Tetrahedron Vol. 49, No. 38, pp. 8637-8644, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

Synthesis of 4-*C*-Hydroxymethyl Hexopyranosyl Nucleosides as Potential Inhibitors of HIV

Magnus Björsne, Björn Classon, Ingemar Kvarnström† and Bertil Samuelsson*#

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

† Department of Chemistry, Linköping University, S-581 83 Linköping Sweden
# Address also: Astra Hässle AB, S-431 83 Mölndal, Sweden

(*Received in UK* 11 *June* 1993; *accepted* 16 *July* 1993)

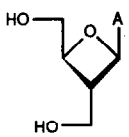
Abstract: *The synthesis of 1-(2,3,4-trideoxy-4-C-hydroxymethyl-β-D-erythro-hexopyranosyl)thymine (**13**); -uracil (**15**), -cytosine (**16**) and 9-(2,3,4-trideoxy-4-C-hydroxymethyl-β-D-erythro-hexopyranosyl)adenine (**18**) are described. The nucleoside analogues were evaluated for their anti-HIV activity in vitro.*

INTRODUCTION

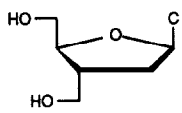
Nucleoside analogues that inhibit HIV-1 reverse transcriptase has proven effective for the treatment of HIV-infection. Three nucleosides, 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxyinosine (DDI) and 2′,3′-dideoxycytidine (DDC) have so far been approved for clinical use against HIV infection. [1,2,3]

Recently hydroxymethyl substituted nucleoside analogues such as Oxetanocin A[4] (**1**) and 1-(2,3-dideoxy-3-*C*-hydroxymethyl-β-D-*erythro*-pentofuranosyl)cytosine[5] (**2**) have been found to have anti-HIV activity *in vitro*. These structures represent lead compounds of a new and different type and are currently being explored in various synthetic programs.

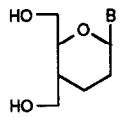
Most modifications of nucleosides have focused around five membered ring systems as bio mimetics of the furanose part and surprisingly few works have been published around the corresponding pyranosides.[6]



1



2



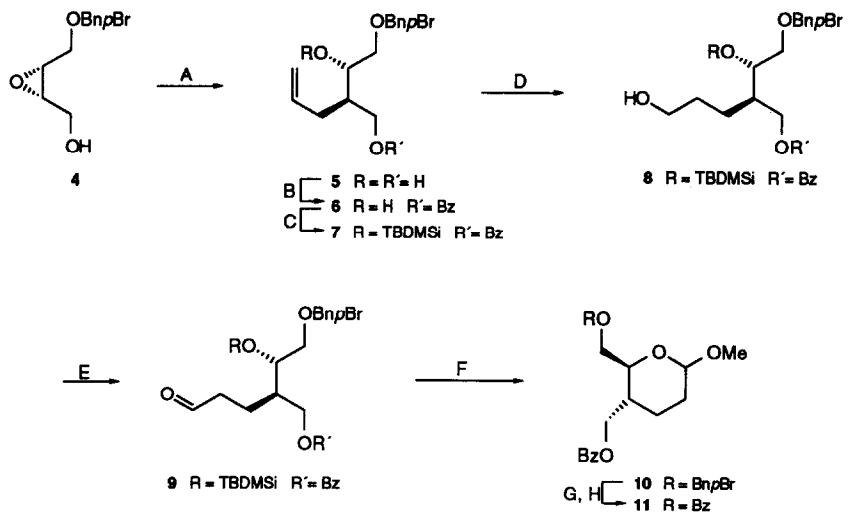
13 B = Thymin-1yl
15 B = Uracil-1-yl
16 B = Cytosin-1-yl
18 B = Adenin-1-yl

As part of a program to evaluate the anti-HIV effect of hydroxymethyl substituted nucleoside analogues we have synthesised 4′-hydroxymethyl substituted hexopyranosyl nucleosides. The prototype compound was the cytidine derivative **2**,[5] which can be viewed as 2′-deoxycytidine where a methylene group has been inserted into the 3′carbon - 3′oxygen bond. A further methylene group insertion between the 2′and 3′carbons of **2** then results in the hexopyranosyl series.

