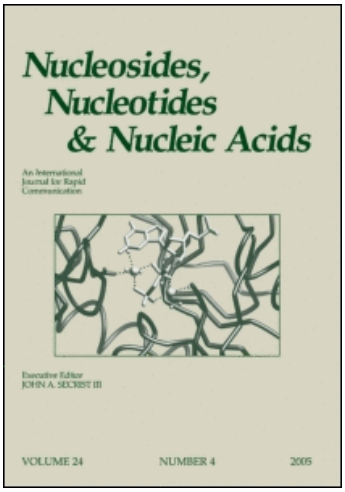


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Some 2',3'-Dideoxy-2'-C-Methyl-Substituted Nucleosides

Panagiotis Ioannidis[a]; Björn Classon[a]; Bertil Samuelsson[ab]; Ingemar Kvarnström[c]
[a] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden [b] Department of Organic Chemistry, Astra Hassle AB, Molndal, Sweden [c] Department of Chemistry, University of Linköping, Linköping, Sweden

To cite this Article Ioannidis, Panagiotis , Classon, Björn , Samuelsson, Bertil and Kvarnström, Ingemar(1992) 'Synthesis of Some 2',3'-Dideoxy-2'-C-Methyl-Substituted Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 11: 6, 1205 — 1218
To link to this Article: DOI: 10.1080/07328319208018336
URL: http://dx.doi.org/10.1080/07328319208018336

NUCLEOSIDES & NUCLEOTIDES, 11(6), 1205-1218 (1992)

SYNTHESIS OF SOME 2′,3′-DIDEOXY-2′-*C*-METHYL-SUBSTITUTED NUCLEOSIDES.

Panagiotis Ioannidis,[a] Björn Classon,[a] Bertil Samuelsson,[# *a] Ingemar Kvarnström[b]

[a]Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden. [b]Department of Chemistry, University of Linköping, S-581 83 Linköping, Sweden.

ABSTRACT

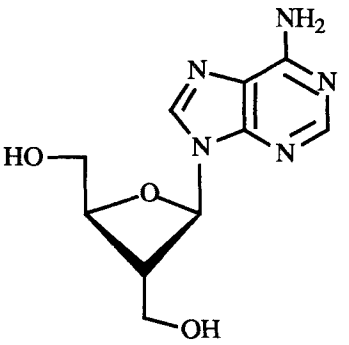
*Nucleoside analogues 1-(2′,3′-dideoxy-2′-C-hydroxymethyl-β-D-erythro-pentofuranosyl)thymine (**1**), 2′,3′-dideoxy-2′-C-hydroxymethylcytidine (**2**), 2′,3′-dideoxy-2′-C-hydroxymethyladenosine (**3**), 1-(2′-C-azidomethyl-2′,3′-dideoxy-β-D-erythro-pentofuranosyl)thymine (**4**), 2′-C-azidomethyl-2′,3′-dideoxycytidine (**5**), and 2′,3′-dideoxy-2′-C-methylcytidine (**6**) have been synthesized from (S)-4-hydroxymethyl-γ-butyrolactone (**7**).*

INTRODUCTION

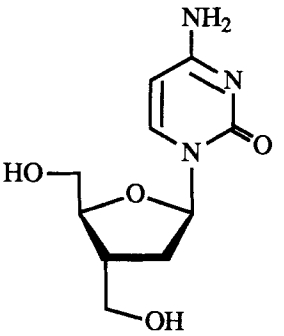
Since 3′-azido-3′-deoxythymidine (AZT, zidovudine)[1] was approved for the treatment of AIDS, there has been an intense focus on synthesis and screening of new nucleoside derivatives with the aim of finding new candidate drugs with improved therapeutic properties over AZT.

It was only recently discovered that some nucleosides having branched chain sugars also show potent anti-HIV activity *in vitro*. Two such compounds are oxetanocin A,[2,3,4] a naturally occuring nucleoside analogue having a C-2 hydroxymethyl substituted oxetane ring which show moderate *in vitro* activity against HIV, and the synthetic 2′,3′-dideoxy-3′-*C*-hydroxymethylcytidine[5,6] which show potent anti-HIV activity. These findings have intensified the interest in nucleosides with branched chain carbohydrate moieties.

Address also: Department of Organic Chemistry, Astra Hässle AB, S-431 83 Mölndal, Sweden.



Oxetanocin A

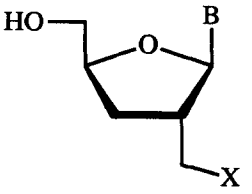


2′,3′-Dideoxy-3′-*C*-hydroxymethylcytidine

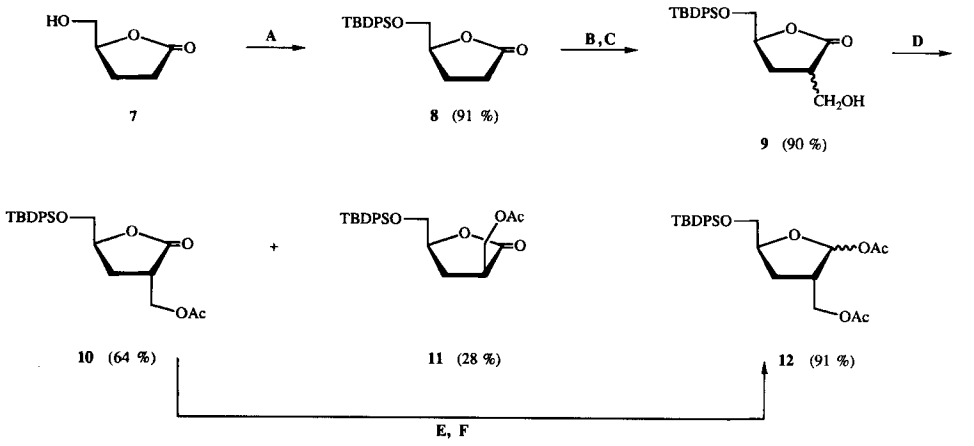
In the present work we wanted to establish the importance between the substitution of the hydroxymethyl group and the anti-HIV activity. Oxetanocin A can in this sense be viewed as an analogue of either 2′,3′-dideoxy-2′-*C*-hydroxymethyl-adenosine or of 2′,3′-dideoxy-3′-*C*-hydroxymethyladenosine.

