Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 628–634

Asymmetric synthesis of 4′-*C*-benzyl-2′,3′-dideoxynucleoside analogues from 3-benzyl-2-hydroxy-2-cyclopenten-1-one

Artur Jõgi,[a] Marit Ilves,[a] Anne Paju,[a] Tõnis Pehk,[b] Tiiu Kailas,[a,c] Aleksander-Mati Müürisepp[a,c] and Margus Lopp[a,*]

[a]*Department of Chemistry, Faculty of Science, Tallinn University of Technology, Ehitajate tee 5, 19086 Tallinn, Estonia*
[b]*National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia*
[c]*Competence Centre for Cancer Research, Akadeemia tee 15, 12618 Tallinn, Estonia*

Received 14 January 2008; accepted 24 January 2008
Available online 4 March 2008

Abstract—Both enantiomers of the key intermediate, 2-benzyl-5-oxo-tetrahydro-furan-2-carboxylic acid were obtained by asymmetric oxidation of 3-benzyl-2-hydroxy-2-cyclopenten-1-one with an ee ⩾96%, using the tartaric ester/Ti(O*i*Pr)$_4$/*t*-BuOOH complex, and transformed to the corresponding 4′-substituted nucleoside analogues with up to 61% overall yield.

1. Introduction

Nucleoside analogues have found use as therapeutic agents against AIDS and cancer.[1] The modifications made in the structure of the analogue usually hinder the replication of DNA in infected cells. For that purpose, various substitutions in the furanose ring at the 2-, 3- and 4-positions are introduced. Also, in many cases the base in the nucleoside analogue is modified. In recent years, the substitution in position 4 of the saccharide moiety has intensively been investigated[2a] (Fig. 1). Various structures with antiviral properties bearing ethynyl,[2a,b] ethenyl,[2c] methyl,[2d,e] ethyl,[2c] fluoromethylene,[2e] cyano[2f,g] and azido[2a] groups in position 4 have been synthesized and investigated.

2. Results and discussion

To alter the lipophilicity of the analogues, we have developed a new synthesis of 4′-alkyl substituted nucleosides with benzyl substituted compounds.

The preparation of 4′-alkyl substituted nucleoside analogues usually starts from natural compounds, such as L-glutamic acid, D-mannitol or D-ribonolactone.[1a] In our approach, we began from a simple achiral 3-alkyl-2-hydroxy-2-cyclopenten-1-one **4**, which was converted by means of asymmetric oxidation to the alkyl substituted γ-butyrolactone skeleton in high enantiomeric purity.[3] These compounds were used as key intermediates in the synthesis of 4′-alkyl substituted nucleoside analogues.

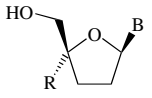


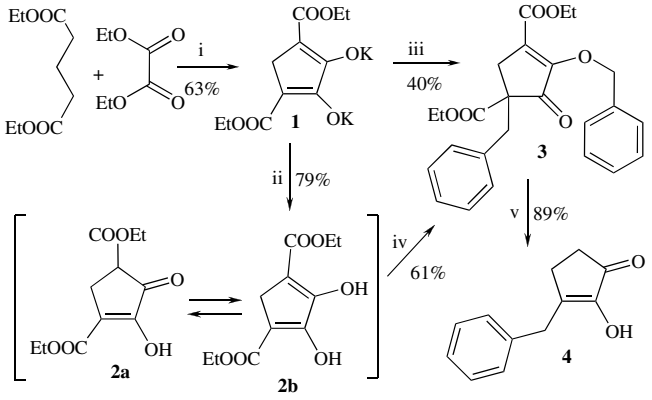
Figure 1. General structure of 4′-substituted-2′,3′-dideoxynucleoside analogues.

The preparation of the starting 3-benzyl-2-hydroxy-2-cyclopenten-1-one was accomplished by using a glutarate and oxalate condensation approach as shown in Scheme 1.[4] Thus, glutarate was condensed with oxalate in THF and isolated as dipotassium salt **1**[5] in 63% yield. After the direct alkylation of salt **1** with benzyl bromide in DMF, dialkylated product **4** was obtained in 40% yield. Salt **1** was hydrolyzed with H_2SO_4 (10% solution) in methanol to afford intermediate **2** as a 1:1 mixture of **2a**/**2b** (the ratio depends upon the solvent).[5]

The alkylation of tautomeric mixture **2** with benzyl bromide in the presence of excess K_2CO_3 in acetonitrile afforded **3** in 61% yield. Enol ether **3** was decarboxylated and hydrolyzed using concentrated HCl, or a mixture of concentrated HCl/CH_3COOH = 1:1.[4b,c] The first option gave

* Corresponding author. Tel.: +372 620 2802; fax: +372 620 2995; e-mail: lopp@chemnet.ee

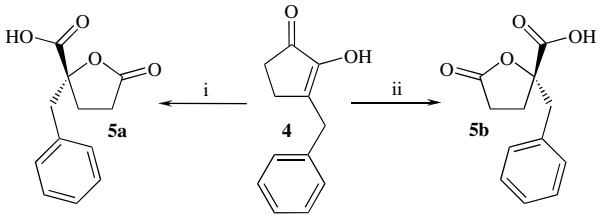
0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.01.028



Scheme 1. Synthesis of 3-benzyl-2-hydroxy-2-cyclopenten-1-one **4**. Reagents: (i) *t*-BuOK/THF; (ii) 10%-H_2SO_4; (iii) BnBr/DMF; (iv) BnBr/K_2CO_3/CH_3CN; (v) HCl/CH_3COOH.

4 in 30% yield, while the second option resulted in the target compound in 89% yield. The improved yield is very likely due to the increased solubility of **3** in the reaction mixture.