RESULTS AND DISCUSSION

The chiral epoxy alcohol **4**, prepared by a Sharpless epoxidation,[7] was regioselectively alkylated by slow addition of epoxide **4**, at low temperature, to allylmagnesium bromide to give the desired 2,4-diol **5** in 69% yield.[5] Attempted alkylations of the oxirane **4** with the Grignard reagent obtained from 2-(2-bromoethyl)-1,3-dioxolane[8] failed in our hands, giving a Payne rearranged epoxide.[9] The primary hydroxyl group of **5** was selectively benzoylated with benzoyl chloride in dichloromethane-pyridine at 0°C to give **6** in 85% yield. The secondary hydroxyl group was protected by reacting **6** with *tert*-butyldimethylsilyl chloride and imidazole in dimethyl formamide to give **7** in quantitative yield. The terminal olefin in **7** was reacted with borane-dimethylsulfide[10] in dimethyl formamide followed by oxidation of the resulting borane with sodium perborate in a mixture of tetrahydrofuran and water to give **8** in 84% yield.[11] Oxidation of the primary hydroxyl group in **8** with pyridinium dichromate-acetic anhydride in dichloromethane-dimethyl formamide[12] gave the aldehyde **9** in 85% yield. Exposing **9** to methanol containing hydrochloric acid (2.5%, w/w) resulted in deprotection of the silyl ether and ring closure to give the methyl pyranoside **10** as an α:β mixture 6:1 in 79% yield. Hydrogenolysis of the *p*-bromobenzylether was carried out with palladium 10% on charcoal in ethyl acetate containing sodium hydrogen carbonate and a small amount of water. The addition of water was necessary for the hydrogenation to proceed in high and reproducible yields. Benzoylation in pyridine-dichloromethane gave the dibenzoylated pyranoside **11** in 94% yield

Scheme 1

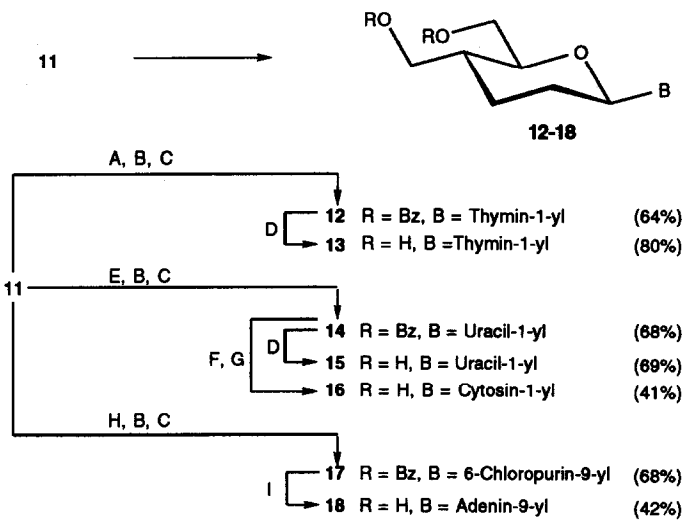


A; Allyl magnesiumbromide, diethylether, -55°C B; BzCl, CH_2Cl_2, pyridine C; TBDMSiCl, Imidazole, DMF D; Borane-dimethylsulfide, $NaBO_3 \cdot 4\,H_2O$, THF-H_2O E; PDC, $(Ac)_2O$, CH_2Cl_2-DMF F; HCl-MeOH G; H_2/Pd, $NaHCO_3$, H_2O, EtOAc H; BzCl, CH_2Cl_2, pyridine.

The anomeric mixture of pyranosides **11** was condensed with silylated thymine in the presence of *tert*-butyldimethylsilyl triflate in dichloromethane-acetonitrile (9:1) to give **12** as an α:β mixture 1:12 in 72% yield.[13] The coupling constants for the anomeric proton was found to be 2.2 Hz and 11.1 Hz for the major anomer. The