In the series of 3′-*C*-hydroxymethyl substituted 2′,3′-dideoxythymidine, -cytidine and -adenosine[5,6] it was only the cytidine derivative that showed potent *in vitro* anti-HIV activity. This promted us to synthesize and evaluate the corresponding 2′-*C*-hydroxymethyl derivatives (**1-3**) and some close analogues (**4-6**).

After the completion of this work the synthesis of 2′,3′-dideoxy-2′-*C*-hydroxymethyladenosine starting from 1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-furanose was published.[7]



1. X = OH B = thymin-1-yl
2. X = OH B = cytosin-1-yl
3. X = OH B = adenin-9-yl
4. X = N_3 B = thymin-1-yl
5. X = N_3 B = cytosin-1-yl
6. X = H B = cytosin-1-yl



Scheme 1. **A.** *tert*-butylchlorodiphenylsilane, imidazole, DMF; **B.** ethyl formate, Na, ethanol, diethyl ether; **C.** $NaBH_4$, ethanol; **D.** acetic anhydride-pyridine (1:2), 60 °C; **E.** diisobutylaluminum hydride, toluene, -78 °C; **F.** acetic anhydride-pyridine (1:2), 40 °C.

RESULTS AND DISCUSSION

For the synthesis of the sugar moiety (*Scheme 1*), (S)-4-hydroxymethyl-γ-butyrolactone (**7**) was protected as *tert*-butyldiphenylsilyl ether by stirring with *tert*-butylchlorodiphenylsilane and imidazole in DMF yielding **8** in 91 % yield.[8,9,10] Acylation of **8** with ethyl formate in diethyl ether containing sodium ethoxide,[9] followed by reduction of the resulting aldehyde using sodium borohydride in ethanol, yielded the 2-*C*-hydroxymethyl lactone **9** as a diastereomeric mixture in 90 % yield. Acetylation of **9** in acetic anhydride-pyridine at 60 °C followed by silica gel column chromatography gave the *erythro*- and *threo*-isomers **10** and **11** in 64 % and 28 % yield respectively.

The stereochemistry of the *erythro*-isomer **10** was confirmed by a NOESY experiment. A NOE cross peak was observed between H-3 and the 4-*C*-hydroxymethyl hydrogens, and H-3′ and the 2-*C*-hydroxymethyl hydrogens, indicating a *trans* relationship between the two hydroxymethyl groups. Furthermore, a NOE-difference spectrum of the *threo*-isomer **11** showed an enhancement of the H-4 signal upon irradiation of H-2, indicating a *cis* relationship between the two hydroxymethyl groups.

Lactone **10** was reduced with diisobutylaluminum hydride in toluene at -78 °C,[8] and *O*-acetylated in acetic anhydride-pyridine at 40 °C to give 2-*C*-acetoxymethyl-1-*O*-acetyl-5-*O*-(*tert*-butyldiphenyl)silyl-D-*erythro*-pentofuranose (**12**) as an anomeric mixture in 91 % yield.

Glycosylation of **12** with silylated thymine, cytosine or 6-chloropurine, in a mixture of dichloromethane-acetonitrile (9:1) using *tert*-butyldimethylsilyl triflate[11,12,13] as Lewis acid catalyst provided exclusively the desired β-anomeric nucleosides 1-(2′-*C*-acetoxymethyl-5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-dideoxy-β-D-*erythro*-pentofuranosyl)-thymine (**13**), 2′-*C*-acetoxymethyl-5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-dideoxycytidine (**14**) and 9-(2′-*C*-acetoxymethyl-5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-dideoxy-β-D-*erythro*-pentofuranosyl)-6-chloropurine (**15**) in 97 %, 84 % and 89 % yield respectively (*Scheme 2*). The high degree of selectivity for the β-isomers resulted from the selection of protective groups, using a non-participating silyl ether in the 5-*O*-position and a potentially participating acetate at the 2-*C*-hydroxymethyl position.

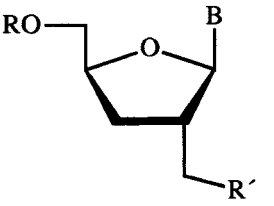
Desilylation of **13** and **14** with 1 M tetrabutylammonium fluoride in tetrahydrofuran,[14] followed by deacetylation with methanol saturated with ammonia, yielded 1-(2′,3′-dideoxy-2′-*C*-hydroxymethyl-β-D-*erythro*-pentofuranosyl)thymine (**1**) and 2′,3′-dideoxy-2′-*C*-hydroxymethylcytidine (**2**) in 80 % and 83 % yield respectively. The 6-chloropurine derivative **15** was desilylated and reacted with methanol saturated with ammonia at 100 °C in a sealed steel vessel, to give 2′,3′-dideoxy-2′-*C*-hydroxymethyladenosine (**3**) in 36 % yield.[15] The ^{1}H NMR and UV spectra of **3** were in accordance with those published,[7] confirming the N-9-substitution of the purine-ring as well as the β-configuration of the sugar moiety.