The asymmetric oxidation of 3-benzyl-2-hydroxy-2-cyclopenten-1-one **4**[3] with the *t*-BuOOH–diethyltartrate–Ti(O*i*Pr)$_4$ complex enables us to choose the absolute configuration of the target nucleoside analogues, since the absolute configuration of the key compound γ-lactone acid

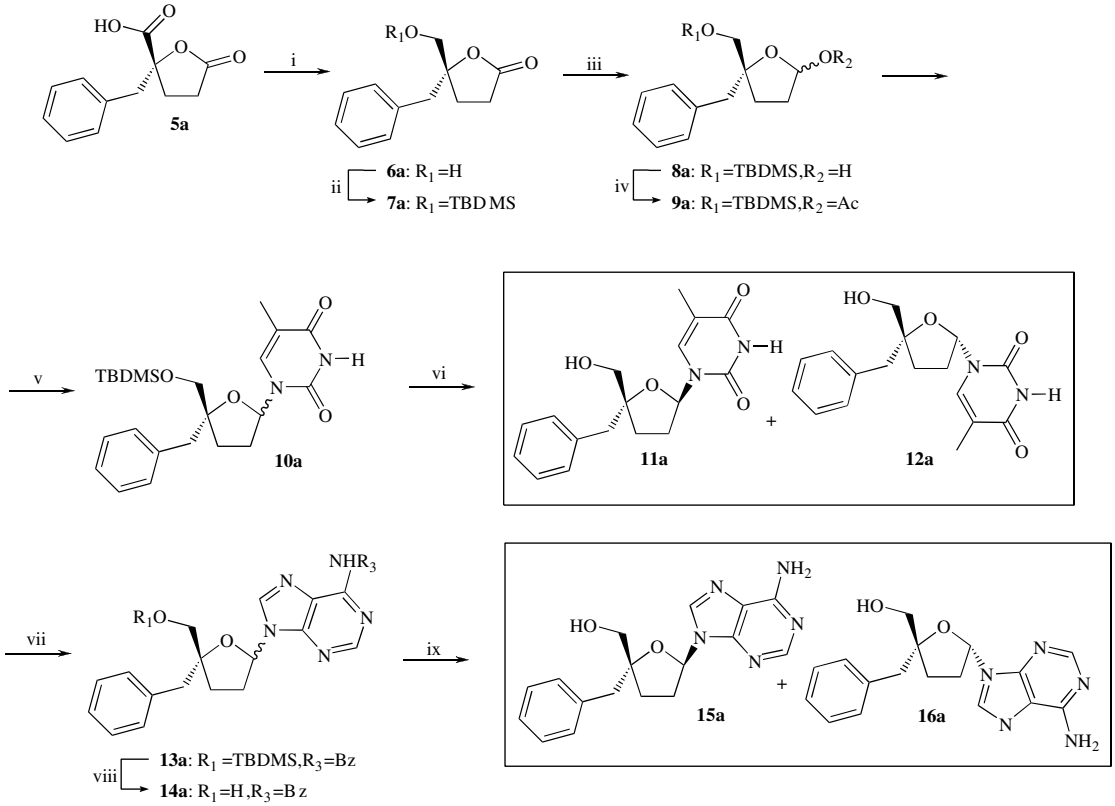


Scheme 2. Synthesis of 4-benzyl substituted γ-lactone acid enantiomers **5a** and **5b** by using (+)- or (−)-diethyltartrate. Reagents: (i) (+)-DET, Ti(O*i*Pr)$_4$, *t*-BuOOH/CH_2Cl_2; (ii) (−)-DET, Ti(O*i*Pr)$_4$, *t*-BuOOH/CH_2Cl_2.

5 can be determined by the use of either (+)- or (−)-diethyltartrate in the oxidation process (Scheme 2).

Thus, we obtained (*R*)-2-benzyl-5-oxo-tetrahydro-furan **5a** with (+)-diethyltartrate in a Ti-complex in 77% yield and with ee ⩾96% (as described in previous work[3]). After recrystallization, the ee of compound **5a** increased to ⩾99%. Analogously, when using (−)-diethyltartrate, (*S*)-2-benzyl-5-oxo-tetrahydro-furan **5b** was obtained in the same yield and enantiopurity.

To transform (−)-γ-lactone acid **5a** into the corresponding nucleoside analogues, literature based methods[6] were used (Scheme 3). First, the carboxyl group of **5a** was reduced to the hydroxyl group using a borane complex in dimethylsulfide.[6a] Lactone alcohol **6a** was obtained in 85% yield. The hydroxyl group was protected by the *tert*-butyldimethylsilyl



Scheme 3. Synthesis of 4′-benzyl substituted nucleoside analogues. Reagents: (i) BH_3·SMe_2/THF; (ii) TBDMSCl, imidazole/CH_2Cl_2; (iii) DIBAH/toluene, (iv) Ac_2O/Et_3N/CH_2Cl_2; (v) Thymine, BSA, TMSOTf/CH_3CN; (vi) TBAF/THF; (vii) N^6-benzoyladenine, BSA, TMSOTf/CH_3CN; (viii) TBAF/ THF; (ix) NH_3/ MeOH.

group with TBDMSCl and imidazole, resulting in TBDMS derivative **7a** in 94% yield. The introduction of the base to the sugar ring was accomplished via acetate **9a**. Thus, the lactone group was reduced to lactol **8a** with DIBAH in 97% yield. The following acetylation with acetic anhydride and triethylamine, in CH_2Cl_2 solvent[6b] (1.0 mmol/mL) afforded **9a** in 88% yield. Without solvent, according to Ref. 6a the acetal dimer was formed in 14% yield.

Protected acetates **9a** were converted to nucleoside thymine and adenine analogues with *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) and trimethylsilyltriflate (TMSOTf).[6b–d] In the case of thymine, nucleoside analogues **10a** were obtained in 97% yield. After removal of the silyl group by tetrabutylammonium fluoride (TBAF),[6b] the target nucleoside analogues **11a/12a** were obtained in 92% yield. The β- and α-anomers were separated by column chromatography to afford **12a**:**13a** in a 1:1 ratio.

To introduce adenine into intermediate **9a**, the procedure described above with N^6-benzoyl-protected adenine[7] derivative was used. Nucleoside analogues **13a** were obtained in 55% yield. After removal of the silyl group by TBAF in THF, compound **14a** was obtained in quantitative yield. Target nucleosides were obtained after the removal of the *N*-benzoyl group with saturated ammonia in methanol, to afford nucleoside analogues **15a/16a** in 82% yield. The β- and α-anomers were easily separated by column chromatography, resulting in β-anomer **15a** and α-anomer **16a** in a 1:1 ratio.

For the preparation of enantiomeric nucleoside analogues the same reaction sequence was repeated with (+)-γ-lactone acid **5b** (Scheme 4). In the case of thymine, the analogues **11b** (β-anomer) and **12b** (α-anomer) were obtained in 59% overall yield from **5b**. The corresponding adenine nucleoside analogues **15b** (β-anomer) and **16b** (α-anomer) were obtained in 33% overall yield from **5b**.

3. Conclusion

The asymmetric oxidation of 3-benzyl-2-hydroxy-2-cyclopenten-1-one **4** easily afforded both enantiomers of γ-lactone acids **5a** and **5b**. These lactone acids were converted to 4′-*C*-benzyl-2′,3′-dideoxynucleoside analogues in six steps. This method can be used for a variety of alkyl substituted nucleoside analogues, which enables us to tune the lipophilicity of the substituents and achieve the best antiviral and anticancer properties of the analogue.

