

SYNTHESIS OF NOVEL CARBOCYCLIC NUCLEOSIDE ANALOGUES DERIVED FROM 7-OXABICYCLO[2.2.1]HEPTANE-2-METHANOL

Hubert HŘEBABECKÝ^{a1,*}, Martin DRAČÍNSKÝ^{a2}, Armando M. De PALMA^{b1}, Johan NEYTS^{b2} and Antonín HOLÝ^{a3}

^a Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., 166 10 Prague 6, Czech Republic; e-mail: ¹ hubert@uochb.cas.cz, ² dracinsky@uochb.cas.cz, ³ holy@uochb.cas.cz

^b Katholieke Universiteit Leuven, Rega Institute for Medical Research, Minderbroedersstraat 10, BE-3000, Leuven, Belgium; e-mail: ¹ armando.depalma@rega.kuleuven.be, ² johan.neyts@rega.kuleuven.ac.be

Received November 5, 2008

Accepted November 26, 2008

Published online March 13, 2009

Hydroboration of [(1R*,2R*,4R*)-7-oxabicyclo[2.2.1]hept-5-en-2-yl]methyl benzoate (**5**), which was prepared by Diels–Alder reaction of furan with acrolein and subsequent reduction and benzylation of the Diels–Alder product, afforded [(1R*,2S*,4S*,6S*)-6-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**6**) and [(1R*,2R*,4R*,5S*)-5-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**7**). The key intermediates, [(1R*,2S*,4S*,6R*)-6-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**10**) and [(1R*,2R*,4R*,5R*)-5-hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl benzoate (**11**), were prepared from **6** and **7**, respectively, by oxidation with pyridinium dichromate and subsequent reduction of the thus obtained ketones. The Mitsunobu reaction of **10** and **11** with 6-chloropurine and subsequent reductive deprotection with diisobutylaluminium hydride afforded 6-chloropurine derivatives, which were converted to other purine analogues. Thymine analogues were prepared by Mitsunobu reaction of **10** and **11** with 3-benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione and subsequent methanolysis. The target compounds were tested for the activity against *Coxsackie* virus.

Keywords: Nucleosides; Carbocyclic nucleosides; Purines; Adenine; Thymine; 5-Methylpyrimidine-2,4(1H,3H)-dione; 6-Chloropurine; 6-(Dimethylamino)purine; 6-(Cyclopropylamino)purine; Mitsunobu reaction; *Coxsackie* virus.

Extensive modifications of naturally occurring nucleosides led to discovery of a great deal of compounds with remarkable biological activity. The most important are the effects on various severe diseases such as cancer or viral infection. A disadvantage of analogues of natural nucleosides is cleavage of N-glycosidic bond by phosphorylases. One of modifications, which were examined to overcome this difficulty, is substitution of the furanose ring of

Chemical structures of compounds **1** and **2** are shown. Compound **1** is 2-((2S,3S)-3-(hydroxymethyl)-2-methyl-5-oxo-2,3-dihydro-1H-benzofuran-4-yl)-1H-imidazole. Compound **2** is 2-((2S,3S)-3-(hydroxymethyl)-2-methyl-5-oxo-2,3-dihydro-1H-benzofuran-4-yl)-1H-imidazole-4-carboxamide.

CHART 1

Chemical structures of compounds 1-6 and the definition of substituent X:

- 1: CC1=C(C)N=CC(=C1)OCC (4-ethoxy-2-methylpyrimidin-5-yl group)
- 2: CC1=C(C)N=CC(=C1)OCC (4-ethoxy-2-methylpyrimidin-5-yl group)
- 3: CC1=C(C)N=CC(=C1)OCC (4-ethoxy-2-methylpyrimidin-5-yl group)
- 4: CC1=C(C)N=CC(=C1)OCC (4-ethoxy-2-methylpyrimidin-5-yl group)
- 5: CC1=C(C)N=CC(=C1)OCC (4-ethoxy-2-methylpyrimidin-5-yl group)
- 6: CC1=C(C)N=CC(=C1)OCC (4-ethoxy-2-methylpyrimidin-5-yl group)

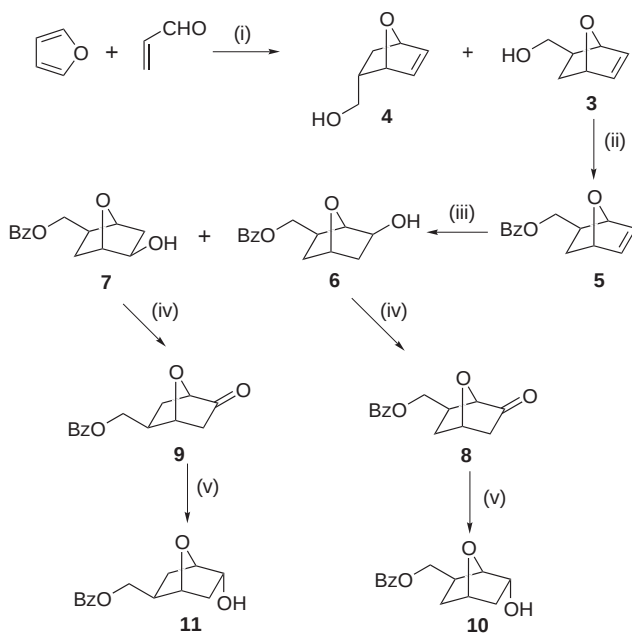
X = Cl, NH₂, NMe₂, NH-

CHART 2

hibit a weak activity^{5a,5c,5f} in tests for anti-HIV-1 and anti-HIV-2 in human T-lymphocyte (CEM) cells and an activity^{5g-5i,6} against the *Coxsackie* virus (CVB3). The virus is a small cytolytic virus, belonging to the genus Enterovirus within the family of *Picornaviridae*. The clinical manifestations associated with enteroviruses range from mild illnesses, such as fever, rash, hand-foot-mouth syndrome, and herpangina, to serious life-threatening infections, such as meningitis, encephalitis, myocarditis, pancreatitis, acute paralysis, or neonatal sepsis. There is currently no approved therapy for treatment of enteroviral infections⁷.

This study concerns synthesis and anti-coxsackievirus assay of novel racemic nucleoside analogues containing 7-oxabicyclo[2.2.1]heptane-2-methanol. Chart 2 describes the target compounds.