minor anomer also displayed one big and one small coupling constant. This implies two possible structures, the product in a β $^4C_1$ conformation or in an α $^1C_4$ conformation. In order to confirm the structure of the major product, the coupling constant between the 5′and 4′-proton was measured and found to be 10.5 Hz. This implies a trans diaxial relationship between the two protons and indicates a $^4C_1$ conformation. Increased ratio of acetonitrile disfavoured formation of the desired β-anomer. Deprotection of **12** with sodium methoxide in methanol followed by silica gel column chromatography gave pure 1-(2,3,4-trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)thymine (**13**) in 80% yield. 1-(2,3,4-Trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)uracil (**15**) was prepared in 47% yield by condensing **11** with silylated uracil cf. *vide supra,* using dichloromethane-acetonitrile (4:1) as solvent, followed by debenzoylation. Attempted condensation of **11** with silylated cytosine resulted in elimination to give the corresponding 1,2-glycal. Instead 9-(2,3,4-trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)cytosine (**16**) was prepared, in 28% yield, by reacting **14** with triazole, phosphorus oxychloride and triethyl amine followed by methanolic ammonia at 40°C.[14] 1-(4-*C*-Benzoyloxymethyl-6-*O*-benzoyl-2,3,4-trideoxy-β-D-*erythro*-hexopyranosyl)6-chloropurine (**17**) was prepared in 68% yield by reacting **11** with silylated 6-chloropurine cf. *vide supra* giving an α:β ratio of 1:13. The 6-chloropurine **17** was reacted with ammonia saturated in methanol in a sealed steel vessel at 100°C for 22 h[15] giving pure 1-(2,3,4-trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)adenine (**18**) in 42% yield.

Scheme 2



A: Thymine B; HMDS, $(NH_4)SO_4$, TMSCl C; TBDPhSTf D; MeOH, NaOMe E; Uracil F; Triazole, $POCl_3$ G; MeOH-NH_3 H; 6-Cl-purine I; MeOH-NH_3, 100 °C

Compounds **13**, **15**, **16** and **18** were tested in an *in vitro* assay for HIV-1 RT inhibition[16] and in a XTT assay for anti HIV-1 and cytopathic effects.[17] All compounds were found to be inactive in the assays.

EXPERIMENTAL

General methods: All solvents were destilled prior to use. Thin layer chromatography was performed using silica gel 60 F-254 (Merck) plates with detection by UV and/or charring with 8% sulphuric acid. Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35-70 μ, Amicon). Organic phases were

dried over anhydrous magnesium sulphate. Concentrations were performed under reduced pressure. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. NMR spectra were recorded on a JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $CDCl_3$ and CD_3OD, and from acetone (^1H: δ 2.23, ^{13}C: δ 31.04) in D_2O. Conformational analysis were performed using 1D proton NMR and COSY-experiments.

(2S,3R)-1-*O*-(4-Bromobenzyl)-3-(2-propenyl)-1, 2, 4-butanetriol (5). To a stirred and cold suspension (-55°C) of allylmagnesiumbromide (16.0 ml, 16.0 mmol) in diethylether under a nitrogen atmosphere was added a solution of (2S,3R)-3-[[(4-bromobenzyl)oxy]methyl]oxirane-2-methanol (**4**) (1.09 g, 4.0 mmol) in diethylether (34 ml) over a period of 2.5 h. After 15 min the temperature was allowed to warm to -20°C and 1 M HCl (50 ml) was added. After warming to room temperature the two layers were separated. The aqueous layer was extracted with diethylether (3 x 50 ml). The combined organic phase was washed with sat. aqueous $NaHCO_3$ (50 ml), dried and concentrated. The residue was dissolved in THF-H_2O, 3:1 (20 ml) and sodium periodate (0.85 g, 4.0 mmol) was added. The mixture was stirred for 45 min and then concentrated. The residue was extracted with diethylether, dried, and concentrated. The resulting clear oil was subjected to column chromatography (toluene-ethyl acetate, 2:1) to give **5** (1.25 g, 27.5 mmol, 69%) as a colourless syrup. $[\alpha]_D^{22}$ + 1.55° (c 1.05, $CHCl_3$). ^1H NMR and ^{13}C NMR were in agreement with those previously reported.[5]

(2S,3R)-4-*O*-Benzoyl-1-*O*-(4-bromobenzyl)-3-(2-propenyl)-1,2,4-butanetriol (6). To a stirred and cold (0°C) mixture of **5** (7.32 g, 23.3 mmol) in CH_2Cl_2 (50 ml) and pyridine (25 ml) was added benzoyl chloride (2.44 ml, 24.2 mmol) dropwise. The reaction mixture was stirred for 1 h. Saturated $NaHCO_3$ (75 ml) was added, and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and washed with 1 M HCl (100 ml), sat. $NaHCO_3$ (100 ml), dried, concentrated, and purified by column chromatography (toluene-ethyl acetate, 20:1) to give **6** (8.28 g, 19.8 mmol, 85 %) as a colourless syrup: $[\alpha]^{22}_D$ +8.7° (c 0.84, $CHCl_3$). ^1H NMR and ^{13}C NMR were in agreement with those previously reported.[5]