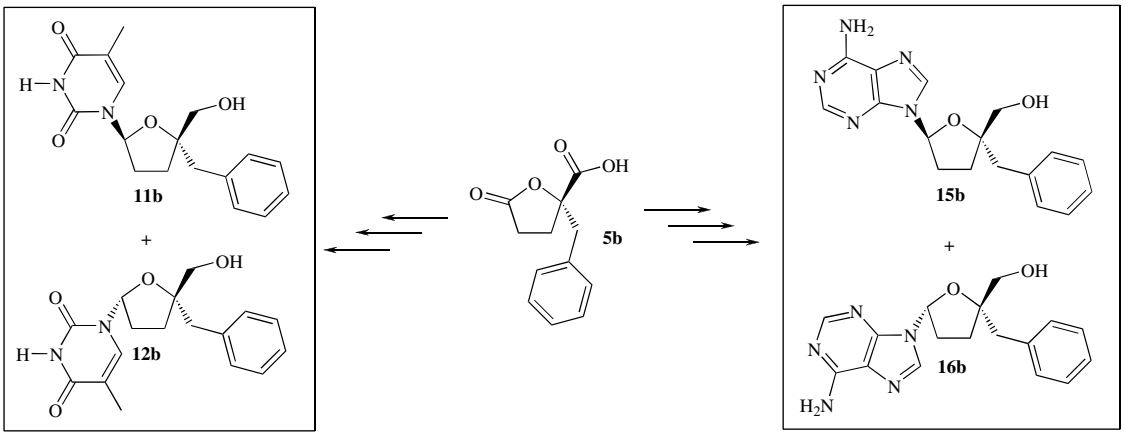
4. Experimental

^1H and ^{13}C NMR spectra were recorded in deuterated solvents ($CDCl_3$, δ 7.27 ppm and 77.00 ppm, CD_3OD, δ 3.30 ppm and 49.00 ppm, or DMSO-d_6, δ 2.50 ppm and 39.50 ppm) on a Bruker AMX-500 spectrometer. Mass spectra were determined on a Hitachi M80B spectrometer using the EI (10 eV and 70 eV) mode. Elemental analyses were performed on a Perkin–Elmer C, H, N, S-Analyzer 2400. Optical rotations were measured with an A. Krüss Optronic GmbH polarimeter P 3002. Enantiomeric purities of the compounds were determined by using a Daicel Chiracel ODH chiral column. IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrometer. TLC analysis was performed on DC-Alufolien Kieselgel 60 F254 (Merck) plates. For column chromatography, Merck Silica Gel 60 (0.063–0.200 mm) was used. The reagents were purchased from Aldrich and used without purification. Dichloromethane was distilled from CaH_2 and stored over 3 Å molecular sieve pellets before use. DMF was distilled from CaH_2, THF from $LiAlH_4$ before use. The petroleum ether fraction bp 40–60 °C was used.

4.1. 1-Benzyl-4-benzyloxy-5-oxo-cyclopent-3-ene-1,3-dicarboxylic acid diethyl ester 3

Ethyl glutarate (6.97 g, 37.1 mmol) was added to a mixture of diethyl oxalate (5.41 g, 37.1 mmol) and *t*-BuOK (8.33 g, 74.4 mmol) in dry THF (150 mL) under argon at reflux. The colour of the reaction mixture changed to brown. The reaction mixture was boiled at reflux for additional 30 min. After cooling the reaction mixture to room temperature, the precipitate was filtered off, washed with dry ether and dried, to afford dipotassium salt **1** (7.46 g, 63%).

Compound **3** was obtained using two different methods.



Scheme 4. Synthesis of 4′-benzyl substituted nucleoside analogues starting from (+)-γ-lactone acid **5b**.

4.1.1. Method 1. A mixture of dipotassium salt **1** (3.18 g, 10 mmol) and benzyl bromide (5.13 g, 30 mmol) in DMF (60 mL) was heated for 2 h under argon at 120 °C. DMF and excess benzyl bromide was removed in vacuum. To the residue a solution of 30% acetic acid (pH 3) was added and the solution was extracted with EtOAc (3 × 15 mL). The combined extracts were dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (petroleum ether/EtOAc = 20:1) to give compound **3** (1.67 g, 40%) as a colourless syrup.

4.1.2. Method 2. To dipotassium salt **1** (4.37 g, 13.75 mmol), 10% H_2SO_4 solution (9.3 mL) was added at 0 °C by portions. The solution was extracted with EtOAc (8 × 40 mL). The combined extracts were dried on $MgSO_4$ and the solvents were evaporated on a rotary evaporator, affording a mixture of tautomers **2a** and **2b** (2.63 g, 79%). The ratio of **2a**:**2b** was 1:1 (in CH_3OD).

A mixture of tautomers **2a** and **2b** (1.21 g, 5 mmol), benzyl bromide (2.57 g, 15 mmol) and K_2CO_3 (4.12 g, 29.8 mmol) in CH_3CN (20 mL) was boiled at reflux for 16 h. The reaction mixture was cooled to room temperature, K_2CO_3 was separated by filtration and CH_3CN was removed on a rotary evaporator. The residue was dissolved in ether (30 mL), washed with 0.1 M NaOH (10 mL) and with water (2 × 10 mL). The ether layer was dried over $MgSO_4$. After filtration of $MgSO_4$ and ether evaporation, the residue was purified by column chromatography (petroleum ether/EtOAc = 20:1) to afford compound **3** (1.29 g, 61%) as a colourless syrup. IR (neat): 3031, 2982, 1743, 1720, 1629, 1604, 1497, 1455, 1368, 1207, 1159, 745, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H, *Ph*-CH_2–C), 7.24–7.19 and 7.11–7.08 (m, 5H, *Ph*-CH_2–O), 5.48 and 5.42 (2d, $J = 12.1$ Hz, 2H, Ph-CH_2–O), 4.22 (q, $J = 7.1$ Hz, 2H, =C–COO–CH_2–CH_3), 4.14 (q, $J = 7.1$ Hz, 2H, –C–COO–CH_2–CH_3), 3.25 (s, 2H, Ph-CH_2–C), 3.08 and 2.72 (2d, $J = 17.9$ Hz, 2H, H-2), 1.28 (t, $J = 7.1$ Hz, 3H, =C–COO–CH_2–CH_3), 1.21 (t, $J = 7.1$ Hz, 3H, –C–COO–CH_2–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7 (C=O), 169.6 (–C–*C*OOEt), 163.7 (=C–*C*OOEt), 155.0 (C-4), 136.5 (*s*, Bn–C), 135.2 (*s*, Bn–O), 135.2 (C-3), 129.9 (*o*, Bn–C), 128.3 (*m*, Bn–C), 128.3 (*m*, Bn–O), 128.0 (*p*, Bn–O), 127.6 (*o*, Bn–O), 127.0 (*p*, Bn–C), 72.2 (Ph-*C*H_2–O), 61.9 (–C–COO–*C*H_2–CH_3), 61.0 (=C–COO–*C*H_2–CH_3), 57.3 (C-1), 39.3 (Ph-*C*H_2–C), 31.9 (C-2), 14.0 (=C–COO–CH_2–*C*H_3), 13.9 (=C–COO–CH_2–*C*H_3).