For the synthesis of **4-6** (*Scheme 2*), substances **13** and **14** were deacetylated in methanol saturated with ammonia and the resulting primary hydroxy groups were converted to the corresponding methanesulfonyl esters in 89 % and 83 % yield respectively. Reacting these with sodium azide in *N,N*-dimethyl formamide at 60 °C gave the two azidomethyl derivatives **16** and **18** in 80 % and 93 % yield respectively. Desilylation of **16** and **18** yielded **4** and **5** in 89 % and 82 % yield respectively. A NOE-difference spectrum of **5** showed an enhancement of the H-6 signal upon irradiation of H-2′, indicating a *trans* relationship between the 2′-*C*-azidomethyl group and the pyrimidine base.

For the synthesis of **6**, the methanesulfonyl ester **17** was reacted with tetrabutylammonium iodide in tetrahydrofuran at 55 °C to yield the corresponding 2′-*C*-iodomethyl derivative **19** in 94 % yield. Hydrogenation of **19** over 10 % Pd/C in ethanol containing 1.5 equiv. triethyl amine followed by desilylation gave 2′,3′-dideoxy-2′-*C*-methylcytidine (**6**) in 75 % yield.

BIOLOGICAL RESULTS

Compounds **1-6** were tested in a H-9 cell system for anti-HIV activity.[16] Of these compounds, all were inactive except **2** which showed a low activity.



12 —G→ (K,L,M)

- **13.** B= Thymin-1-yl; R= TBDPS; R´= OAc (97 %)
- (J,K) → **1.** B= Thymin-1-yl; R= H; R´= OH (80 %)
- **16.** B= Thymin-1-yl; R= TBDPS; R´= N_3 (80 %)
- (J) → **4.** B= Thymin-1-yl; R= H; R´= N_3 (91 %)

12 —H→ (K,L)

- **14.** B= Cytosin-1yl; R= TBDPS; R´=OAc (84 %)
- (J,K) → **2.** B= Cytosin-1-yl; R= H; R´= OH (83 %)
- **17.** B= Cytosin-1-yl; R= TBDPS; R´= OSO_2CH_3 (92 %)
- (N) (M) → **18.** B= Cytosin-1-yl; R= TBDPS; R´= N_3 (93 %)
- (N) (J) → **5.** B= Cytosin-1-yl; R= H; R´= N_3 (82 %)
- **19.** B= Cytosin-1-yl; R=TBDPS; R´= I (94 %)
- (O,J) → **6.** B= Cytosin-1-yl; R= H; R´= H (75 %)

12 —I→ (J, P)

- **15.** B= 6-chloro-purin-9-yl; R= TBDPS, R´= OAc (87 %)
- → **3.** B= Adenin-9-yl; R= H; R´= OH (36 %)

Scheme 2. **G.** silylated thymine, TBDMSOTf, dichloromethane-acetonitrile (9:1); **H.** silylated cytosine,TBDMSOTf, dichloromethane-acetonitrile (9:1); **I.** silylated 6-chloropurine, TBDMSOTf, dichloromethane-acetonitrile (9:1); **J.** 1 M tetrabutyl-ammonium fluoride in THF; **K.** methanol saturated with ammonia; **L.** methanesulfonyl chloride, pyridine, **M.** sodium azide, DMF, 60 °C; **N.** tetrabutylammonium iodide, THF, 55 °C; **O.** H_2, 10 % Pd/C, triethylamine, ethanol; **P.** methanol saturated with ammonia, sealed steel vessel, 100 °C.

EXPERIMENTAL

General methods: All solvents were distilled prior to use. Thin layer chromatography was performed using silica gel 60 F-254 (Merck) plates with detection by UV and/or by charring with 8% sulfuric acid. Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35-70 m, Amicon). Organic phases were dried over anhydrous magnesium sulfate. Concentrations were performed under reduced pressure. HPLC was performed on a Gilson HPLC with a Dynamax C_{18} (60A, 10 mm) column. Optical rotations were recorded using a Perkin-Elmer 241 polarometer. IR-spectra were recorded on a Perkin Elmer 257 IR-Spectrophotometer. UV-spectra were recorded on a Varian Cary 3 UV-Visible Spectrophotometer. NMR-spectra were recorded on a JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $CDCl_3$, and from acetone (^1H: d 2.23, ^{13}C: d 31.04) in D_2O.

(S)-4-(*tert*-Butyldiphenylsilyloxy)methyl-γ-butyrolactone (8). *Tert*-butylchlorodiphenylsilane (13.04 g, 47.4 mmol) was added dropwise to a stirred and cooled (ice bath) solution of (S)-4-hydroxymethyl-γ-butyrolactone (**7**) (5.00 g, 43.1 mmol) and imidazole (6.46 g, 94.8 mmol) in DMF (30 ml). Stirring was continued at room temperature for 3 h, the solution was diluted with sat. $NaHCO_3$(aq), extracted with toluene, the organic phase dried, concentrated and the residue crystalized from petroleum ether (60-70 °C) yielding **8** (13.9 g, 91 %): $[\alpha]_D$ +28.3° (*c* 1.21, $CHCl_3$): m.p 68-72 °C: ^{13}C NMR ($CDCl_3$) δ 19.3 (C-tert), 23.7 (C-3), 26.9 (3 x CH_3), 28.7 (C-2), 65.6 (C-5), 80.1 (C-4), 127.9-135.8 (ArC), 177.6 (carbonyl); ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H, 3 x CH_3), 2.05-2.58 (m, 4H, H-2, H-2´, H-3, H-3´), 3.81 (m, 2H, H-5, H-5´), 4.58 (m, 1H, H-4), 7.20-7.80 (m, 10H, ArH).