(2S,3R)-4-*O*-Benzoyl-1-*O*-(4-bromobenzyl)-2-*O*-*tert*-butyldimethylsilyl-3-(2-propenyl)-1,2,4-butanetriol (7). To a stirred solution of **6** (14.73 g, 35.2 mmol) in DMF (75 ml) were added imidazole (83.6 g, 52.8 mmol) and *tert*-butyldimethylsilylchloride (7.96 g, 52.8 mmol). The resulting mixture was stirred for 10 h at room temperature. Saturated aqueous $NaHCO_3$ (25 ml) and toluene (50 ml) were added and the organic layer was separated, dried and concentrated. Purification by column chromatography (toluene-ethyl acetate, 40:1) gave **7** (18.65 g, 34.9 mmol, 99 %) as a colourless syrup. $[\alpha]^{22}_D$ +2.15°(c 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 25 °C) δ 0.20 (s, 6H, Me), 0.86 (s, 9H, tBu), 2.05-2.36 (m, 3H, H-1´and H-3), 3.47 (m, 2H, H-1a and H-1b), 4.08-4.53 (m, 5H, H-2, H-4 and CH_2Ph), 5.14 and 5.0 (m, 2H, H-3´a and H-3´b), 5.83 (m, 1H, H2´), 7.16-8.05 (m, 9H, arom.). Anal. Calcd. for $C_{27}H_{37}O_4BrSi$: C, 60.77; H, 6.99. Found: C, 60.52; H, 6.86.

(2S,3R)-4-*O*-Benzoyl-1-*O*-(4-bromobenzyl)-2-*O*-*tert*-butyldimethylsilyl-3-(3-hydroxy-propyl)-1,2,4-butanetriol (8). To a cold (0°C) solution of borane:dimethyl sulfide (2.01 ml, 1.0 M, 21.1 mmol) in THF (100 ml) under a nitrogen atmosphere was added a solution of **7** (16.065 g, 30.1 mmol) in THF (8 ml) over a period of 15 min. After 10 min, the mixture was warmed to room temperature and stirred for an additional 3 h, when t.l.c. (toluene-ethyl acetate 10:1) indicated no remaining starting material. Water (30 ml) and sodium perborate (10.73 g, 70.3 mmol) were added and the reaction mixture was stirred over night. Diethylether

(75 ml) and brine (30 ml) were added. The organic layer was separated, dried, and concentrated. The residue was purified by column chromatography (light petroleum ether-ethyl acetate, 4:1) to give **8** (13.92 g, 25.2 mmol, 84%) as a colourless syrup. $[\alpha]^{22}_D$ -2.20° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 25 °C) δ 0.20 (s, 6H, Me), 0.86 (s, 9H, tBu), 1.35-1.80 (m, 5H, H-1′, H-2′and H-3), 2.06 (m, 1H, OH), 3.48 (m, 2H, H-1a and H-1b), 3.63 (t, 2H, H-3′), 4.08-4.53 (m, 5H, H-2, H-4 and CH_2Ph), 7.16-8.05 (m, 9H, arom.); ^{13}C NMR ($CDCl_3$, 25 °C) ∂ -4.9 and -4.1 ($SiCH_3$), 18.2 (C-t-Bu), 22.5 (C-1′), 26.0 (t-$BuCH_3$), 30.9 (C-2′), 41.3 (C-3), 63.0 (C-3′), 64.8 (C-2), 71.1 (C-4), 72.7 and 73.0 (C-1 and CH_2Ph), 121.6-137.3 (C-Ar), 166.7 (COPh). Anal. Calcd. for $C_{27}H_{39}O_5BrSi$: C, 58.79; H, 7.13. Found: C, 58.90; H, 7.09.