4.2. 3-Benzyl-2-hydroxy-cyclopent-2-en-1-one 4

To compound **3** (1.31 g, 3.1 mmol), a mixture of HCl and CH_3COOH (1:1, 12 mL) was added and the resulting mixture heated at reflux for 3 h. The excess acids were neutralized by 20% NaOH solution (to pH 3) and the mixture extracted with EtOAc (5 × 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc = 10:2) giving compound **4** (0.519 g, 89%). Mp = 99–100 °C (97–99 °C, lit.[4d]); IR (KBr): 3319, 3023, 2922, 1696, 1651, 1600, 1494, 1451, 1385, 1219, 1195, 1107, 762, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.31 (m, 2H, *m*-Ph), 7.27–7.23 (m, 3H, *m,p*-Ph), 6.95 (s, 1H, OH), 3.78 (s, 2H, Ph-CH_2–), 2.41–2.39 (m, 2H, H-5), 2.38–2.35 (m, 2H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8 (CO), 148.8 (C-3), 146.6 (C-2), 137.6 (*s*), 128.9 (*o*), 128.5 (*m*), 126.5 (*p*), 34.8 (Ph-*C*H_2–), 31.9 (C-5), 24.6 (C-4); MS (EI, 70 eV): *m*/*z* (%) = 188 (100, M^+), 159 (20.7), 142 (23.2), 117 (42.5), 104 (20.5), 91 (23.5, Bn^+); Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.63; H, 6.39.

4.3. (*R*)-5-Benzyl-5-hydroxymethyl-dihydro-furan-2(3*H*)-one 6a

To a solution of **5a** (0.88 g, 4.0 mmol) in THF (3.0 mL) at 0 °C $BH_3{\cdot}Me_2S$ complex in THF. (0.52 mL, 4.8 mmol) was added dropwise. The reaction mixture was stirred additionally for 1 h at room temperature and methanol (1.0 mL) was added after cooling. The mixture was concentrated in vacuo and purified by column chromatography (petroleum ether/acetone = 10:2), affording compound **6a** (0.702 g, 85%) as white crystals, mp 80–81 °C; $[\alpha]_D^{23} = +62.8$ (*c* 3.0, $CHCl_3$); IR (KBr): 3405, 3026, 2948, 2921, 1753, 1735, 1604, 1498, 1455, 1428, 1236, 1068, 946, 769, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22–7.32 (m, 5H, Ph), 3.75 and 3.59 (2d, $J = 12.1$ Hz, 2H, CH_2–OH), 3.02 and 2.83 (2d, $J = 14.0$ Hz, 2H, Ph-CH_2), 2.42–2.49 (m, 1H, H-3), 2.19–2.25 (m, 1H, H-4), 2.00–2.06 (m, 1H, H-4), 1.92–1.99 (m, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7 (C-2), 134.8 (*s*), 130.3 (*o*), 128.4 (*m*), 127.0 (*p*), 88.5 (C-5), 67.3 (C-6), 41.9 (C-7), 29.3 (C-3), 26.5 (C-4); MS (EI, 70 eV): *m*/*z* (%) = 206 (5.2, M^+), 175 (7.9), 157 (1.5), 129 (6.2), 115 (100), 105 (2.1), 91 (58.2, Bn^+); Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.83; H, 6.86.

The (*S*)-enantiomer **6b** was obtained in the same way from **5b** in 83% yield. $[\alpha]_D^{23} = -59.8$ (*c* 3.0, $CHCl_3$).

4.4. (*R*)-5-Benzyl-5-(*tert*-butyl-dimethyl-silyloxymethyl)-dihydro-furan-2(3*H*)-one 7a

To a solution of **6a** (0.36 g, 1.75 mmol) and imidazole (0.16 g, 2.32 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C TBDMSCl (0.317 g, 2.1 mmol) was added. Stirring was continued for 15 min at 0 °C and then for 2 h at room temperature. Water (5.0 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/acetone = 20:1) to give compound **7a** (0.529 g, 94%) as white crystals, mp 66–67 °C; $[\alpha]_D^{23} = +24.2$ (*c* 1.0, $CHCl_3$); IR (KBr): 3032, 2955, 2932, 2857, 1766, 1604, 1496, 1457, 1253, 1186, 1117, 1080, 945, 845, 778, 704 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.23–7.32 (m, 5H, Ph), 3.67 and 3.60 (2d, $J = 10.6$ Hz, 2H, OCH_2), 3.02 and 2.83 (2d, $J = 14.1$ Hz, 2H, Ph-CH_2), 2.44–2.52 (m, 1H, H-3), 2.16–2.22 (m, 1H, H-4), 1.98–2.08 (m, 2H, H-3, H-4), 0.90 (s, 9H, (CH_3)$_3$C–Si), 0.08 and 0.07 (2s, 6H, (CH_3)$_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C-2), 135.0 (*s*), 130.4 (*o*), 128.4 (*m*), 126.9 (*p*), 87.7 (C-5), 68.3 (*C*H_2O), 42.0 (*C*H_2Ph), 29.4 (C-3), 27.1 (C-4), 25.7 ((*C*H_3)$_3$C–Si), 18.1 ((CH$_3$)$_3$*C*–Si), −5.6 ((*C*H_3)$_2$–Si); MS (EI, 10 eV): *m*/*z* (%) = 305 (0.21, M^+-CH_3), 287 (0.79), 263 (27.9), 245 (71.1), 171 (13.9, $M^+-Bn-C_4H_9$), 129 (100.0), 91 (70.2,

Bn^+); Anal. Calcd for $C_{18}H_{28}SiO_3$: C, 67,46; H, 8,81. Found: C, 67,44; H, 9,02.