(S)-4-(*tert*-Butyldiphenylsilyloxy)methyl-(R,S)-2-hydroxymethyl-γ-butyrolactone (9). Ethanol (28 µl, 0.48 mmol) was added to sodium (280 mg, 12.17 mmol) in dry diethyl ether (5 ml), and the mixture was stirred at room temperature for 2 h. A solution of **8** (3.50 g, 9.87 mmol) and ethyl formate (980 mg, 13.23 mmol) in diethyl ether (6 ml) was added and the stirring was continued for 16 h at room temperature. Diethyl ether (20 ml) and 1 M NaH_2PO_4 (10 ml) were added and the phases were separated. The organic phase was washed with water, dried and concentrated. The residue was dissolved in ethanol (10 ml), and a solution of $NaBH_4$ (500 mg, 13.22 mmol) in ethanol (10 ml) was added. After 5 min, the reaction was terminated by the addition of a few drops of 80 % acetic acid. The mixture was partitioned between ethyl acetate and water. The organic phase was dried, concentrated and the residue purified by column cromatography (toluene-acetone 9:1) yielding **9** (3.40 g, 90 %).

Anal.Calcd for $C_{22}H_{28}O_4Si$: C, 68.71; H, 7.34. Found: C, 68.58; H, 7.36.

(S)-2-Acetoxymethyl-(S)-4-(*tert*-butyldiphenylsilyloxy)methyl-γ-butyrolactone (10) and (R)-2-Acetoxymethyl-(S)-4-(*tert*-butyldiphenylsilyloxy)methyl-γ-butyrolactone (11). A solution of **9** (2.00 g, 5.20 mmol) in pyridine (20 ml) and acetic anhydride (10 ml) was stirred at 60 °C for 30 min. The solution was concentrated and the residue purified by column chromatography (toluene-acetone 10:1) to give **10** (1.41 g, 64 %): $[\alpha]_D$ +22.4° (*c* 1.00, $CHCl_3$): ^{13}C NMR ($CDCl_3$) δ 19.2 (C, tert), 20.8 (CH_3, acetate), 26.9 (3 x CH_3), 27.3 (C-3), 39.8 (C-2), 63.1, 65.7 ($\underline{C}H_2OAc$, C-5), 78.1 (C-4), 127.9, 128.3-135.7 (ArC), 170.7 (acetate), 176.4 (carbonyl); ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, 3 x CH_3), 2.07 (s, 3H, CH_3, acetate), 2.16 (m, 1H, H-3), 2.33 (m, 1H, H-3'), 3.13 (m, 1H, H-2), 3.79, 4.35 (m, m, 4H, H-5, H-5', H-6, H-6'), 4.58 (m, 1H, H-4) 7.17-7.72 (m, 10H, ArH).

Anal. Calcd. for $C_{24}H_{30}O_5Si$: C, 67.57; H, 7.09. Found: C, 67.48; H, 7.15.

Further elution gave **11** (0.62 g, 28 %): $[\alpha]_D$ +19.2° (*c* 1.00, $CHCl_3$): ^{13}C NMR ($CDCl_3$) δ 19.4 (C, tert), 20.8 (CH_3, acetate), 26.9 (3 x CH_3), 27.3 (C-3), 40.6 (C-2), 62.4, 64.5 ($\underline{C}H_2OAc$, C-5), 78.6 (C-4), 128.0-135.8 (ArC), 170.7 (acetate), 175.5 (carbonyl); ^1H NMR ($CDCl_3$) δ 1.05 8 (s, 9H, 3 x CH_3), 2.00 (s, 3H, CH_3, acetate), 2.24 (m, 1H, H-3), 2.41 (m, 1H, H-3'), 2.98 (m, 1H, H-2), 3.83, 4.36 (m, m, 4H, H-5, H-5', H-6, H-6'), 4.51 (m, 1H, H-4), 7.18-7.69 (m, 10H, ArH).

2-*C*-Acetoxymethyl-1-*O*-acetyl-5-*O*-(*tert*-butyldiphenyl)silyl-2',3'-dideoxy-D-*erythro*-pentofuranose (12). To a solution of lactone **10** (500 mg, 1.17 mmol) in toluene (30 ml) at -78 °C was added diisobutylaluminum hydride (20 % in hexane, 3.00 ml, 2.95 mmol). The solution was stirred for 1.5 h, allowed to warm up to room temperature, and methanol (0.5 ml) was added. To the solution was added ethyl acetate (30 ml) and aqueous sat. $NaHCO_3$ (4 ml). After stirring for 2 h, dry $MgSO_4$ (2.0 g) was added and after stirring for an additional 3 h, the mixture was filtered. The filtrate was concentrated, the residue dissolved in pyridine (6 ml) and acetic anhydride (3 ml) and heated to 40 °C for 30 min, concentrated and the residue purified by column chromatography (toluene-acetone 10:1) to yield **12** (500 mg, 91 %) as an anomeric mixture. ^{13}C NMR ($CDCl_3$, selected signals) δ 19.4 (C, tert.), 20.9, 21.3, 21.4 (CH_3, acetates), 26.9 (3 x CH_3), 28.4 (C-3), 42.3, 44.8 (C-2), 62.8, 63.7, 65.8, 66.8 (C-5 and C-6), 80.0, 81.4 (C-4), 97.6, 100.2 (C-1), 127.8-135.7 (ArC), 170.2, 170.9 (acetates).