Alcohol **3**, which was prepared by Diels–Alder reaction between furan and acrolein and subsequent reduction with lithium aluminium hydride, was used as the key starting material (Scheme 1). The Diels–Alder products

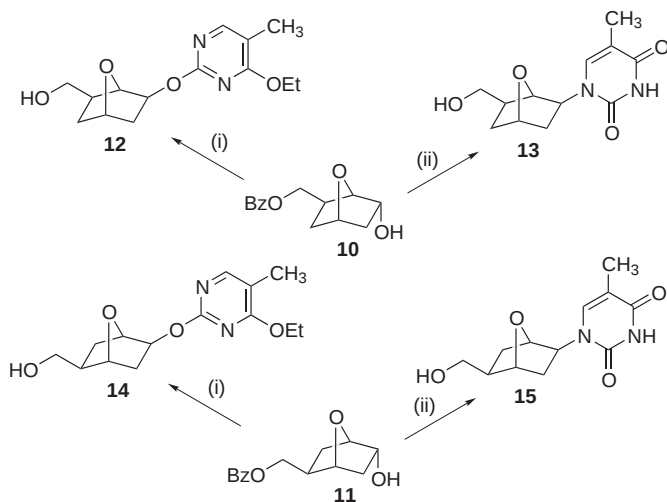


- (i) 1. 100 °C, pressure, 2. $\text{LiAlH}_4/\text{THF}$, 0 °C, 16.5% of **3**, 8.5% of **4**, both based on acrolein; (ii) benzoyl chloride/pyridine, 89%; (iii) 1. $\text{BF}_3 \cdot \text{THF}$, 0 °C, 2. NaBO_3 , 48% of **6**, 46% of **7**; (iv) PDC/ CH_2Cl_2 , 75% of **8**, 85% of **9**; (v) $\text{NaBH}_4/\text{MeOH}/\text{THF}$, 0 °C, 84% of **10**, 79% of **11**

SCHEME 1

were immediately reduced without isolation to prevent the back reaction leading to starting materials⁸. *Exo*-**3** (16.5% based on acrolein) and *endo*-**4** (8.5% based on acrolein) were separated by chromatography on silica gel and isomer **3** was benzoylated. Hydroboration of the protected norbornene derivative **5** with the borane-tetrahydrofuran complex afforded a mixture of hydroxy derivatives **6** and **7** which were separated by chromatography on silica gel. The desired 2-*endo*-hydroxy derivatives **10** and **11** were prepared by oxidation of **6** and **7** with pyridinium dichromate and subsequent reduction of the thus obtained ketones **8** or **9** with sodium borohydride, respectively.

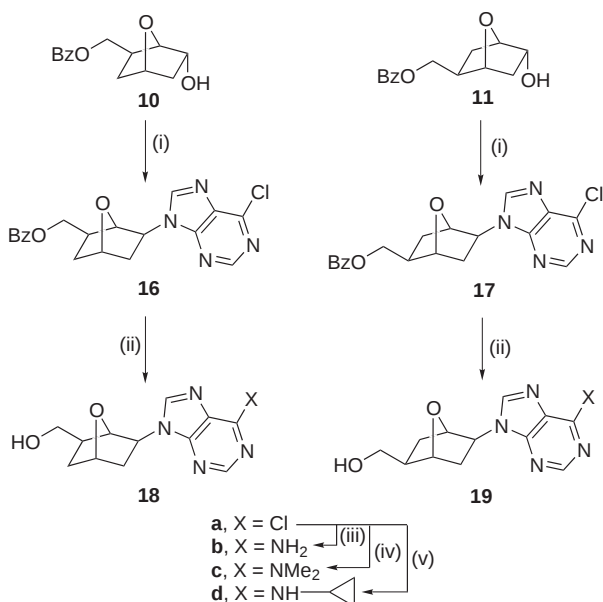
The reaction of alcohols **10** and **11** with 4-ethoxy-5-methylpyrimidin-2(1*H*)-one was performed under Mitsunobu conditions⁹ and afforded, after treatment with methanolic sodium methoxide, pyrimidinyloxy derivatives **12** (85%) and **14** (77%), respectively (Scheme 2). The same reaction of **10** and **11** with 3-benzoyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione gave, after deprotection, the expected thymine derivative **13** (59%) and **15** (60%), respectively.



(i) 1. 4-ethoxy-5-methylpyrimidin-2(1*H*)-one, PPh₃, DIAD, THF, 2. MeONa/MeOH, 85% of **12** based on **10**, 77% of **14** based on **11**;
 (ii) 3-benzoyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione, PPh₃, DIAD, THF, 2. MeONa/MeOH, 59% of **13** based on **10**, 60% of **15** based on **11**

SCHEME 2

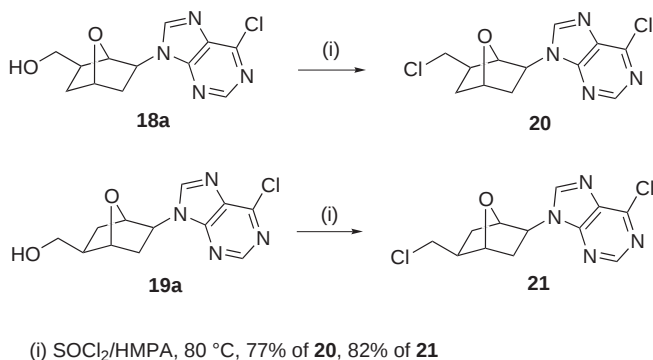
The Mitsunobu reaction of **10** and **11** with 6-chloro-9H-purine afforded 6-chloropurine derivatives **16** (59%) and **17** (56%), respectively, which were deprotected with diisobutylaluminium hydride in dichloromethane at $-78\text{ }^{\circ}\text{C}$ (Scheme 3). Chloropurine derivatives **18a** and **19a** were converted to adenine derivatives **18b** (72%) and **19b** (80%), respectively, by ammonolysis with liquid ammonia at $75\text{ }^{\circ}\text{C}$. Treatment of **18a** and **19a** with dimethylammonium dimethylcarbamate led to 6-(dimethylamino)purine analogues **18c** (79%) and **19c** (80%), respectively. Aminolysis of **18a** and **19a** with cyclopropylamine afforded 6-(cyclopropylamino)purine derivatives **18d** (83%) and **19d** (79%), respectively.



(i) 6-chloro-9H-purine, PPh₃, DIAD, THF, 59% of **16**, 56% of **17**; (ii) DIBAL-H/CH₂Cl₂, $-78\text{ }^{\circ}\text{C}$, 71% of **18a**, 88% of **19a**; (iii) NH₃ (l), $70\text{ }^{\circ}\text{C}$, 72% of **18b**, 80% of **19b**; (iv) Me₂NCOO·Me₂NH₂⁺, r.t., 79% of **18c**, 80% of **19c**; (v) cyclopropylamine, r.t., 83% of **18d**, 79% of **19d**

SCHEME 3

Substitution of the hydroxymethyl group for the chloromethyl group led, in some cases, to increasing antiviral activity⁵ⁱ. Therefore, the chloromethyl derivatives **20** and **21** were prepared by the treatment of **18a** or **19a** with thionyl chloride in hexamethylphosphoramide (HMPA) at $80\text{ }^{\circ}\text{C}$ in 77 and 82% yields, respectively (Scheme 4).



SCHEME 4

The structures of the prepared compounds were confirmed by NMR spectroscopy. Complete assignment of all ¹H and ¹³C resonances was made on the basis of combination of ¹H, ¹³C APT, H,H-COSY, H,C-HSQC, and H,C-HMBC experiments.

In conclusion, novel racemic conformationally-locked carbocyclic nucleoside analogues of thymine, 6-chloropurine, adenine, 6-(dimethylamino)purine, and 6-(cyclopropylamino)purine derived from (1*R**,2*R**,4*S**)-7-oxabicyclo[2.2.1]heptane-2-methanol substituted with a base in the position 5-*exo* or 6-*exo* were prepared. The target compounds were tested for the activity against *Coxsackie* virus (CVB3). Preliminary data showed that the 6-chloropurine analogues **18a**, **19a**, **20**, and **21** exhibit some activity (**18a**: EC₅₀ 1.40 μM and CC₅₀ > 50 μM; **19a**: EC₅₀ 2.21 μM and CC₅₀ > 50 μM; **20**: EC₅₀ 0.84 μM and CC₅₀ > 50 μM; **21**: EC₅₀ 5.08 μM and CC₅₀ > 50 μM). The antiviral activity will be discussed in detail in a separate paper.

EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus and are not corrected. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian Unity 500 and/or Bruker Avance-500 instruments (500 MHz for ¹H and 125.7 MHz for ¹³C) in hexadeuterated dimethyl sulfoxide and referenced to the solvent signal (δ 2.50 and 39.70, respectively). Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using the FAB ionization (Xe, accelerating voltage 8 kV, thioglycerol-glycerol 3:1 or bis(2-hydroxyethyl) disulfide matrix) and LTQ Orbitrap XL (Thermo Fischer Scientific) using the ESI. Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol Silica gel 60 F₂₅₄ foils (Merck). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; compounds were dried at 13 Pa and 50 °C.

(1R*,2R*,4R*)-7-Oxabicyclo[2.2.1]hept-5-ene-2-methanol (**3**) and
(1R*,2S*,4R*)-7-Oxabicyclo[2.2.1]hept-5-ene-2-methanol (**4**)

A mixture of furan (50 ml), acrolein (10 ml), and hydroquinone (300 mg) was kept at room temperature under argon for 15 days and then evaporated. A solution of the residue in tetrahydrofuran (18 ml) was added dropwise to a stirred 1 M solution of lithium aluminium hydride in tetrahydrofuran (20 ml) at 0 °C under argon. The mixture was stirred at room temperature for 3 h and excess of the hydride was decomposed by slow addition of water. Then solid CO₂ was added to adjust pH of the mixture to ~8. The thick suspension was filtered with a Celite pad, the filter was washed with tetrahydrofuran (3 × 30 ml) and the combined filtrates were evaporated. Chromatography of the residue on a silica gel column in ethyl acetate–toluene (22:3) afforded 4.46 g (16.5%) of **3** and 2.26 g (8.5%) of **4**, both as a syrup.

Compound 3: For C₇H₁₀O₂ (126.2) calculated: 66.64% C, 7.99% H; found: 66.45% C, 8.10% H. ESI MS, *m/z*: 149.1 [M + Na]. ¹H NMR: 1.05 ddd, 1 H, *J*_{gem} = 11.4, *J*(3ex,4) = 4.6, *J*(3ex,2) = 3.5 (H-3ex); 1.23 dd, 1 H, *J*_{gem} = 11.3, *J*(3en,2) = 8.0 (H-3en); 1.58 dddd, 1 H, *J*(2,3en) = 7.9, *J*(2,3ex) = 3.5, *J*(2,CH₂) = 9.5 and 4.8 (H-2); 3.24 m, 1 H and 3.41 m, 1 H (CH₂O); 4.68 t, 1 H, *J*(OH,CH₂) = 5.4 (OH); 4.74 m, 1 H (H-1); 4.84 m, 1 H (H-4); 6.30–6.33 m, 2 H (H-5 and H-6). ¹³C NMR: 28.37 (C-3); 40.48 (C-2); 64.21 (CH₂O); 77.14 (C-4); 78.64 (C-1); 135.08 (C-6); 135.97 (C-5).

Compound 4: For C₇H₁₀O₂ (126.2) calculated: 66.64% C, 7.99% H; found: 66.37% C, 8.13% H. ESI MS, *m/z* (%): 149 (100) [M + Na], 150 (9) [M + Na + H]. ¹H NMR: 0.56 dd, 1 H, *J*_{gem} = 11.1, *J*(3en,2) = 4.2 (H-3en); 1.79 ddd, 1 H, *J*_{gem} = 11.1, *J*(3ex,2) = 9.1, *J*(3ex,4) = 4.8 (H-3ex); 2.21 m, 1 H (H-2); 2.92 td, 1 H, *J*_{gem} = *J*(CH₂,2) = 10.1, *J*(CH₂,OH) = 5.0 and 3.27 ddd, 1 H, *J*_{gem} = 10.5, *J*(CH₂,OH) = 6.1, *J*(CH₂,2) = 4.5 (CH₂O); 4.54 t, 1 H, *J*(OH,CH₂) = 5.1 (OH); 4.83 m, 1 H (H-4); 4.85 m, 1 H (H-1); 6.24 d, 1 H, *J*(6,5) = 5.9, *J*(6,1) = 1.6 (H-6); 6.37 dd, 1 H, *J*(5,6) = 5.9, *J*(5,4) = 1.7 (H-5). ¹³C NMR: 27.97 (C-3); 40.83 (C-2); 63.74 (CH₂O); 77.66 (C-4); 78.98 (C-1); 132.36 (C-6); 136.42 (C-5).

[(1R*,2R*,4R*)-7-Oxabicyclo[2.2.1]hept-5-en-2-yl]methyl Benzoate (**5**)

Benzoyl chloride (20.9 ml, 18 mmol) was added at 0 °C to a stirred solution of alcohol **3** (18.91 g, 150 mmol) in pyridine (200 ml) and the mixture was allowed to stand at room temperature overnight. Pyridine was then evaporated and the residue was partitioned between ethyl acetate (600 ml) and water (300 ml). The organic phase was washed with water (300 ml), 5% hydrochloric acid (to acidic reaction of the aqueous phase), 10% sodium hydrogencarbonate solution (3 × 300 ml), dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on silica gel (1 kg) in toluene–ethyl acetate (22:3) afforded 30.74 g (89%) of benzoate **5** as a thick sirup. For C₁₄H₁₄O₃ (230.3) calculated: 73.03% C, 6.13% H; found: 72.89% C, 6.10% H. ¹H NMR: 1.31 ddd, 1 H, *J*_{gem} = 11.5, *J*(3ex,4) = 4.6, *J*(3ex,2) = 3.4 (H-3exo); 1.39 dd, 1 H, *J*_{gem} = 11.5, *J*(3en,2) = 7.9 (H-3en); 1.95 dddd, 1 H, *J*(2,CH₂O) = 9.4 and 6.2, *J*(2,3en) = 7.9, *J*(2,3ex) = 3.6 (H-2); 4.12 dd, 1 H, *J*_{gem} = 10.8, *J*(CH₂,2) = 9.4 and 4.32 dd, 1 H, *J*(CH₂,2) = 6.2 (CH₂O); 4.85 m, 1 H (H-1); 4.95 dm, 1 H, *J*(4,3ex) = 4.5 (H-4); 6.37 dd, 1 H, *J*(5,6) = 5.8, *J*(5,4) = 1.7 (H-5); 6.39 dd, 1 H, *J*(6,5) = 5.8, *J*(6,1) = 1.6 (H-6); 7.54 m, 2 H, 7.67 m, 1 H and 8.01 m, 2 H (arom.). ¹³C NMR: 28.49 (C-3); 36.95 (C-2); 67.43 (CH₂O); 77.38 (C-4); 78.82 (C-1); 128.99, 2 C, 129.45, 2 C, 129.97 and 133.58 (arom.); 134.79 (C-6); 136.52 (C-5); 165.94 (C=O).