The (*S*)-enantiomer **7b** was obtained in the same way from **6b** in 97% yield. $[\alpha]_D^{23} = -24.3$ (*c* 3.0, $CHCl_3$).

4.5. (*R*)-5-Benzyl-5-(*tert*-butyl-dimethyl-silyloxymethyl)-tetrahydro-furan-2-ol 8a

To a solution of **7a** (1.31 g, 4.1 mmol) in toluene (8.2 mL) at −78 °C, a 1.5 M solution of DIBAH in toluene (3.0 mL, 4.5 mmol) was added dropwise. The reaction mixture was stirred additionally for 15 min at −76 °C, then methanol (0.9 mL) was added dropwise and the mixture was allowed to warm to room temperature. EtOAc (6.2 mL) and saturated $NaHCO_3$ solution (0.83 mL) were added and stirring was continued for 2 h. Powdered Na_2SO_4 (4.1 g) was added and the mixture was stirred overnight. The precipitate was filtered off and washed with EtOAc. The solvent was removed in vacuum and the residue was purified by column chromatography (petroleum ether/EtOAc = 20:1) to give compound **8a**, as a 2:1 mixture of (2*R*)- and (2*S*)-diastereoisomers (1.278 g, 97%) as a colourless syrup, $[\alpha]_D^{24} = -8.3$ (*c* 10.14, $CHCl_3$); IR (neat): 3423, 3029, 2954, 2930, 2858, 1605, 1496, 1462, 1257, 1097, 1079, 1016, 967, 838, 777, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, data for (2*S*) isomer labelled with ∗) δ 7.22–7.32 (m, 10H, Ph), 5.45 (t, $J = 2 \times 4.4$ Hz, 1H, H-2*), 5.29 (dd, $J = 4.6$ and 8.3 Hz, 1H, H-2), 3.90 (d, $J = 8.3$ Hz, 1H, OH), 3.65 and 3.54 (2d, $J = 10.0$ Hz, 4H, CH_2–OSi), 3.34 and 3.30 (2d, $J = 10.0$ Hz, 4H, CH_2^*–OSi), 3.00 and 2.96 (2d, $J = 13.5$ Hz, 2H, Ph-CH_2^*–), 2.84 and 2.64 (2d, $J = 13.5$ Hz, 2H, Ph-CH_2–), 2.45 (d, $J = 4.4$ Hz, 1H, OH*), 2.04–2.11 and 1.69–1.73 (m, 2H, H-4), 1.92–1.97 (m, 2H, H-4*), 1.97–2.03 and 1.75–1.80 (m, 2H, H-3*), 1.65–1.70 and 1.19–1.28 (m, 2H, H-3), 0.95 (s, 9H, (CH_3)$_3$C–Si), 0.93 (s, 9H, (CH_3^*)$_3$C–Si), 0.13 (2s, 6H, (CH_3)$_2$–Si), 0.05 (2s, 6H, (CH_3^*)$_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7* and 136.8 (s), 130.7* and 130.5 (*o*), 127.9 (*m*), 126.3 (*p*), 99.1* and 99.0 (C-2), 87.2* and 87.1 (C-5), 68.5 and 66.7* (C-7), 43.5* and 42.6 (C-6), 34.9 and 33.5* (C-3), 29.3* and 27.1 (C-4), 25.9 ((*C*H_3)$_3$C–Si), 18.3 and 18.2* ((CH$_3$)$_3$*C*–Si), −5.5 and −5.6 ((*C*H_3)$_2$–Si); Anal. Calcd for $C_{18}H_{30}SiO_3$: C, 67.03; H, 9.38. Found: C, 67.18; H, 9.63.

The (5*S*)-enantiomer **8b** was obtained in the same way from **7b** in 96% yield. $[\alpha]_D^{23} = +6.5$ (*c* 10.13, $CHCl_3$).

4.6. (*R*)-5-Benzyl-5-(*tert*-butyl-dimethyl-silyloxymethyl)-tetrahydro-furan-2-yl acetate 9a

To a mixture of compound **8a** (0.32 g, 1.0 mmol) and Et_3N (0.42 mL, 3 mmol) in CH_2Cl_2 (1.0 mL), acetic anhydride (0.28 mL, 3 mmol) was added dropwise at 0 °C. The reaction mixture was stirred overnight at room temperature. Water (5 mL) was added and the mixture extracted with EtOAc (4 × 5 mL). The combined extracts were dried over $MgSO_4$. After solvent evaporation in vacuo, the residue was purified by column chromatography (petroleum ether/EtOAc = 20:1) to afford compound **9a**, as a 5:3 mixture of (2*S*) and (2*R*)-diastereoisomers (0.32 g, 88%), as a colourless syrup, $[\alpha]_D^{24} = -15.3$ (*c* 3.02, $CHCl_3$); IR (neat): 3029, 2954, 2930, 2858, 1747, 1604, 1496, 1462, 1251, 1099, 1004, 959, 838, 778, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, data for (2*R*)-isomer labelled with ∗) δ 7.22–7.29 (m, 10H, Ph), 6.21 (d, $J = 4.7$ Hz, 1H, H-2*), 6.19 (d, $J = 4.7$ Hz, 1H, H-2), 3.62 and 3.54 (2d, $J = 9.8$ Hz, 2H, CH_2–OSi), 3.36 and 3.33 (2d, $J = 10.0$ Hz, 2H, CH_2^*–OSi), 2.97 and 2.92 (2d, $J = 13.8$ Hz, 2H, Ph-CH_2^*), 2.89 and 2.83 (2d, $J = 13.7$ Hz, 2H, Ph-CH_2–), 2.11–2.19 and 1.91–1.94 (m, 2H, H-3*), 2.02–2.08 and 1.89–1.92 (m, 2H, H-4*), 2.01 (s, 3H, Ac), 1.93 (s, 3H, Ac*), 1.81–1.88 (m, 2H, H-4), 1.72–1.76 and 1.26–1.34 (m, 2H, H-3), 0.96 (s, 9H, (CH_3)$_3$C–Si), 0.92 (s, 9H, (CH_3^*)$_3$C–Si), 0.11 and 0.10 (2s, 6H, (CH_3)$_2$–Si), 0.04 (2s, 6H (CH_3^*)$_2$–Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5* and 170.2 (*C*O–CH$_3$), 137.4 and 137.2* (*s*), 130.8* and 130.5 (*o*), 127.9 and 127.8* (*m*), 126.3 and 126.2* (*p*), 99.5 and 99.2* (C-2), 89.2 and 88.8* (C-5), 69.5 and 66.5* (C-7), 43.3* and 41.9 (C-6), 32.1 and 32.0* (C-3), 29.0 and 28.9* (C-4), 25.9 and 25.8* ((*C*H$_3$)$_3$C–Si), 21.4 and 21.3* (CO–*C*H$_3$), 18.3 and 18.2* ((CH$_3$)$_3$*C*–Si), −5.4 and −5.5 and −5.6 ((*C*H$_3$)$_2$–Si); MS (EI, 70 eV): *m*/*z* (%) = 305 (6.4, M^+−Ac−CH$_3$), 273 (4.7), 247 (33.8), 213 (16.0), 191 (7.0), 177 (11.0), 173 (10.8), 159 (26.7), 135 (11.6), 129 (64.8), 117 (100.0), 91 (68.4, Bn^+); Anal. Calcd for $C_{20}H_{32}SiO_4$: C, 65.89; H, 8,85. Found: C, 65.92; H, 9.09.