Anal. Calcd. for $C_{26}H_{34}O_6Si$: C, 66.35; H, 7.29. Found: C, 66.51; H, 7.28.

1-(2'-*C*-Acetoxymethyl-5'-*O*-*tert*-butyldiphenylsilyl-2',3'-dideoxy-β-D-*erythro*-pentofuranosyl)thymine (13). A mixture of thymine (253 mg, 2.01

mmol), chlorotrimethylsilane (0.300 ml) and some crystals of $(NH_4)_2SO_4$ in hexamethyldisilazane (4 ml) was refluxed under nitrogen for 6 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 (9:1, 10 ml) and a solution of **12** (630 mg, 1.34 mmol) in the same solvent mixture as above (5 ml) was added. The solution was cooled on an ice bath and *tert*-butyldimethylsilyl triflate (0.370 ml, 1.61 mmol) was added. The mixture was stirred for 30 min on an ice bath followed by 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-acetone 1:1) yielding **13** (697 mg, 97 %): $[\alpha]_D$ +37.4° (*c* 1.15, $CHCl_3$): ^{13}C NMR ($CDCl_3$) δ 12.1 (CH_3, thymine), 19.4 (C, tert.), 20.8 (CH_3, acetate), 27.0 (3 x CH_3), 29.2 (C-3´), 44.1 (C-2´), 63.6, 65.5 (C-5´, C-6´), 79.0 (C-4´), 87.3 (C-1´), 111.2 (C-5), 128.0-135.6 (ArC), 150.2 (C-4), 163.4 (C-2), 170.7 (acetate); ^1H NMR ($CDCl_3$) δ 1.11 (s, 9H, 3 x CH_3), 1.64 (s, 3H, CH_3, thymine), 1.89-2.30 (s, m, 5H, CH_3 acetate, H-3´, H-3´´), 2.67 (m, 1H, H-2´), 3.89, (m, 2H, H-6´, H-6´´), 4.18 (m, 3H, H-4´, H-5´, H-5´´), 5.97 (d, *J*= 6.59 Hz, 1H, H-1´), 7.40-7.68 (11H, 10ArH, H-6), 8.30 (s, 1H, H-3).

Anal. Calcd. for $C_{29}H_{36}O_6N_2Si$: C, 64.90; H, 6.76; N, 5.22. Found: C, 65.12; H, 6.81; N, 5.10.

2´-*C*-Acetoxymethyl-5´-*O*-*tert*-butyldiphenylsilyl-2´,3´-dideoxycytidine (14). A mixture of cytosine (99 mg, 0.892 mmol), chlorotrimethylsilane (0.100 ml) and some crystals of $(NH_4)_2SO_4$ in hexamethyldisilazane (2 ml) was refluxed under nitrogen for 6 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 (9:1, 5 ml) and a solution of **12** (280 mg, 0.595 mmol) in the same solvent mixture as above (5 ml) was added. The solution was cooled on an ice bath and *tert*-butyldimethylsilyl triflate (0.164 ml, 0.714 mmol) was added. The mixture was stirred for 30 min on an ice bath followed by 15 h at room temperature. Pyridine (1 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 (chloroform-methanol 12:1) yielding **14** (261 mg, 84 %): $[\alpha]_D$ +46.3° (*c* 1.55, $CHCl_3$): ^{13}C NMR ($CDCl_3$) δ 19.3 (C, tert), 20.9 (CH_3, acetate), 26.9 (3 x CH_3), 28.3 (C-3´), 45.8 (C-2´), 64.2, 64.7 (C-5´, C-6´), 80.5 (C-4´), 88.6 (C-1´), 94.4 (C-5), 127.9- 135.6 (ArC), 140.7 (C-6), 156.0 (C-4), 165.8 (C-2), 170.9 (acetate); ^1H NMR ($CDCl_3$) δ 1.09 (s, 9H, 3 x CH_3), 1.80 (m, 1H, H-3´), 2.05 (s, 3H, CH_3 acetate), 2.27 (m, 1H, H-3´´), 2.67 (m, 1H, H-2´), 3.89 (m, 2H, H-6´, H-6´´), 4.28 (m, 3H, H-4´, H-5´, H-5´´), 5.40 (d, *J*=

7.33 Hz, 1H, H-5), 5.96 (d, *J*= 3.28 Hz, 1H, H-1'), 7.40-7.67 (10H, ArH), 8.00 (d, *J*=7.33 Hz, 1H, H-6).

Anal. Calcd. for $C_{28}H_{35}O_5N_3Si$: C, 64.47; H, 6.76; N, 8.05. Found: C, 64.20; H, 6.76; N, 7.96.