[(1R*,2S*,4S*,6S*)-6-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**6**) and [(1R*,2R*,4R*,5S*)-5-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**7**)

A 1 M solution of borane in tetrahydrofuran (20 ml) was added dropwise under argon to a stirred solution of alkene **5** (9.21 g, 40 mmol) in tetrahydrofuran (10 ml) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Excess of borane was decomposed by addition of water (0.5 ml) and then a suspension of sodium perborate tetrahydrate (18.5 g, 120 mmol) in water (70 ml) was added in one portion. The reaction mixture was stirred at room temperature overnight and then diluted with ethyl acetate (300 ml). The organic phase was separated, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed on silica gel (1.3 kg) in toluene–ethyl acetate (1:1).

Compound 6: Yield 4.80 g (48%) of a sirup. For $C_{14}H_{16}O_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.72% C, 6.64% H. FAB MS, m/z (%): 249 (48) [M + H], 105 (100) [benzoyl]. 1H NMR: 1.13 m, 1 H (H-3ex); 1.36 m, 1 H (H-5ex); 1.49 dd, 1 H, $J_{gem} = 11.9$, $J(3en,2) = 8.5$ (H-3en); 1.81 dd, 1 H, $J_{gem} = 12.4$, $J(5en,6) = 7.1$ (H-5en); 2.05 m, 1 H (H-2); 3.82 ddd, 1 H, $J(6,5en) = 7.0$, $J(6,OH) = 4.7$, $J(6,5ex) = 2.5$ (H-6); 4.00 dd, 1 H, $J_{gem} = 10.7$, $J(CH_2,2) = 9.3$ and 4.06 dd, 1 H, $J_{gem} = 10.7$, $J(CH_2,2) = 6.4$ (CH_2O); 4.09 bs, 1 H (H-1); 4.50 t, 1 H, $J(4,3ex) = J(4,5ex) = 5.3$ (H-4); 4.78 d, 1 H, $J(OH,6) = 4.7$ (OH); 7.54 m, 2 H (H-3'); 7.67 m, 1 H (H-4'); 7.98 m, 2 H (H-2'). ^{13}C NMR: 32.76 (C-3); 37.25 (C-2); 41.98 (C-5); 66.52 (CH_2O); 72.49 (C-6); 74.67 (C-4); 83.64 (C-1); 129.00 (C-3'); 129.37 (C-2'); 129.93 (C-1'); 133.59 (C-4'); 165.89 (C=O).

Compound 7: Yield 4.57 g (46%) of a sirup. For $C_{14}H_{16}O_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.56% C, 6.69% H. FAB MS, m/z (%): 249 (41) [M + H], 105 (100) [benzoyl]. 1H NMR: 1.14 bddd, 1 H, $J_{gem} = 12.6$, $J(3ex,4) = 5.7$, $J(3ex,2) = 3.6$ (H-3ex); 1.40 dddd, 1 H, $J_{gem} = 12.6$, $J(6ex,1) = 5.7$, $J(6ex,5) = 2.4$, $J_{1r.} = 0.9$ (H-6ex); 1.47 dd, 1 H, $J_{gem} = 12.6$, $J(3en,2) = 8.5$ (H-3en); 1.83 dd, 1 H, $J_{gem} = 12.5$, $J(6en,5) = 7.0$ (H-6en); 2.03 m, 1 H (H-2); 3.78 ddd, 1 H, $J(5,6en) = 7.0$, $J(5,OH) = 4.8$, $J(5,6ex) = 2.4$ (H-5); 3.97 dd, 1 H, $J_{gem} = 10.8$, $J(CH_2,2) = 9.3$ and 4.02 dd, 1 H, $J_{gem} = 10.8$, $J(CH_2,2) = 6.4$ (CH_2O); 4.20 d, 1 H, $J(4,3ex) = 5.7$ (H-4); 4.38 d, 1 H, $J(1,6ex) = 5.6$ (H-1); 4.77 d, 1 H, $J(OH,5) = 4.8$ (OH); 7.53 m, 2 H (H-3'); 7.66 m, 1 H (H-4'); 7.97 m, 2 H (H-2'). ^{13}C NMR: 28.52 (C-3); 40.92 (C-2); 41.31 (C-6); 66.74 (CH_2O); 72.85 (C-5); 75.94 (C-1); 81.88 (C-4); 128.97 (C-3'); 129.38 (C-2'); 129.93 (C-1'); 133.54 (C-4'); 165.90 (C=O).

[(1R*,2S*,4S*)-6-Oxo-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**8**) and [(1R*,2R*,4R*)-5-Oxo-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**9**)

A solution of alcohol **6** or **7** (2.48 g, 10 mmol) in dichloromethane (20 ml) was added to a suspension of powdered molecular sieves (5.5 g) and pyridinium dichromate (5.83 g, 15.5 mmol) in dichloromethane (60 ml). The reaction mixture was stirred at room temperature for 3 days. Solids were filtered off and washed with ethyl acetate. The filtrate was evaporated, the residue was dissolved in ethyl acetate (100 ml), filtered and the filtrate evaporated. The residue was chromatographed on silica gel (150 g) in toluene–ethyl acetate (4:1) and crystallized from methanol.

Compound 8: Yield 1.85 g (75%). M.p. 105–106 °C. For $C_{14}H_{14}O_4$ (246.3) calculated: 68.28% C, 5.73% H; found: 68.26% C, 5.78% H. 1H NMR: 1.56 dddd, 1 H, $J_{gem} = 12.4$, $J(3ex,4) = 5.4$, $J(3ex,2) = 4.3$, $J(3ex,5ex) = 2.5$ (H-3ex); 1.97 dd, 1 H, $J_{gem} = 12.4$, $J(3en,2) = 8.7$ (H-3en); 2.14 d, 1 H, $J_{gem} = 15.5$ (H-5en); 2.37–2.45 m, 2 H (H-2 and H-5ex); 4.12 dd, 1 H, $J_{gem} = 10.8$, $J(CH_2,2) = 9.1$ and 4.20 dd, 1 H, $J(CH_2,2) = 6.3$ (CH_2O); 4.35 bs, 1 H (H-1);

4.93 t, 1 H, $J(4,3ex) = J(4,5ex) = 5.6$ (H-4); 7.54 m, 2 H, 7.67 m, 1 H and 7.99 m, 2 H (arom.). ^{13}C NMR: 31.97 (C-3); 36.93 (C-2); 43.87 (C-5); 65.32 (CH_2O); 76.31 (C-4); 80.70 (C-1); 129.03, 2 C, 129.47, 2 C, 129.75 and 133.70 (arom.); 165.85 (C=O); 211.80 (C-6).

