118.84 (C-5), 138.61 (C-8), 148.50 (C-4), 152.55 (C-2), 156.00 (C-6). Anal. Calcd for $C_{12}H_{17}O_3N_5$x1.2H_2O: C, 47.90; H, 6.50; N, 23.27. Found: C, 48.05; H, 6.44; N, 22.96.

Acknowledgement. We thank the National Swedish Board of Industrial and Technical Development and Medivir AB for financial support, and Medivir AB for the biological testings.

References

1. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S.; *Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
2. Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J.-P.; Jones, D. G.; Broder, S. *Science* **1989**, *245*, 412.

3. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.
4. (a) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162. (b) Hamamoto, N.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. *Antimicrob. Agents Chemoter.* **1987**, *31*, 907.
5. De Clercq, E. *Design of Anti-AIDS Drugs*; Elsevier: Amsterdam-Oxford-New York-Tokyo, **1990**.
6. Hoshino, H.; Shimizu, N.; Simada, N.; Talita, T.; Takeuchi, T. *J. Antibiotics* **1987**, *40*, 1077.
7. Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993.
8. Rosenquist, Å.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Samuelsson, B. *Acta Chem. Scand.* **1992**, *46*, 1127.
9. Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468.
10. Vorbrüggen, H.; Krolikiewich, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
11. (a) Böhringer, A. M.; Roth, H.-J.; Hunziker, J.; Göbel, M.; Krishnan, R.; Giger, A.; Schweizer, B.; Schreiber, J.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1992**, *75*, 1416. (b) Augustyns, K.; Rozenski, J.; Van Aerschot, A.; Janssen, G.; Herdewijn, P. *J. Org. Chem.* **1993**, *58*, 2977. (c) De Winter, H. L.; De Ranter, C. J.; Blaton, N. M.; Peeters, O. M. Van Aerscot, A.; Herdewijn, P. *Acta Cryst.* **1992**, *B48*, 95. (d) Nord, L. D.; Dalley, N. K.; McKernan, P. A.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1044.
12. Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Clarke-Katzenburg, R. H.; Cheng, Y.-C.; Prusoff, W. H.; Mancini, W. R.; Birnbaum, G. I.; Gabe, E. J.; Giziewicz, J. *J. Med. Chem.* **1991**, *34*, 2607.
13. Albert, A. *Synthetic procedures in nucleic acid chemistry*, Wiley-Interscience: New York, **1973**,Vol. 2, p 47.
14. Chenon, M.-T.; Pugmire, R. J.; Grant, D. M.; Panzia, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4628.
15. (a) Sztaricskai, F.; Dinya, Z.; Batta, G.; Gergely, L.; Szabo, B. *Nucleosides & Nucleotides* **1992**, *11*, 11. (b) Augusyns, K.; Rosenski, J.; Van Aerschot, A.; Busson, R.; Claes, P.; Herdewijn, P. *Tetrahedron* **1994**, *50*, 1189.
16. Vial, J.-M.; Johansson, N. G.; Wrang, L.; Chattopadhyaya, J. *Antiviral Chem. Chemother.* **1990**, *1*, 1983.

Received January 1, 1995
Accepted April 11, 1995