9-(2'-*C*-Acetoxymethyl-5'-*O*-*tert*-butyldiphenylsilyl-2',3'-dideoxy-β-D-*erythro*-pentofuranosyl)-6-chloropurine (15). A mixture of 6-chloropurine (123 mg, 0.797 mmol), chlorotrimethylsilane (0.150 ml) and some crystals of $(NH_4)_2SO_4$ in hexamethyldisilazane (2.5 ml) was refluxed under nitrogen for 6 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 (9:1, 5 ml) and a solution of **12** (250 mg, 0.531 mmol) in the same solvent mixture as above (5 ml) was added. The solution was cooled on an ice bath and *tert*-butyldimethylsilyl triflate (0.146 ml, 0.637 mmol) was added. The mixture was stirred for 30 min on an ice bath followed by 15 h at room temperature. Pyridine (1 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-acetone 10:1) yielding **15** (260 mg, 87 %): $[\alpha]_D$ +5.14° (*c* 1.05, $CHCl_3$): ^{13}C NMR ($CDCl_3$) δ 19.3 (C, tert.), 20.7 (CH_3, acetate), 26.9 (3 x CH_3), 29.2 (C-3'), 44.7 (C-2'), 63.7, 65.3 (C-5', C-6'), 80.9 (C-4'), 88.2 (C-1'), 127.9-151.9 (ArC). 170.6 (acetate); ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H, 3 x CH_3), 1.98 (s, m, 4H, CH_3 acetate, H-3'), 2.35 (m, 1H, H-3''), 3.20 (m, 1H, H-2'), 3.74 (m, 2H, H-5', H-5''), 4.30 (m, 3H, H-4', H-6', H-6''), 6.16 (d, *J*= 4.40 Hz, 1H, H-1'), 7.26-7.66 (10H, ArH), 8.41, 8.68 (s, s, 2H, H-2, H-8).

Anal. Calcd. for $C_{29}H_{33}O_4N_4SiCl$: C, 61.52; H, 5.87; N, 9.90. Found: C, 61.87 ; H, 5.97 ; N, 9.51.

1-(2',3'-Dideoxy-2'-*C*-hydroxymethyl-β-D-*erythro*-pentofuranosyl)thymine (1). Compound **13** (100 mg, 0.186 mmol) was dissolved in 1 M tetrabutylammonium fluoride x 3 H_2O in THF (9 ml) and stirred for 20 min at room temperature. The solution was concentrated and the residue purified by column chromatography (toluene-acetone 1:1). The product was dissolved in methanol (4 ml) and methanol saturated with ammonia (2 ml) was added. The solution was stirred over night, concentrated and the residue purified by column chromatography (chloroform-methanol 9:1) yielding **1** (38 mg, 80 %): $[\alpha]_D$ +9.1° (*c* 0.70, H_2O): ^{13}C NMR (D_2O, 40 °C) δ 12.3 (CH_3, thymine), 29.2 (C-3'), 46.7 (C-2'), 62.4, 63.8 (C-5', C-6'), 81.0 (C-4'),

88.8 (C-1′), 112.2 (C-5), 138.6 (C-6), 152.5 (C-4), 167.2 (C-2); ^{1}H NMR (D_2O, 40 °C) δ 1.90 (s, 3H, CH_3, thymine), 2.09 (m, 2H, H-3′, H-3′′), 2.64 (m, 1H, H-2′), 3.76 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.31 (m, H-4′), 5.93 (d, *J*= 5.13 Hz, 1H, H-1′), 7.68 (s, 1H, H-6).

Anal. Calcd. for $C_{11}H_{16}O_5N_2$: C, 51.56; H, 6.29; N, 10. 93. Found: C, 51.28; H, 6.11; N, 10.71.

2′,3′-Dideoxy-2′-*C*-hydroxymethylcytidine (2). Compound **14** (110 mg, 0.211 mmol) was dissolved in 1 M tetrabutylammonium fluoride x 3 H_2O in THF (8 ml) and stirred for 20 min at room temperature. The mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 5:1). The product was dissolved in methanol saturated with ammonia (4 ml) and stirred over night, concentrated and the residue purified by column chromatography (chloroform-methanol 2:1) yielding **2** (41 mg, 83 %): $[\alpha]_D$ +31.2° (*c* 1.20, H_2O): ^{13}C NMR (D_2O, 40 °C) δ 29.2 (C-3′), 47.6 (C-2′), 62.5, 64.0 (C-5′, C-6′), 81.2 (C-4′), 89.8 (C-1′), 96.8 (C-5), 142.6 (C-6), 158.3 (C-4), 166.9 (C-2); ^{1}H NMR (D_2O, 40 °C) δ 2.04 (m, 2H, H-3′, H-3′′), 2.55 (m, 1H, H-2′), 3.77 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.33 (m, 1H, H-4′), 5.91 (d, *J*= 4.77 Hz, 1H, H-1′), 6.05 (d, *J*= 7.32 Hz, 1H, H-5), 7.85 (d, *J*= 7.32 Hz, 1H, H-6).

Anal. Calcd. for $C_{10}H_{15}O_4N_3$ x H_2O: C, 46.33; H, 6.61; N, 16.21. Found: C, 46.41; H, 6.31; N, 16.16.

2′,3′-Dideoxy-2′-*C*-hydroxymethyladenosine (3). Compound **15** (120 mg, 0.212 mmol) was dissolved in 1 M tetrabutylammonium fluoride x 3 H_2O in THF (9 ml) and stirred for 20 min at room temperature. The mixture was concentrated and the residue purified by column chromatography (toluene-acetone 1:1). The product was dissolved in methanol saturated with ammonia (10 ml) and heated to 100 °C over night in a sealed steel vessel. The solution was concentrated and the residue purified by column chromatography (chloroform-methanol 3:1) yielding **3** which was further purified on a SEP-PAK C_{18} cartridge [prewashed with methanol (40 ml), acetonitrile (5 ml) and finally water (5 ml)] with water as eluant. The fractions containing **3** were lyophilized yielding (20 mg, 36 %): $[\alpha]_D$ -10.3° (*c* 0.20, H_2O): UV(H_2O) λ_{max} 260 nm; ^{13}C NMR (D_2O, 40 °C) δ 29.4 (C-3′), 46.8 (C-2′), 62.2, 64.4 (C-5′, C-6′), 81.4 (C-4′), 88.3 (C-1′), 141.2-169.4 (5ArC); ^{1}H NMR (D_2O, 40 °C) δ 2.21 (m, 2H, H-3′, H-3′′), 3.06 (m, 1H, H-2′), 3.76 (m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.45 (m, 1H, H-4′), 6.07 (d, *J*= 5.32 Hz, 1H, H-1′), 8.15, 8.30 (s, s, 2H, H-2, H-8).