(4R, 5S)-4-Benzoyloxymethyl-6-(4-bromobenzyloxy)-5-*tert*-butyldimethyl-silyloxy-1-hexanal (9). To a stirred solution of pyridinium dichromate (6.07 g, 16.1 mmol) and acetic anhydride (6.52 ml, 69.0 mmol) in CH_2Cl_2-DMF 4:1 (85 ml) was added compound **8** (12.72 g, 23.0 mmol). The reaction mixture was stirred at 40°C for 1 h. After concentration and co-evaporation with added toluene (3 x 50 ml), the residue was added to a column of silica gel-ethyl acetate (5 cm ethyl acetate on the top of the silica gel). The dichromate salts were allowed to precipate in the layer of ethyl acetate for 10 min after which the product was flashed through the silica gel using ethyl acetate as eluent. The solution was concentrated and the crude product was purified by column chromatography (toluene-ethyl acetate, 20:1) to give **9** (11.35 g, 19.5 mmol, 85%). ^1H NMR ($CDCl_3$, 25 °C) δ 0.20 (s, 6H, Me), 0.86 (s, 9H, tBu), 1.60-2.12 (m, 3H, H-1′and H-3), 2.48 (m, 2H, H-2′) 3.50 (m, 2H, H1a and H1b), 4.05-4.55 (m, 5H, H2, H4 and CH_2Ph), 7.16-8.05 (m, 9H, arom.), 9.78 (s, 1H, H3′).^{13}C NMR ($CDCl_3$, 25 °C) δ -4.9 and -4.1 ($SiCH_3$), 18.2 and 18.6 (t-Bu and C-1′), 25.9 (t-$BuCH_3$), 40.8 and 42.1 (C-3 and C-2′), 64.7 (C-2), 71.1 (C-4), 72.7 and 72.8 (C-1 and CH_2Ph), 121.6-137.2 (C-Ar), 166.5 (COPh), 201.9 (C-3′).

Methyl 4-*C*-benzoyloxymethyl-6-*O*-(4-bromobenzyl)-2,3,4-trideoxy-α,β-D-*erythro*-hexopyranoside (10). To a solution of **9** (8.11 g, 14.0 mmol) in MeOH, was added methanolic HCl (80 ml, 2.5 % w/w). After stirring for 2 h at room temperature, the solution was neutralised by adding triethylamine. The solution was concentrated and the residue partitioned between toluene and sat. aqueous $NaHCO_3$. The organic layer was separated, dried, concentrated and purified by column chromatography (toluene-ethyl acetate, 20:1) to give **10** as an α:β mixture 6:1 (4.91 g, 10.93 mmol, 79%). An early fraction containing only the α anomer was subjected to analysis. $[\alpha]^{22}_D$ +78.8° (c 1.45, $CHCl_3$) ^1H NMR ($CDCl_3$, 25 °C) δ 1.65-1.80 (m, 4H, H2 and H3), 2.15 (m, 1H, H4), 3.35 (s, 3H, OMe), 3.65 (m, 2H, CH_2OBz), 3.85 (m, 1H, H5), 4.22 (m, 2H, CH_2OBn), 4.51 (m, 2H, CH_2Bn), 4.77 (m, 1H, H1), 7.15-8.08 (m, 9H, Ar).^{13}C NMR ($CDCl_3$, 25 °C) δ 21.6 (C-3), 29.3 (C-2), 36.1 (C-4), 54.5 (O-Me), 66.0 (CH_2OBz), 70.0 (C-5), 71.3 (CH_2OBn), 72.7 (CH_2Ph), 100.0 (C-1), 121.3-137.3 (C-Ar), 166.3 (COPh). Anal. Calcd. for $C_{22}H_{25}O_5Br$: C, 58.80; H, 5.61. Found: C, 58.91; H, 5.62.

Methyl 6-*O*-benzoyl-4-*C*-benzoyloxymethyl-2,3,4-trideoxy-α,β-D-*erythro*-hexopyranoside (11). Compound **10** (α:β mixture, 6:1) (2.06 g, 4.59 mmol) in ethyl acetate (170 ml), water (1 ml) and $NaHCO_3$ (407 mg, 4.84 mmol) was hydrogenated over 10% palladium on charcoal at 5 atm for 6 h. The mixture was filtered through a pad of celite and concentrated. The residue was dissolved in CH_2Cl_2 (15 ml) and pyridine (3 ml). Benzoyl chloride (760 µl, 7.38 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 40 min. Water (4 ml) and CH_2Cl_2 (50 ml) was added. The organic layer was separated, washed

with 1 M HCl, aqueous $NaHCO_3$, dried and concentrated. The residue was purified by column chromatography (toluene-ethyl acetate, 14:1) to give **11** (1.67 g, 4.33 mmol, 94 %). ^1H NMR ($CDCl_3$, 25 °C) (selected signals for the α compound) δ 1.65-1.95 (m, 4H, H2 and H3), 2.23 (m, 1H, H4) 3.38 (s, 3H, OMe), 4.05 (m, 1H, H5), 4.20-4.65 (m, 4H, CH_2OBz), 4.81 (m, 1H, H1), 7.20-8.10 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$, 25 °C) (selected signals for the α anomer) δ 21.5 (C-3), 29.2 (C-2), 36.5 (C-4), 54.6 (OMe), 65.8 and 66.0 (CH_2OBz), 63.9 (C-5), 97.8 (C-1), 128.3-133.0 (C-Ar), 166.3 (CO). Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.74%; H, 6.29%. Found: C, 68.94%; H, 6.35%.