Compound 9: Yield 2.09 (85%). M.p. 103–104 °C. For $\text{C}_{14}\text{H}_{14}\text{O}_4$ (246.3) calculated: 68.28% C, 5.73% H; found: 68.33% C, 5.82% H. FAB MS, m/z (%): 247 (8) [M + H], 105 (100) [benzoyl]. ^1H NMR: 1.58 dddm, 1 H, $J_{\text{gem}} = 13.4$, $J(3en,2) = 6.4$, $J(3ex,2) = 4.2$ (H-3ex); 1.82 dd, 1 H, $J_{\text{gem}} = 13.4$, $J(3en,2) = 8.6$ (H-3en); 2.17 d, 1 H, $J_{\text{gem}} = 17.5$ (H-6en); 2.45 ddm, 1 H, $J_{\text{gem}} = 17.5$, $J(6ex,1) = 6.1$ (H-6ex); 2.52 m, 1 H (H-2); 4.11 dd, 1 H, $J_{\text{gem}} = 10.9$, $J(\text{CH}_2,2) = 9.1$ and 4.18 dd, 1 H, $J_{\text{gem}} = 10.9$, $J(\text{CH}_2,2) = 6.3$ (CH_2O); 4.41 bd, 1 H, $J(4,3ex) = 6.3$ (H-4); 4.80 bd, 1 H, $J(1,6ex) = 6.0$ (H-1); 7.54 m, 2 H (H-3'); 7.67 m, 1 H (H-4'); 8.00 m, 2 H (H-2'). ^{13}C NMR: 27.80 (C-3); 40.34 (C-2); 42.90 (C-6); 66.23 (CH_2O); 77.55 (C-1); 78.96 (C-4); 128.97 (C-3'); 129.45 (C-2'); 129.83 (C-1'); 133.62 (C-4'); 165.87 (C=O); 211.79 (C-5).

[(1R*,2S*,4S*,6R*)-6-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**10**) and [(1R*,2R*,4R*,5R*)-5-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**11**)

Sodium borohydride (760 mg, 20 mmol) was added to a stirred solution of ketone **8** or **9** (4.93 g, 20 mmol) in methanol (75 ml) and tetrahydrofuran (25 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min and then a saturated aqueous solution of ammonium chloride was slowly added. The mixture was extracted with ethyl acetate (400 ml), the ethyl acetate solution was dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (450 g) in toluene–ethyl acetate (1:1) and compound **10** was then crystallized from diethyl ether–cyclohexane.

Compound 10: Yield 4.17 g (84%). M.p. 117–118 °C. For $\text{C}_{14}\text{H}_{16}\text{O}_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.53% C, 6.59% H. FAB MS, m/z (%): 249 (17) [M + H], 105 (100) [benzoyl]. ^1H NMR: 1.04 dd, 1 H, $J_{\text{gem}} = 12.2$, $J(5en,6) = 3.3$ (H-5en); 1.30 dtd, 1 H, $J_{\text{gem}} = 11.8$, $J(3ex,2) = J(3ex,4) = 5.0$, $J(3ex,5ex) = 2.6$ (H-3ex); 1.73 dd, 1 H, $J_{\text{gem}} = 11.9$, $J(3en,2) = 8.7$ (H-3en); 1.96 dddd, 1 H, $J_{\text{gem}} = 12.2$, $J(5ex,6) = 10.0$, $J(5ex,4) = 5.7$, $J(5ex,3ex) = 2.6$ (H-5ex); 2.90 tdd, 1 H, $J(2,\text{CH}_2) = J(2,3en) = 8.9$, $J(2,\text{CH}_2) = 6.7$, $J(2,3ex) = 4.5$ (H-2); 4.05 dd, 1 H, $J_{\text{gem}} = 10.6$, $J(\text{CH}_2,2) = 9.2$ and 4.10 dd, 1 H, $J_{\text{gem}} = 10.6$, $J(\text{CH}_2,2) = 6.6$ (CH_2O); 4.10 m, 1 H (H-6); 4.18 d, 1 H, $J(1,6) = 5.0$ (H-1); 4.42 t, 1 H, $J(4,3ex) = J(4,5ex) = 5.4$ (H-4); 5.09 d, 1 H, $J(\text{OH},6) = 4.0$ (OH); 7.53 m, 2 H (H-3'); 7.66 m, 1 H (H-4'); 7.98 m, 2 H (H-2'). ^{13}C NMR: 33.81 (C-2); 34.26 (C-3); 39.11 (C-5); 66.62 (CH_2O); 69.95 (C-6); 77.22 (C-4); 79.91 (C-1); 128.95 (C-3'); 129.38 (C-2'); 130.02 (C-1'); 133.53 (C-4'); 165.94 (C=O).

Compound 11: Yield 3.92 g (79%) as a solid foam. For $\text{C}_{14}\text{H}_{16}\text{O}_4$ (248.3) calculated: 67.73% C, 6.50% H; found: 67.57% C, 6.66% H. ESI MS, m/z (%): 271.1 (100) [M + Na], 249 (5) [M + H]. ^1H NMR: 1.04 dd, 1 H, $J_{\text{gem}} = 12.3$, $J(6en,5) = 3.4$ (H-6en); 1.10 m, 1 H (H-3en); 2.01 ddd, 1 H, $J_{\text{gem}} = 12.3$, $J(6ex,5) = 10.0$, $J(6ex,1) = 6.0$ (H-6ex); 2.24 tdd, 1 H, $J(2,3en) = J(2,\text{CH}_2) = 8.8$, $J(2,\text{CH}_2) = 6.5$, $J(2,3ex) = 3.8$ (H-2); 2.32 dd, 1 H, $J_{\text{gem}} = 12.1$, $J(3en,2) = 8.7$ (H-3en); 3.99 dd, 1 H, $J_{\text{gem}} = 10.7$, $J(\text{CH}_2,2) = 8.9$ and 4.02 dd, 1 H, $J_{\text{gem}} = 10.8$, $J(\text{CH}_2,2) = 6.5$ (CH_2O); 4.07 m, 1 H (H-5); 4.26–4.30 m, 2 H (H-1 and H-4); 5.03 d, 1 H, $J(\text{OH},5) = 4.1$ (OH); 7.53 m, 2 H (H-3'); 7.66 m, 1 H (H-4'); 7.98 m, 2 H (H-2'). ^{13}C NMR: 25.78 (C-3); 38.55 (C-6); 42.28 (C-2); 66.82 (CH_2O); 70.15 (C-5); 78.14 (C-4); 78.35 (C-1); 128.98 (C-3'); 129.39 (C-2'); 129.95 (C-1'); 133.54 (C-4'); 165.94 (C=O).

(1R*,2S*,4S*,6S*)-6-[(4-Ethoxy-5-methylpyrimidin-2-yl)oxy]-7-oxabicyclo[2.2.1]heptane-2-methanol (**12**) and

(1R*,2R*,4R*,5S*)-5-[(4-Ethoxy-5-methylpyrimidin-2-yl)oxy]-7-oxabicyclo[2.2.1]heptane-2-methanol (**14**)

A solution of diisopropyl azodicarboxylate (1.18 ml, 6 mmol) in tetrahydrofuran (8 ml) was added dropwise to a stirred solution of 4-ethoxy-5-methylpyrimidin-2(1H)-one (924 mg, 6 mmol), triphenylphosphine (2.10 g, 8 mmol), and alcohol **10** or **11** (1.24 g, 5 mmol) in tetrahydrofuran (20 ml). The mixture was then heated to reflux for 4 h and evaporated. The residue was chromatographed on a silica gel column (250 g) in toluene–ethyl acetate (18:7) and the fractions containing pyrimidine derivative were evaporated. A solution of the residue in methanolic 0.1 M sodium methoxide (75 ml) was kept at room temperature overnight. Dowex 50 (H⁺) was then added until UV-absorption of the solution disappeared; **12** or **14** was adsorbed on the resin. The resin was filtered off and washed with methanol–aqueous 25% ammonia (8:2; 150 ml). The washings were evaporated and the residue was crystallized from water (**12**) or chromatographed on silica gel (100 g) in ethyl acetate–toluene (4:1) (**14**).