Anal. Calcd. for $C_{11}H_{15}O_3N_5$: C, 49.81; H, 5.70; N, 26.40. Found: C, 50.01; H, 5.54; N, 26.35.

1-(2′-*C*-Azidomethyl-2′,3′-dideoxy-β-D-*erythro*-pentofuranosyl)-thymine (4). A solution of **13** (440 mg, 0.820 mmol) in methanol saturated with ammonia (15 ml) was stirred over night. The mixture was concentrated and the residue purified by column chromatography (toluene-acetone 1:1). The residue (170 mg, 344 mmol) was dissolved in pyridine (5 ml) and methanesulfonyl chloride (0.030 ml, 378 mmol) was added. After 1 h at room temperature, the solution was concentrated and the residue co-evaporated with added toluene. The residue was purified by column chromatography (toluene-acetone 2:1) yielding 1-(5′-*O*-*tert*-butyldiphenylsilyl-2′-*C*-methanesulfonylmethyl-2′,3′-dideoxy-β-D-*erythro*-pentofuranosyl)thymine which was dissolved in DMF (2 ml). Sodium azide (72 mg, 1.11 mmol) was added and the resulting suspension was stirred at 60 °C for 3 h. The mixture was concentrated and purified by column chromatography (toluene-acetone 2:1) yielding **16** (151 mg, 82 %) (IR ($CHCl_3$) 2100 cm^{-1}), which was dissolved in 1 M tetrabutylammonium fluoride x 3 H_2O in THF (10 ml) at room temperature. After 10 min, the mixture was concentrated and the residue purified by column chromatography (toluene-acetone 1:1) yielding **4** (72 mg, 91 %). $[\alpha]_D$ -31.3° (*c* 0.76, $CHCl_3$): IR ($CHCl_3$) 2100 cm^{-1} (azide): ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3, thymine), 29.6 (C-3′), 44.5 (C-3′), 52.0 (C-6′), 63.8 (C-5′), 79.8 (C-4′), 89.0 (C-1′), 111.0 (C-5), 136.6 (C-6), 150.9 (C-4), 164.4 (C-2); ^1H NMR ($CDCl_3$) δ 1.89 (s, 3H, CH_3, thymine), 1.96 (m, 1H, H-3′), 2.28 (m, 1H, H-3′′), 2.61 (m, 1H, H-2′), 3.53, 3.82 (m, m, 4H, H-5′, H-5′′, H-6′, H-6′′), 4.29 (m, 1H, H-4′) 5.81 (d, *J*= 5.50 Hz, 1H, H1′), 7.56 (s, 1H, H-6), 9.90 (s, 1H, H-3).

Anal. Calcd. for $C_{11}H_{15}O_4N_5$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.83; H, 5.21; N, 24.71.

2′-*C*-Azidomethyl-2′,3′-dideoxycytidine (5). A solution of **14** (260 mg, 0.489 mmol) in methanol saturated with ammonia (10 ml) was stirred over night at room temperature. The mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 9:1) to give 5′-*O*-*tert*-butyldiphenylsilyl-2′-hydroxymethyl-2′,3′-dideoxycytidine (395 mg, 97 %).To this compound (100 mg, 0.208 mmol) in pyridine (3 ml) was added methanesulfonyl chloride (0.020 ml, 0.250 mmol). After 1 h the solution was concentrated and the residue was co-evaporated with added toluene. The residue was purified by column chromatography (chloroform-methanol 9:1) yielding **17** (110 mg, 95 %) [^{13}C NMR ($CDCl_3$) δ 37.3 (CH_3), 69.7 (C-6′); ^1H NMR ($CDCl_3$) δ 3.08 (s, 3H, CH_3), 4.50 (d, *J*= 4.21 Hz, 2H, H-6′, H-6′′)].

Compound **17** (100 mg, 0.179 mmol) was dissolved in DMF (2 ml) and sodium azide (41 mg, 0.628 mmol) was added. The resulting suspension was stirred for 3.5 h at 60 °C. The mixture was concentrated and the residue purified by column chromatography (toluene-acetone 2:1) yielding **18** (84 mg, 93 %), (IR ($CHCl_3$) 2100 cm^{-1}), which was dissolved in 1 M tetrabutylammonium fluoride x 3 H_2O in THF (4 ml) at room temperature. After 15 min, the mixture was concentrated and the residue purified by column chromatography (chloroform-methanol 5:1) and then HPLC (reversed phase, methanol-water 85:15) yielding **5** (36 mg, 82 %): $[\alpha]_D$ +54.4° (*c* 0.95, H_2O): IR ($CHCl_3$) 2100 cm^{-1}, (azide): ^{13}C NMR (D_2O, 40 °C) δ 29.9 (C-3′), 44.9 (C-2′), 52.6 (C-6′), 64.0 (C-5′), 80.8 (C-4′), 90.0 (C-1′), 97.1 (C-5), 142.6 (C-6), 158.3 (C-4), 166.9 (C-2); ^1H NMR (D_2O, 40 °C) δ 2.03 (m, 2H, H-3′, H-3′′), 2.61 (m, 1H, H-2′), 3.56 (m, 2H, H-6′, H-6′′), 3.75 (m, 2H, H-5′, H-5′′), 4.33 (m, 1H, H-4′), 5.92 (d, *J*= 5.50 Hz, 1H, H-1′), 6.05 (d, *J*=7.32 Hz, 1H, H-5), 7.82 (d, *J*=7.32 Hz, 1H, H-6).