The (5*S*)-enantiomer **9b** was obtained in the same way from **8b** in 89% yield. $[\alpha]_D^{22} = +12.0$ (*c* 3.01, $CHCl_3$).

4.7. 1-[(2*RS*,5*R*)-5-Benzyl-5-(*tert*-butyl-dimethyl-silyloxy-methyl)-tetrahydro-furan-2-yl]-5-methyl-1*H*-pyrimidine-2,4(1*H*,3*H*)-dione 10a

To a solution of thymine (0.13 g, 1.03 mmol) in dry CH_3CN (8.6 mL), BSA (0.750 mL, 2.93 mmol) and compound **9a** (0.358 g, 0.982 mmol) in CH_3CN (5.7 mL) were added at room temperature. After cooling to 0 °C, TMSOTf (0.177 mL, 0.982 mmol) was added dropwise, the reaction mixture was stirred for 2 h at room temperature and poured into a mixture of CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ solution (10 mL). The CH_2Cl_2 layer was removed and the water layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and, after the solvent was removed, the residue was purified by column chromatography (petroleum ether/acetone = 10:1) to afford compound **10a** as a 5:4 mixture of (2*R*)- and (2*S*)-diastereoisomers (0.411 g, 97%) as white crystals. IR (KBr): 3183, 3031, 2954, 2929, 2857, 1690, 1496, 1471, 1272, 1098, 1081, 838, 778, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, data for 2*S* isomer labelled with ∗) δ 9.5 (br s, NH), 7.56 and 6.34* (q, $J = 1.0$ Hz, 2H, H-6), 7.20–7.34 (m, 10H, Ph), 6.23* (dd, $J = 5.6$ and 6.9 Hz, 1H, H-2′), 5.88 (t, $J = 6.5$ Hz, 1H, H-2′), 3.70 and 3.59 (2d, $J = 10.6$ Hz, 4H, CH_2–O–Si), 3.56* and 3.49* (2d, $J = 10.1$ Hz, 2H, CH_2–O–Si), 2.95* and 2.86* (2d, $J = 13.8$ Hz, 2H, Ph-CH_2–), 2.86 and 2.72 (2d, $J = 13.7$ Hz, 2H, Ph-CH_2–), 2.37* and 1.51* (m, 2H, H-3′), 2.14 and 1.89 (m, 2H, H-3′), 2.06* and 1.93* (m, 2H, H-4′), 2.05 and 1.89 (m, 2H, H-4′), 1.90 and 1.72* (d, $J = 1.0$ Hz, 6H, CH$_3$–C=), 0.92 and 0.93* (s, 18H, *t*-Bu), 0.09 (s, 12H, Si–(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0

and 163.8* (C-4), 150.5* and 150.4 (C-2), 136.3* and 136.2 (*s*), 135.6* and 135.4 (C-6), 131.1* and 130.4 (*o*), 128.2 and 128.0* (*m*), 126.7 (*p*), 110.5* and 110.3 (C-5), 87.2 and 86.8* (Bn–*C*–O), 85.5 and 84.5* (C-2′), 68.8* and 68.6 (*C*H_2–OSi), 42.8 and 41.2* (Ph-*C*H_2), 32.4 and 31.3* (C-3′), 30.0 and 28.6* (C-4′), 25.8 ((*C*H_3)$_3$C–), 18.3 and 18.1* ((CH$_3$)$_3$*C*–), 12.4 (*C*H_3–C═), −5.3, −5.4 and −5.5 ((*C*H_3)$_2$Si).

The (5*S*)-enantiomer **10b** was obtained in the same way from **9b** in 93% yield.

4.8. 1-(5-Benzyl-5-hydroxymethyl-tetrahydro-furan-2-yl)-5-methyl-1*H*-pyrimidine-2,4-diones (2*R*,5*R*)-11a and (2*S*,5*R*)-12a

1-(4′-Benzyl-2′,3′-dideoxy-D-ribo-pentofuranosyl)-thymine 11a (β) and 12a (α). To a solution of compound **10a** (0.375 g, 0.87 mmol) in THF (8.0 mL). 1.0 M TBAF solution in THF (1.8 mL, 1.8 mmol) was added dropwise. The reaction mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 10:1), to afford β-anomer **11a** and α-anomer **12a**.

Compound **11a** (0.127g, 46%) was obtained as white crystals; mp = 71–76 °C; $[\alpha]_D^{23} = +23.5$ (*c* 1.0, MeOH); IR (KBr): 3431, 3193, 3033, 2928, 1689, 1495, 1472, 1405, 1273, 1070, 704 cm^{-1}; ^{1}H NMR (500 MHz, CH_3OD) δ 7.88 (q, $J = 1.1$ Hz 1H, H-6), 7.18–7.30 (m, 5H, Ph), 5.90 (dd, $J = 5.0$ and 6.5 Hz, 1H, H-2′), 3.64 and 3.59 (2d, $J = 11.7$ Hz, 2H, –CH_2–OH), 2.84 and 2.76 (2d, $J = 13.7$ Hz, 2H, Ph-CH_2–), 2.09–2.17 and 1.86–1.92 (m, 2H, H-4′), 1.90–2.00 (m, 2H, H-3′), 1.84 (s, 3H, CH_3–C═); ^{13}C NMR (125 MHz, CH_3OD) δ 166.4 (C-4), 152.4 (C-2), 138.5 (C-6), 138.3 (*s*), 131.6 (*o*), 129.2 (*m*), 127.6 (*p*), 111.1 (C-5), 89.8 (C-5′), 87.2 (C-2′), 67.7 (–*C*H_2–OH), 43.6 (Ph-*C*H_2–), 32.9 (C-3′), 30.0 (C-4′), 12.4 (*C*H_3–C═); MS (EI, 70 eV): *m*/*z* (%) = 316 (0.11, M^+), 299 (1.9, M^+−OH), 285 (2.5, M^+−CH_2OH), 249 (2.2), 226 (0.95, M^+−Bn), 233 (0.85), 218 (0.77), 191 (33.0), 173 (14.5), 158 (100.0), 129 (28.4), 116 (39.2), 91 (83.0, Bn^+); Anal. Calcd for $C_{17}H_{20}N_2O_4$, C, 64.54; H, 6.37; N, 8.85. Found: C, 64.37; H, 6.31; N, 8.69.