Compound 12: Yield 1.19 g (85%). M.p. 90–91 °C. For C₁₄H₂₀N₂O₄ (280.3) calculated: 59.98% C, 7.19% H, 9.99% N; found: 59.85% C, 7.18% H, 9.83% N. ESI MS, *m/z* (%): 304.1 (16) [M + Na + H], 303.1 (100) [M + Na], 281.0 (53) [M + H], 155.1 (6) [base + H]. ¹H NMR: 0.99 dm, 1 H, *J*_{gem} = 11.8 (H-3ex); 1.30 t, 3 H, *J*(CH₃,CH₂) = 7.1 (CH₂CH₃); 1.51 dd, 1 H, *J*_{gem} = 11.9, *J*(3en,2) = 8.5 (H-3en); 1.62 dm, 1 H, *J*_{gem} = 13.1 (H-5ex); 1.89 m, 1 H (H-2); 1.96 d, 3 H, *J*(CH₃,5') = 0.9 (5'-CH₃); 2.07 dd, 1 H, *J*_{gem} = 13.1, *J*(5en,6) = 7.2 (H-5en); 3.12–3.18 m, 2 H (CH₂O); 4.28 q, 2 H, *J*(CH₂,CH₃) = 7.1 (OCH₂CH₃); 4.43 bs, 1 H (H-1); 4.55 bt, 1 H, *J*(4,3ex) = *J*(4,5ex) = 5.2 (H-4); 4.74 bt, 1 H, *J*(OH,CH₂) = 5.4 (OH); 5.02 dd, 1 H, *J*(6,5en) = 7.1, *J*(6,5ex) = 2.6 (H-6); 8.08 q, 1 H, *J*(6',CH₃) = 0.9 (H-6'). ¹³C NMR: 11.59 (5'-CH₃); 14.57 (CH₂CH₃); 32.44 (C-3); 39.84 (C-5); 40.80 (C-2); 62.70 (OCH₂CH₃); 63.41 (CH₂O); 74.77 (C-4); 78.44 (C-6); 80.81 (C-1); 110.46 (C-5'); 157.99 (C-6'); 163.10 (C-4'); 168.16 (C-2').

Compound 14: Yield 1.08 g (77%) as a thick sirup. For C₁₄H₂₀N₂O₄ (280.3) calculated: 59.98% C, 7.19% H, 9.99% N; found: 59.91% C, 7.30% H, 9.75% N. ESI MS, *m/z* (%): 304.1 (15), 303.1 (100) [M + Na]. ¹H NMR: 1.05 ddd, 1 H, *J*_{gem} = 12.6, *J*(3ex,4) = 6.0, *J*(3ex,2) = 4.0 (H-3ex); 1.30 t, 3 H, *J*(CH₃,CH₂) = 7.1 (CH₂CH₃); 1.57 dd, 1 H, *J*_{gem} = 12.6, *J*(3en,2) = 8.5 (H-3en); 1.66 dddd, 1 H, *J*_{gem} = 13.1, *J*(6ex,1) = 5.6, *J*(6ex,5) = 2.6, *J*_{l.r.} = 0.8 (H-6ex); 1.82 m, 1 H (H-2); 1.96 d, 3 H, *J*(CH₃,6') = 0.9 (5'-CH₃); 2.04 dd, 1 H, *J*_{gem} = 13.1, *J*(6en,5) = 7.2 (H-6en); 3.09–3.17 m, 2 H (CH₂OH); 4.27 q, 2 H, *J*(CH₂,CH₃) = 7.1 (OCH₂CH₃); 4.44 bd, 1 H, *J*(1,6ex) = 5.7 (H-1); 4.49 bd, 1 H, *J*(4,3ex) = 5.9 (H-4); 4.68 bt, 1 H, *J*(OH,CH₂) = 5.3 (OH); 5.00 dd, 1 H, *J*(5,6en) = 7.1, *J*(5,6ex) = 2.6 (H-5); 8.08 q, 1 H, *J*(6',CH₃) = 0.9 (H-6'). ¹³C NMR: 11.61 (5'-CH₃); 14.54 (CH₂CH₃); 28.44 (C-3); 39.09 (C-6); 44.42 (C-2); 62.64 (OCH₂CH₃); 63.69 (CH₂OH); 76.09 (C-1); 78.64 (C-5); 79.07 (C-4); 110.59 (C-5'); 157.83 (C-6'); 163.06 (C-4'); 168.26 (C-2').

1-[(1R*,2S*,4S*,6S*)-6-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (**13**) and

1-[(1R*,2S*,4R*,5R*)-5-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (**15**)

A solution of diisopropyl azodicarboxylate (0.59 ml, 3 mmol) in tetrahydrofuran (4 ml) was added dropwise to a stirred solution of 3-benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (805 mg, 3.5 mmol), triphenylphosphine (1.05 g, 4 mmol), and alcohol **10** or **11** (620 mg, 2.5 mmol) in tetrahydrofuran (10 ml). The mixture was heated to reflux for 4 h and then evaporated. The residue was chromatographed on a silica gel column (120 g) in toluene–ethyl acetate (18:7) and the fractions containing the pyrimidine derivative were evaporated. A solution of the residue in methanolic 0.1 M sodium methoxide (40 ml) was left at room temperature overnight. The solution was neutralized with Dowex 50 (H⁺), filtered, and evaporated. The residue was crystallized from diethyl ether.

Compound 13: Yield 372 mg (59%). M.p. 179–181 °C. For C₁₂H₁₆N₂O₄ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 56.96% C, 6.32% H, 10.89% N. ESI MS, *m/z* (%): 275.0 (100) [M + Na], 253.1 (18) [M + H]. ¹H NMR: 1.02 m, 1 H (H-5'ex); 1.57 dd, 1 H, *J*_{gem} = 12.0, *J*(5'en,6') = 8.5 (H-5'en); 1.65 m, 1 H (H-3'ex); 1.76 d, 3 H, *J*(CH₃,6) = 1.2 (CH₃); 1.91 m, 1 H (H-6'); 2.08 dd, 1 H, *J*_{gem} = 13.1, *J*(3'en,2') = 8.7 (H-3'en); 3.10–3.14 m, 2 H (CH₂O); 4.34 s, 1 H (H-1'); 4.64 bt, 1 H, *J*(4',3'ex) = *J*(4',5'ex) = 5.2 (H-4'); 4.69 dd, 1 H, *J*(2',3'en) = 8.6, *J*(2',3'ex) = 3.9 (H-2'); 4.74 bs, 1 H (OH); 7.48 q, 1 H, *J*(6,CH₃) = 1.2 (H-6); 11.25 bs, 1 H (NH). ¹³C NMR: 12.60 (CH₃); 32.72 (C-5'); 39.32 (C-3'); 43.40 (C-6'); 56.15 (C-2'); 63.40 (CH₂O); 75.36 (C-4'); 81.61 (C-1'); 109.51 (C-5); 137.27 (C-6); 151.27 (C-2); 163.97 (C-4).