1-(2,3,4-Trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)thymine (13). A mixture of thymine (123 mg, 0.98 mmol), chlorotrimethylsilane (185 µl), and some crystals of $(NH_4)_2SO_4$ in hexamethyldisilazane (3 ml) was refluxed in an argon atmosphere for 5 h. The clear solution was concentrated and residual volatiles were co-evaporated with added toluene (6 ml). The residue was dissolved in a mixture of dichloromethane-acetonitrile (9:1, 5 ml) and a solution of **11** (250 mg, 0.65 mmol) in the same solvent mixture as above (5 ml) was added. The solution was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (270 µl, 1.17 mmol) was added. The icebath was removed and the mixture was stirred for 15 h at room temperature. Pyridine (2 ml) was added and the mixture was filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by column chromatography (toluene-ethyl acetate, 1:1) yielding *1-(2,3,4-trideoxy-4-C-benzoyloxymethyl-6-O-benzoyl-α,β-D-erythro-hexopyranosyl)thymine* (**12**) (224 mg, 0.46 mmol, 72%) as an α:β mixture 1:12. ^1H NMR for the β anomer ($CDCl_3$, 25 °C) δ 1.60-1.85 (m, 2H, H3´), 1.90 (s, 3H, Thy-CH_3), 2.05-2.33 (m, 3H, H2´ and H4´), 4.0 (ddd, $J_{5',4'}$=10.5 Hz, 1H, H5´), 4.32 (ddd, 2H, CH_2O), 4.57 (dd, $J_{6',5'}$= 3.1 Hz J_{gem}= 12.2 Hz, 1H, H6´), 4.71 (dd, $J_{6'',5'}$= 5.0 Hz, J_{gem}= 12.2 Hz, 1H, H6´´), 5.75 (dd, $J_{1',2'}$= 2.2 Hz, $J_{1',2''}$= 11.1 Hz, 1H, H1´), 7.20-8.72 (m, 11H, H arom. and H6).^{13}C NMR for the β anomer ($CDCl_3$, 25 °C) δ 12.6 (Thy-CH_3), 25.7 (C-3´), 30.3 (C-2´), 36.1 (C-4´), 64.9 and 65.0 (CH_2OBz), 78.6 (C-5´), 81.7 (C-1´), 111.1 (C-5), 125.1-133.4 (C-arom.), 135.3 (C-6), 150.4 (C-2), 164.0 (C-4), 166.3 (CO). To a solution of **12** (154 mg, 0.32 mmol) in methanol (10 ml) was added 1M sodium methoxide (60 µl, 0.06 mmol) and the solution was stirred for 1 h at room temperature. The solution was neutralised with Dowex H^+ and filtered. The filtrate was concentrated and the residue subjected to column chromatography (chloroform-methanol, 10:1) to give **13** (69 mg, 0.26 mmol, 80%) (58% from **11**) as a white solid. $[\alpha]^{22}_D$ +11.5° (c 1.03, DMSO) ^1H NMR (CD_3OD, 40 °C) δ 1.73 (m, 4H, H3' and H2'), 2.04 (m, 1H, H4'), 3.54 (m, 3H, H5' and CH_2OBz), 3.75 (ddd, 2H, H6'), 5.60 (dd, $J_{1',2'}$= 2.8 Hz, $J_{1',2''}$= 10.5 Hz, 1H, H1'), 7.63 (s, 1H, H6). Anal. Calcd. for $C_{12}H_{18}O_5N_2$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.18; H, 6.60; N, 10.39.