Compound **12a** (0.127 g, 46%) was obtained as white crystals; mp = 84–90 °C; $[\alpha]_D^{24} = +61.6$ (*c* 1.0, MeOH). IR (KBr): 3412, 3178, 3033, 2926, 1688, 1496, 1469, 1411, 1274, 1062, 704 cm^{-1}; ^{1}H NMR (500 MHz, CH_3OD) δ 7.20–7.28 (m, 5H, Ph), 6.54 (q, 1H, $J = 1.2$ Hz, H-6), 6.15 (dd, $J = 4.8$ and 7.1 Hz, 1H, H-2′), 3.49 (s, 2H, –CH_2–OH), 2.99 and 2.86 (2d, $J = 13.7$ Hz, 2H, Ph-CH_2–), 2.34–2.41 and 1.65–1.71 (m, 2H, H-3′), 1.95–2.05 (m, 2H, H-4′), 1.66 (d, $J = 1.2$ Hz, 3H, CH_3–C═); ^{13}C NMR (125 MHz, CH_3OD) δ 166.2 (C-4), 152.5 (C-2), 138.0 (*s*), 137.4 (C-6), 132.3 (*o*), 129.1 (*m*), 127.7 (*p*), 111.2 (C-5), 88.6 (C-5′), 86.1 (C-2′), 68.6 (–*C*H_2–OH), 41.9 (Ph-*C*H_2–), 31.5 (C-3′), 29.7 (C-4′), 12.7 (*C*H_3–C═); MS (EI, 70 eV): *m*/*z* (%) = 316 (0.22, M^+), 299 (2.3, M^+−OH), 285 (2.4, M^+−CH_2OH), 225 (15.1, M^+−Bn), 191 (40.7), 173 (20.9), 129 (50.0), 116 (14.2), 91 (100.0, Bn^+); Anal. Calcd for $C_{17}H_{20}N_2O_4$, C, 64.54; H, 6.37; N, 8.85. Found: C, 64.57; H, 6.36; N, 8.58.

The corresponding enantiomers **11b** (β-anomer) and **12b** (α-anomer) were prepared in the same way from **10b** and separated by column chromatography, affording white crystals in 92% overall yield. Ratio of **11b**:**12b** = 1:1.

Compound **11b**: $[\alpha]_D^{24} = -20.7$ (*c* 1.01, MeOH).

Compound **12b**: $[\alpha]_D^{24} = -62.3$ (*c* 1.0, MeOH).

4.9. (2*RS*,5*R*)-*N*-{9-[5-Benzyl-5-(*tert*-butyl-dimethyl-silyl-oxymethyl)-tetrahydro-furan-2-yl]-9*H*-purin-6-yl}-benzamide 13a

To a solution of 6-benzyladenine (0.40 g, 1.67 mmol) in CH_3CN (9.0 mL), BSA (1.17 mL, 4.56 mmol) was added and the mixture stirred for 20 min at room temperature. To the mixture a solution of compound **9a** (0.554 g, 1.52 mmol) in CH_3CN (8.0 mL) was added. After cooling at 0 °C TMSOTf (0.247 mL, 1.52 mmol) was added dropwise and the reaction mixture was stirred for 6 h at room temperature. Now the mixture was poured into a mixture of CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ solution (10 mL). The CH_2Cl_2 layer was removed and the water layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$. After the solvent was removed the residue was purified by column chromatography (CH_2Cl_2/MeOH = 20:1) on silica gel to give compound **13a** (0.420 g, 51%) as white crystals. IR (KBr): 3253, 3030, 2954, 2929, 2857, 1699, 1611, 1581, 1514, 1455, 1331, 1295, 1253, 1079, 838, 777, 704 cm^{-1}.

The (5*S*)-enantiomer **13b** was obtained in the same way from **9b** in 55% yield.

4.10. (2*RS*,5*R*)-*N*-[9-(5-Benzyl-5-hydroxymethyl-tetrahydro-furan-2-yl)-9*H*-purin-6-yl]-benzamide 14a

To a solution of **13a** (0.32 g, 0.59 mmol) in THF (5.5 mL) 1.0 M TBAF solution (1.22 mL, 1.22 mmol) was added dropwise. The reaction mixture was stirred for 2 h at room temperature and concentrated in vacuum. After column chromatography (CH_2Cl_2/MeOH = 20:1) compound **14a** (0.254 g, 100%) was obtained as white crystals. IR (KBr): 3268, 3028, 2924, 2855, 1699, 1613, 1582, 1514, 1493, 1454, 1401, 1332, 1296, 1253, 1070, 937, 704 cm^{-1}.

Compound **14b** was obtained in the same way from **13b**, also in quantitative yield.

4.11. 5-[(6-Amino-9*H*-purin-9-yl)-2-benzyltetrahydro-furan-2-yl]methanol (2*R*,5*R*)-15a and (2*R*,5*S*)-16a

9-(4′-Benzyl-2′,3′-dideoxy-D-ribo-pentofuranosyl)-adenine 15a (β) and 16a (α). A solution of compound **14a** (0.270 g, 0.629 mmol) in MeOH (26 mL) saturated with NH_3 was stirred overnight. After the solvent was removed in vacuo the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 10:1), affording β-anomer **15a** and α-anomer **16a**.