Compound 15: Yield 380 mg (60%). M.p. 249–251 °C. For C₁₂H₁₆N₂O₄ (252.3) calculated: 57.13% C, 6.39% H, 11.10% N; found: 57.00% C, 6.41% H, 10.91% N. ESI MS, *m/z*: 275.0 [M + Na]. ¹H NMR: 1.05 m, 1 H (H-6'ex); 1.59 dd, 1 H, *J*_{gem} = 12.6, *J*(6'en,5') = 8.5 (H-6'en); 1.70 m, 1 H (H-3'ex); 1.76 d, 3 H, *J*(CH₃,6) = 1.2 (CH₃); 1.87 m, 1 H (H-5'); 2.06 dd, 1 H, *J*_{gem} = 13.2, *J*(3'en,2') = 8.7 (H-3'en); 3.08–3.15 m, 2 H (CH₂O); 4.48 d, 1 H, *J*(1',6'ex) = 5.7 (H-1'); 4.52 d, 1 H, *J*(4',3'ex) = 5.6 (H-4'); 4.66 dd, 1 H, *J*(2',3'en) = 8.6, *J*(2',3'ex) = 3.8 (H-2'); 4.73 bt, 1 H, *J*(OH,CH₂) = 5.2 (OH); 7.49 q, 1 H, *J*(6,CH₃) = 1.2 (H-6); 11.24 bs (NH). ¹³C NMR: 12.63 (CH₃); 30.96 (C-6'); 38.51 (C-3'); 44.80 (C-5'); 56.57 (C-2'); 63.68 (CH₂O); 76.73 (C-4'); 79.97 (C-1'); 109.30 (C-5); 137.38 (C-6); 151.28 (C-2); 163.98 (C-4).

[(1R*,2R*,4S*,6S*)-6-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**16**) and

[(1R*,2R*,4R*,5S*)-5-(6-Chloro-9H-purin-9-yl)-7-oxabicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**17**)

A solution of diisopropyl azodicarboxylate (8.9 ml, 45 mmol) in tetrahydrofuran (50 ml) was slowly added to a solution of alcohol **10** or **11** (7.45 g, 30 mmol), triphenylphosphine (15.74 g, 60 mmol), and 6-chloropurine (6.96 g, 45 mmol) in THF (250 ml). The reaction mixture was then heated to reflux for 6 h and evaporated. The residue was chromatographed on silica gel (1 kg) in ethyl acetate–toluene (1:1) and crystallized from butyl acetate.

Compound 16: Yield 6.86 g (59%). M.p. 186.5–188.5 °C. For C₁₉H₁₇ClN₄O₃ (384.8) calculated: 59.30% C, 4.45% H, 9.21% Cl, 14.56% N; found: 59.21% C, 4.51% H, 9.29% Cl, 14.42% N. ESI MS, *m/z* (%): 794.5 (15), 793.5 (24), 792.5 (64), 790.5 (100), 789.7 (16), 409.1/407.1 (27/79) [M + Na], 387/385.2 (9/26) [M + H]. ¹H NMR: 1.37 dm, 1 H, *J*_{gem} = 12.0

(H-3ex); 1.84 dd, 1 H, $J_{\text{gem}} = 12.1$, $J(3\text{en},2) = 8.6$ (H-3en); 2.08 dm, 1 H, $J_{\text{gem}} = 13.3$ (H-5ex); 2.35 dd, 1 H, $J_{\text{gem}} = 13.3$, $J(5\text{en},6) = 8.4$ (H-5en); 2.54 m, 1 H (H-2); 4.06 dd, 1 H, $J_{\text{gem}} = 10.9$, $J(\text{CH}_2,2) = 9.2$ and 4.14 dd, 1 H, $J_{\text{gem}} = 10.9$, $J(\text{CH}_2,2) = 6.3$ (CH_2O); 4.71 bs, 1 H (H-1); 4.86 bt, 1 H, $J(4,5\text{ex}) = J(4,3\text{ex}) = 5.2$ (H-4); 5.05 dd, 1 H, $J(6,5\text{en}) = 8.4$, $J(6,5\text{ex}) = 3.3$ (H-6); 7.50 m, 2 H, 7.64 m, 1 H, and 7.97 m, 2 H (arom.); 8.66 s, 1 H (H-8'); 8.77 s, 1 H (H-2'). ^{13}C NMR (DMSO): 33.03 (C-3); 38.82 (C-2); 39.46 (C-5); 56.92 (C-6); 66.09 (CH_2O); 75.79 (C-4); 81.81 (C-1); 128.90, 129.44, 129.85, and 133.54 (C-4'); 130.96 (C-5'); 145.22 (C-8'); 149.10 (C-6'); 151.54 (C-2'); 151.87 (C-4'); 165.89 (C=O).

Compound 17: Yield 6.50 g (56%). M.p. 183–185 °C. For $\text{C}_{19}\text{H}_{17}\text{ClN}_4\text{O}_3$ (384.8) calculated: 59.30% C, 4.45% H, 9.21% Cl, 14.56% N; found: 59.10% C, 4.44% H, 9.42% C, 14.33% N. ESI MS, m/z (%): 409.1/407.1 (27/78) [M + Na], 391.3 (100), 387.2/385.1 (22/66) [M + H]. ^1H NMR (DMSO): 1.43 dm, 1 H, $J_{\text{gem}} = 12.9$ (H-3ex); 1.96 dd, 1 H, $J_{\text{gem}} = 12.9$, $J(3\text{en},2) = 8.6$ (H-3en); 2.14 dddd, 1 H, $J_{\text{gem}} = 13.4$, $J(6\text{ex},1) = 5.6$, $J(6\text{ex},5) = 5.6$, $J_{1,\text{r.}} = 0.9$ (H-6ex); 2.38 dd, 1 H, $J_{\text{gem}} = 13.4$, $J(6\text{en},5) = 8.4$ (H-6en); 2.38 m, 1 H (H-2); 4.06–4.14 m, 2 H (CH_2O); 4.73 m, 2 H (H-1 and H-4); 5.01 dd, 1 H, $J(5,6\text{en}) = 8.4$, $J(5,6\text{ex}) = 3.1$ (H-5); 7.55 m, 2 H (H-3'); 7.68 m, 1 H, 8.01 m, 2 H, and 8.66 s, 1 H (arom.); 8.79 s, 1 H (H-2'). ^{13}C NMR (DMSO): 29.87 (C-3); 38.58 (C-6); 41.24 (C-2); 57.21 (C-5); 66.36 (CH_2O); 76.96 (C-1); 80.25 (C-4); 128.99, 129.42, 129.89, and 133.60 (arom.); 130.92 (C-5'); 145.34 (C-8'); 149.12 (C-6'); 151.60 (C-2'); 151.85 (C-4'); 165.92 (C=O).