1-(2,3,4-Trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)uracil (15). A mixture of uracil (110 mg, 0.98 mmol), chlorotrimethylsilane (185 µl), and some crystals of $(NH_4)_2SO_4$ in hexamethyldisilazane (2 ml) was refluxed in an argon atmosphere for 5 h. The clear solution was concentrated and residual volatiles were co-evaporated with added toluene (6 ml). The residue was dissolved in a mixture of dichloromethane-acetonitrile (4:1, 5 ml) and a solution of **11** (250 mg, 0.65 mmol) in the same solvent mixture as above (5 ml) was added. The solution was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (270 µl, 1.17 mmol) was added. The icebath was removed and the mixture was stirred for 15 h at room temperature. Pyridine (2 ml) was added and the mixture was filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by column chromatography (toluene-ethyl acetate, 1:1) yielding *1-(2,3,4-trideoxy-4-C-*

benzoyloxymethyl-6-O-benzoyl-β-D-erythro-hexopyranosyl)uracil (**14**) (205 mg, 0.44 mmol, 68%). ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.71 (m, 2H, H3′), 2.13 (m, 3H, H2′and H4′), 4.02 (ddd, 1H, H5′), 4.36 (ddd, 2H, -CH_2O), 4.59 (ddd, 2H, H6′), 5.74 (m, 2H, H1′and H5), 7.16-8.05 (m, 11H, H arom. and H6), 9.48 (s, 1H, H3). To a solution of **11** (85 mg, 0.18 mmol) in methanol (10 ml) was added 1 M sodium methoxide (30 µl, 0.03 mmol) and the solution was stirred for 1 h at room temperature. The solution was neutralised with Dowex H^+ and filtrated. The filtrate was concentrated and the residue subjected to column chromatography (chloroform-methanol, 9:1) to give **15** (32 mg, 0.12 mmol, 69%) (47% from **11**) as a white solid. $[\alpha]^{22}_D$ +12.6° (c 1.06, DMSO) ^{1}H NMR (CD_3OD, 40°C) δ 1.77 (m, 5H, H2′, H3′and H4′), 3.55 (m, 3H, H5′and -CH_2O), 3.75 (ddd, 2H, H6′), 5.58 (dd, $J_{1',2'}$= 2.4 Hz, $J_{1',2''}$= 10.4 Hz, 1H, H1′), 5.70 (d, $J_{5,6}$=8.06 Hz, 1H, H5), 7.75 (d, 1H, H6).Anal. Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.56%; H, 6.29%; N, 10.93%. Found: C, 51.37%; H, 6.17%; N, 10.96%.

1-(2,3,4-Trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)cytosine (16). A mixture of uracil (110 mg, 0.98 mmol), chlorotrimethylsilane (185 µl), and some crystals of $(NH_4)_2SO_4$ in hexamethyldisilazane (2 ml) was refluxed in an argon atmosphere for 5 h. The clear solution was concentrated and residual volatiles were co-evaporated with added toluene (5 ml). The residue was dissolved in a mixture of dichloromethane-acetonitrile (4:1, 5 ml) and a solution of **11** (250 mg, 0.65 mmol) in the same solvent mixture as above (5 ml) was added. The solution was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (270 µl, 1.17 mmol) was added. The icebath was removed and the mixture was stirred for 15 h at room temperature. Pyridine (2 ml) was added and the mixture was filtered through a pad of silica gel. The filtrate was concentrated and the residue dissolved in 2 ml dry acetonitrile and added to an ice cold solution of triazole (321 mg, 4.65 mmol), phosphorus oxychloride (150 mg, 0.975 mmol), and triethylamine (614 µl, 4.4 mmol) in 3 ml of dry acetonitrile. The solution was stirred for 2 h at room temperature and triethylamine (400 µl) and water (200 µl) was added. The reaction mixture was concentrated and dissolved in dichloromethane, extracted with water, dried and concentrated. The residue was dissolved in methanolic ammonia and stirred at 40°C for 72 h, concentrated and purified by silica gel column chromatography (chloroform-methanol, 5:1) to give **16** (46 mg, 0.18 mmol, 28% from **11**).$[\alpha]^{22}_D$ +8.54° (c 1.03, H_2O) ^{1}H NMR (CD_3OD, 40°C) δ 1.73 (m, 5H, H3′, H2′and H4′), 3.50 (m, 3H, H5′and -CH_2O), 3.64 (ddd, 2H, H6′), 5.62 (dd, $J_{1',2'}$= 2.2 Hz, $J_{1',2''}$= 10.1 Hz, 1H, H1′), 5.90 (d, $J_{5,6}$ = 7.33 Hz, 1H, H5), 7.75 (d, 1H, H6). Anal. Calcd. for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.53; H, 6.60; N, 16.20.