Anal. Calcd. for $C_{10}H_{14}O_3N_6$: C, 45.11; H, 5.30; N, 31.56. Found: C, 45.02; H, 5.41; N, 31.28.

2′,3′-Dideoxy-2′-*C*-methylcytidine (6). To a solution of **17** (77 mg, 0.138 mmol) in THF (5 ml), was added tetrabutylammonium iodide (255 mg, 0.690 mmol). The resulting solution was stirred for 24 h at 55 °C. The solution was cooled on an ice bath, filtered and the filtrate concentrated. The residue was purified by column chromatography (chloroform-methanol (10:1) yielding **19** (76 mg, 94 %), [^{13}C NMR ($CDCl_3$) δ 6.21 (C-6′); ^1H NMR ($CDCl_3$) δ 3.4 (m, 2H, H-6′, H-6′′)] which was dissolved in ethanol (5 ml) containing triethyl amine (0.023 ml), and hydrogenated over 10 % Pd/C for 6 h. The mixture was filtered through Celite and the filtrate concentrated. The residue was dissolved in 1M tetrabutylammonium fluoride x 3 H_2O in THF (4 ml) and stirred for 15 min at room temperature. The mixture was concentrated and the residue purified by column chromatography (chloroform-methanol, 5:1) and then HPLC (reversed phase, methanol-water, 1:1) yielding **6** (18 mg 75 %): $[\alpha]_D$ +32.0° (*c* 0.6, H_2O): ^{13}C NMR (D_2O, 40 °C) δ 16.5 (C-6′), 33.4 (C-3′), 39.9 (C-2′), 64.2 (C-5′), 80.8 (C-4′), 93.2 (C-1′), 96.7 (C-5), 142.4 (C-6), 158.7 (C-4), 167.0 (C-2); ^1H NMR (D_2O, 40 °C) δ 1.12 (d, *J*=6.96 Hz, 3H, CH_3), 1.83 (m, 1H, H-3′), 1.99 (m, 1H, H-3′′), 2.39 (m, 1H, H-2′), 3.75 (m, 2H, H-5′, H-5′′), 4.36 (m, 1H, H-4′), 5.71 (d, *J*=4.76 Hz, 1H, H-1′), 6.03 (d, *J*=7.33 Hz, 1H, H-5), 7.84 (d, *J*=7.33 Hz, 1H, H-6).

Anal. Calcd. for $C_{10}H_{15}O_3N_3$: C, 53.32; H, 6.71: N, 18.66. Found: C, 53.04; H, 6.50; N, 18.49.

Acknowledgement.

We thank the Swedish National Board for 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. and Broder, S. *Proc. Natl. Acad. Sci. USA,* 82 (1985) 7096.

2. Hoshino, H., Shimizu, N., Shimada, N., Talita, T. and Takeuchi,T. *J. Antibiotics* 40 (1987) 1077.

3. Nasr, M., Litterst, C. and McGowan, J. *J. Antiviral Res.* 14 (1990) 125.

4. De Clercq, E. *Design of anti-AIDS drugs.* 14. (1990) Pharmaco Chemistry Library, Elsevier.

5. USP no 4, 954, 504.

6. Svansson, L., Kvarnström, I., Classon, B. and Samuelsson, B. *J. Org. Chem.* 56 (1991) 2993.

7. Tseng, C.K-H., Marquez, V.E., Milne, G.W.A., Wysocki, Jr, R.J., Mitsuya, H., Shirasaki, T. and Driscoll, J.S. *J. Med. Chem.* 34 (1991) 343.

8. Okabe, M., Sun, R-C., Tam, S. Y-K., Todaro, L.J. and Coffen, D. L. *J. Org.Chem.* 53 (1988) 4780.

9. Taniguchi, M., Koga, K. and Yamada, S. *Tetrahedron* 30 (1974) 3547.

10. Maier, M.E. and Schöffling, B. *Tetrahedron Lett.* 32 (1991) 53.

11. Padyukova, N.S., Karpeisky,M.Y., Kolobushkina, L.I. and Mikhailov, S.N. *Tetrahedron Lett.* 28, (1987) 3623.

12. Vorbrüggen, H., Krolikiewich, K. and Bennua B. *Chem. Ber.* 114 (1981) 1234.

13. Mazur, A., Tropp, B.E. and Engel, R. *Tetrahedron* 20 (1984) 3949.

14. Ogilvie, K.K., Beaucage, S.L., Schifman, A.L., Theriault, N.Y. and Sadana, K.L. *Can. J. Chem.* 56 (1978) 2768.

15. Seela, F., Muth, H.P. and Bindig, U.
Synthesis (1988) 670.

16. Vial, J.M., Johansson, N.G., Vrang, L. and Chattopadhyaya, J.
Antiviral Chem. Chemotherapy 3 (1990) 183.

Received 10/8/91
Accepted 12/30/91