Compound **15a** (0.083 g, 41%) was obtained as white crystals; mp = 158–164 °C; IR (KBr): 3330, 3268, 3113, 2931, 1685, 1644, 1607, 1571, 1495, 1476, 1418, 1338, 1303, 1244, 1215, 1088, 1071, 1005, 940, 704 cm^{-1}; (**15a**) ^1H NMR (500 MHz, DMSO-d_6) δ 8.33 (s, 1H, H-8′), 8.13 (s, 1H, H-2′), 7.27 (br s, 2H, $-NH_2$), 7.21–7.35 (m, 5H, Ph), 6.09 (dd, $J = 5.0$ and 6.4 Hz, 1H, H-5), 5.32 (dd, $J = 5.3$ and 6.2 Hz, 1H, –O*H*), 3.46 (dd, 1H, $J = 5.3$ and 11.4 Hz, H-1), 3.40 (dd, 1H, $J = 6.2$ and 11.4 Hz, H-1), 2.82 and 2.81 (2d, 2H, $J = 13.8$ Hz, Ph-CH_2–), 2.32–2.39 and 2.03–2.10 (m, 2H, H-4), 2.22–2.28 (m, 2H, H-3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.0 (C-6′), 152.4 (C-2′) 148.8 (C-4′), 139.2 (C-8′), 137.5 (*s*), 130.4 (*o*), 128.0 (*m*), 126.3 (*p*), 119.1 (C-5′), 88.5 (C-2), 84.6 (C-5), 66.1 (C-1), 42.0 (Ph-*C*H_2–), 31.6 (C-4), 29.7 (C-3); MS (EI, 70 eV): *m*/*z* (%) = 325 (4.17, M^+), 295 (17.8, M^+-CH_2OH), 234 (8.16, M^+-Bn), 162 (49.5), 136 (89.3), 129 (22.3), 115 (10.4), 117 (10.2), 108 (14.5), 91 (100.0, Bn^+); Anal. Calcd for $C_{17}H_{19}N_5O_2$, C, 62.76; H, 5.89; N, 21.52. Found: C, 62.60; H, 5.74; N, 21.55.

Compound **16a** (0.084 g, 41%) was obtained as white crystals; mp = 137–178 °C; $[\alpha]_D^{22} = +6.6$ (*c* 4.0, DMSO); IR (KBr): 3435, 3313, 3137, 2920, 1649, 1601, 1577, 1481, 1454, 1419, 1325, 1303, 1250, 1214, 1091, 1068, 1054, 942, 703 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.14 (s, 1H, H-2′), 7.87 (s, 1H, H-8′), 7.25 (br s, 2H, $-NH_2$), 7.08–7.17 (m, 5H, Ph), 6.25 (dd, $J = 4.5$ and 6.4 Hz, 1H, H-5), 5.00 (t, $J = 5.5$ Hz, 1H, –OH), 3.30 and 3.29 (both dd, $J = 5.5$ and 11.5 Hz, 2H, H-1), 2.93 and 2.88 (2d, $J = 13.8$ Hz, 2H, Ph-CH_2–), 2.47–2.53 and 2.33–2.39 (m, 2H, H-4), 2.13–2.19 and 2.05–2.11 (m, 2H, H-3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.9 (C-6′), 152.5 (C-2′), 149.1 (C-4′), 138.7 (C-8′), 137.3 (*s*), 130.4 (*o*), 127.6 (*m*), 126.0 (*p*), 118.9 (C-5′), 87.8 (C-2), 83.9 (C-5), 65.5 (C-1), 41.7 (Ph-*C*H_2–), 31.0 (C-4), 30.0 (C-3); MS (EI, 70 eV): *m*/*z* (%)=325 (14.1, M^+), 295 (3.3, M^+-CH_2OH), 234 (4.8, M^+-Bn), 162 (5.7), 136 (88.4), 129 (23.1), 115 (5.5), 117 (9.2), 108 (14.6), 91 (100.0, Bn^+); Anal. Calcd for $C_{17}H_{19}N_5O_2$, C, 62.81; H, 5.94; N, 20.90. Found: C, 62.72; H, 5.82; N, 21.40.

The corresponding enantiomers **15b** and **16b** were prepared in the same way from **14b** in 86% overall yield. The β-anomer **15b** and α-anomer **16b** were separated by column chromatography on silica gel and isolated as white crystals. Ratio of **15b**:**16b** = 1:1.

Compound **16b**: $[\alpha]_D^{22} = -5.5$ (*c* 4.57, DMSO).

Acknowledgements

We are grateful to the Estonian Ministry of Education and Research (Grant No. 0142725s06), the Estonian Science Foundation (Grant Nos. 5628 and 6778) and the Competence Centre for Cancer Research for financial support of this research.

References

1. (a) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768; (b) Yili, D. *Chem. Lett.* **2006**, *35*, 952–953.
2. (a) Siddiqui, M. A.; Hughes, S. H.; Boyer, P. L.; Mitsuya, H.; Van, Q. N.; George, C.; Sarafinanos, S. G.; Marquez, V. E. *J. Med. Chem.* **2004**, *47*, 5041–5048; (b) Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. *J. Med. Chem.* **2000**, *43*, 4516–4525; (c) Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 385–388; (d) Kitano, K.; Miura, S. *Tetrahedron* **1997**, *53*, 13315–13322; (e) Kitano, K.; Machida, H.; Miura, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 827–830; (f) Obika, S.; Andoh, J.-I.; Sugimoto, T.; Miyashita, K.; Imanishi, T. *Tetrahedron Lett.* **1999**, *40*, 6465–6468; (g) Yang, C. O.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 37–40.
3. Paju, A.; Laos, M.; Jõgi, A.; Päri, M.; Jäälaid, R.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron Lett.* **2006**, *47*, 4491–4493.
4. (a) Hesse, G.; Böckmann, K. W. F. *Justus Liebigs Ann. Chem.* **1949**, *563*, 37–53; (b) Ito, S.; Hatakeda, K.; Saito, N.; Asano, T. *Yukagaku* **1975**, *24*, 191–192; (c) Ito, S.; Saito, N.; Hatakeda, K.; Asano, T. *Yukagaku* **1976**, *25*, 326–328; (d) Strunz, G. M.; Lal, G. S. *Can. J. Chem.* **1982**, *60*, 572–573; (e) McFearin, T. C. U.S. Patent 4 007 216, 1977.
5. Aqad, E.; Leriche, P.; Mabon, G.; Gorgues, A.; Allain, M.; Riou, A.; Ellern, A.; Khodorkovsky, V. *Tetrahedron* **2003**, *59*, 5775–5782.
6. (a) Okabe, M.; Steve, R.-C. S.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780–4786; (b) Alibes, R.; Alvarez-Larena, A.; March, P.; Figueredo, M.; Font, J.; Parella, T.; Rustullet, A. *Org. Lett.* **2006**, *8*, 491–494; (c) Rozners, E.; Xu, Q. *Org. Lett.* **2003**, *21*, 3999–4001; (d) Barral, K.; Hider, R. C.; Balzarini, J.; Neyts, J.; De Clercq, E.; Camplo, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4371–4374.
7. Waga, T.; Ohrui, H.; Meguro, H. *Nucleosides Nucleotides* **1996**, *15*, 287–304.