9-(6-*O*-Benzoyl-4-*C*-benzoyloxymethyl-2,3,4-trideoxy-β-D-*erythro*-hexopyranosyl)-6-chloropurine (17) A mixture of 6-chloropurine (193 mg, 1.25 mmol), chlorotrimethylsilane (220 µl), and some crystals of $(NH_4)_2SO_4$ in hexamethyldisilazane (3 ml) was refluxed in an argon atmosphere for 5 h. The clear solution was concentrated and residual volatiles were co-evaporated with added toluene (5 ml). The residue was dissolved in a mixture of dichloromethane-acetonitrile (4:1, 5 ml) and a solution of **11** (300 mg, 0.78 mmol) in the same solvent mixture as above (5 ml) was added. The solution was cooled to 0°C and *tert*-butyldimethylsilyl triflate (320 µl, 1.50 mmol) was added. The icebath was removed and the mixture was stirred for 15 h at room temperature. Pyridine (2 ml) was added and the mixture was filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by column chromatography (toluene-ethyl acetate, 2:1) yielding **17** (272 mg, 0.53 mmol, 68%). The last fractions were contamined with α anomer (5% of total). $[\alpha]^{22}_D$ -7.30° (c 1.11, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.90-2.42 (m, 5H, H3′, H2′ and H4′), 4.13 (ddd,

1H, H5'), 4.44 (ddd, 2H, CH_2O), 4.64 (ddd, 2H, H6'), 5.93 (dd, $J_{1',2'}$= 2.1 Hz, $J_{1',2''}$= 10.8 Hz, 1H, H1'), 7.15-8.73 (m, 12H, H arom.) Anal. Calcd. for $C_{26}H_{23}N_4O_5Cl$: C, 61.48; H, 4.56; N, 11.03. Found: C, 61.34; H, 4.59, N, 10.94.

9-(2,3,4-Trideoxy-4-*C*-hydroxymethyl-β-D-*erythro*-hexopyranosyl)adenine (18) Compound **17** (200 mg, 0.37 mmol) was dissolved in methanol saturated with ammonia (15 ml) in a sealed steel vessel and heated to 100°C over night. The solution was concentrated and the residue purified by column chromatography (chloroform-methanol; 5:1) yielding **18** in 42% yield (43 mg, 0.16 mmol). $[\alpha]^{22}_D$ -2.83° (c 0.99, DMSO) ^{1}H NMR (D_2O, 40 °C) δ 1.65-2.30 (m, 5H, H3',H2'and H4'), 3.52-3.86 (m, 5H, H6', H5'and CH_2O), 5.67 (dd, $J_{1',2'}$= 2.5 Hz, $J_{1',2''}$= 10.6 Hz, 1H, H1'), 8.14 (s, 1H, H arom.), 8.27 (s, 1H, H arom.). Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.13; N, 25.07. Found: C, 51.51; H, 6.09, N, 24.93.

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

REFERENCES

1. Fischl, M. A.; Richman D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. L.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King, D. *New England Journal of Medicine* **1987**, *317*, 185.
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. Merigan, T. C.; Skowron, G.; Bozette, S. A.; Richman, D. D.; Uttamchandani, R.; Fischl, M.; Schooley, R.; Hirsch, M.; Soo, W.; Pettinelli, C.; Schaumburg, H. *Ann. Int. Med.* **1989**, *110*, 189.
4. Hoshino, H.; Shimizu, N.; Shimada, N.; Talita, T.; Takeuchi, T. *J. Antibiotics* **1987**, *40*, 1077.
5. Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993-2997.
6. Sztariicskai, F.; Dinya, Z.; Batta, G.; Gergely, L.; Szaba, B *Nucleosides & Nucleotides* **1992**, *11*, 11.
7. Martin, V. S.; Ma, P.; Masamune, S.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 1380.
8. Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560-561.
9. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.
10. Lane, C. F. *J. Org. Chem.* **1974**, *39*, 1437-1438.
11. Kabalka, W. G.; Shoup, M. T.; Naganna, G. M. *Tetrahedron Letters* **1989**, *30*, 1483-1486.
12. Andersson, F. ; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1990**, *55*, 4699-4704.
13. Vorbrüggen, H.; Krolikiewich, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
14. Divakar, K. J.; Reese, C. B. *J. Chem. Soc. Perkin I* **1982**, 1171.
15. Seela, F.; Muth, H. P.; Binding, U. *Synthesis* **1988**, 670.
16. Vrang, L.; Remand, G.; Chattopadhyaya, J.; Öberg, B. *Antiviral Research* **1987**, *7*, 139.
17. Ouen, S.; Weislow, R. K.; Fine, D. L.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. *Journal of the National Cancer Institute* **1989**, *81*, 577-586.