(1R*,2S*,4S*,6S*)-6-(6-Chloro-9H-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**18a**) and

(1R*,2R*,4R*,5S*)-5-(6-Chloro-9H-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**19a**)

A 1 M solution of DIBAL-H in dichloromethane (42 ml) was added dropwise to a solution of compound **16** or **17** (5.45 g, 14 mmol) in dichloromethane (100 ml) at -78 °C under argon. The reaction mixture was stirred for 1 h, excess DIBAL-H was decomposed by addition of methanol and temperature was allowed to rise to room temperature. Then water (3 ml) and methanol (400 ml) were added and the mixture was filtered with a Celite pad. The filter was washed with methanol and the filtrate was evaporated. The residue was crystallized from methanol.

Compound 18a: Yield 2.8 g (71%). M.p. 191.5–193 °C. For $\text{C}_{12}\text{H}_{13}\text{ClN}_4\text{O}_2$ (280.7) calculated: 51.34% C, 4.67% H, 12.63% Cl, 19.96% N; found: 51.15% C, 4.74% H, 12.85% Cl, 19.81% N. ESI MS, m/z (%): 305.1/303.1 (10/25) [M + Na], 288.3 (60), 283.1/281.1 (36/100) [M + H]. HR ESI MS (M + H) calculated 281.0800, found 281.0796. ^1H NMR (DMSO): 1.11 dtd, 1 H, $J_{\text{gem}} = 11.9$, $J(3\text{ex},4) = J(3\text{ex},2) = 4.9$, $J(3\text{ex},5\text{ex}) = 2.6$ (H-3ex); 1.67 dd, 1 H, $J_{\text{gem}} = 11.9$, $J(3\text{en},2) = 8.5$ (H-3en); 2.06 dm, 1 H, $J_{\text{gem}} = 13.3$ (H-5ex); 2.11 m, 1 H (H-2); 2.30 dd, 1 H, $J_{\text{gem}} = 13.3$, $J(5\text{en},6) = 8.4$ (H-5en); 3.13–3.22 m, 2 H (CH_2O); 4.47 s, 1 H (H-1); 4.75 t, 1 H, $J(\text{OH},\text{CH}_2) = 5.4$ (OH); 4.77 t, 1 H, $J(4,3\text{ex}) = J(4,5\text{ex}) = 5.2$ (H-4); 4.97 dd, 1 H, $J(6,5\text{en}) = 8.4$, $J(6,5\text{ex}) = 3.2$ (H-6); 8.63 s, 1 H (H-8'); 8.78 s, 1 H (H-2'). ^{13}C NMR (DMSO): 33.00 (C-3); 39.62 (C-5); 42.34 (C-2); 57.04 (C-6); 63.41 (CH_2O); 75.59 (C-4); 82.00 (C-1); 130.89 (C-5'); 145.19 (C-8'); 149.14 (C-6'); 151.60 (C-2'); 151.77 (C-4').

Compound 19a: Yield 3.47 g (88%). M.p. 182–183.5 °C. For $\text{C}_{12}\text{H}_{13}\text{ClN}_4\text{O}_2$ (280.7) calculated: 51.34% C, 4.67% H, 12.63% Cl, 19.96% N; found: 51.15% C, 4.60% H, 12.59% Cl, 19.80% N. negESI MS, m/z (%): 281.1/279 (31/88) [M – H], 155/153 (32/100) [6-chloropurine – H]. ^1H NMR (DMSO): 1.15 ddd, 1 H, $J_{\text{gem}} = 12.7$, $J(3\text{ex},4) = 5.8$, $J(3\text{ex},2) = 3.8$ (H-3ex); 1.78 dd, 1 H, $J_{\text{gem}} =$

12.7, $J(3\text{en},2) = 8.6$ (H-3en); 1.97 m, 1 H (H-2); 2.10 dddd, 1 H, $J_{\text{gem}} = 13.3$, $J(6\text{ex},1) = 5.7$, $J(6\text{ex},5) = 3.2$, $J_{1,1r} = 0.8$ (H-6ex); 2.27 dd, 1 H, $J_{\text{gem}} = 13.3$, $J(6\text{en},5) = 8.4$ (H-6en); 3.14 dd, 1 H, $J_{\text{gem}} = 10.5$, $J(\text{CH}_2,2) = 6.1$ and 3.19 dd, 1 H, $J_{\text{gem}} = 10.5$, $J(\text{CH}_2,2) = 9.6$ (CH_2O); 4.60 d, 1 H, $J(4,3\text{ex}) = 5.8$ (H-4); 4.65 d, 1 H, $J(1,6\text{ex}) = 5.7$ (H-1); 4.78 bs, 1 H; 4.94 dd, 1 H, $J(5,6\text{en}) = 8.4$, $J(5,6\text{ex}) = 3.2$ (H-5); 8.64 s, 1 H (H-8'); 8.76 s, 1 H (H-2'). ^{13}C NMR (DMSO): 29.93 (C-3); 38.82 (C-6); 44.94 (C-2); 57.45 (C-5); 63.61 (CH_2O); 76.83 (C-1); 80.23 (C-4); 130.95 (C-5'); 145.29 (C-8'); 149.14 (C-6'); 151.62 (C-2'); 151.87 (C-4').

(1R*,2S*,4S*,6S*)-6-(6-Amino-9H-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**18b**) and

(1R*,2R*,4R*,5S*)-5-(6-Amino-9H-purin-9-yl)-7-oxabicyclo[2.2.1]heptane-2-methanol (**19b**)

A solution of chloropurine derivative **18a** or **19a** (281 mg, 1 mmol) in liquid ammonia (20 ml) was heated in an autoclave at 75 °C for 48 h and then ammonia was evaporated. The residue was crystallized from water.

Compound 18b: Yield 188 mg (72%). M.p. 268–269.5 °C. For $\text{C}_{12}\text{H}_{15}\text{N}_5\text{O}_2$ (261.3) calculated: 55.16% C, 5.79% H, 26.80% N; found: 54.98% C, 5.76% H, 26.62% N. ESI MS, m/z (%): 284.1 (57) [M + Na], 262.1 (100) [M + H]. ^1H NMR: 1.08 m, 1 H (H-3ex); 1.64 dd, 1 H, $J_{\text{gem}} = 11.8$, $J(3\text{en},2) = 8.5$ (H-3en); 1.94 dm, 1 H, $J_{\text{gem}} = 13.1$ (H-5ex); 2.06 m, 1 H (H-2); 2.25 dd, 1 H, $J_{\text{gem}} = 13.1$, $J(5\text{en},6) = 8.6$ (H-5en); 3.12–3.21 m, 2 H (CH_2O); 4.35 s, 1 H (H-1); 4.72–4.77 m, 2 H (H-4 and OH); 4.80 dd, 1 H, $J(6,5\text{en}) = 8.4$, $J(6,5\text{ex}) = 3.2$ (H-6); 7.22 bs, 2 H (NH_2); 8.08 s, 1 H (H-8'); 8.14 s, 1 H (H-2'). ^{13}C NMR: 32.95 (C-3); 39.97 (C-5); 42.51 (C-2); 55.52 (C-6); 63.47 (CH_2O); 75.47 (C-4); 82.35 (C-1); 118.61 (C-5'); 138.39 (C-8'); 149.40 (C-4'); 152.60 (C-2'); 156.19 (C-6').

Compound 19b: Yield 193 mg (74%). M.p. 225–226.5 °C. For $\text{C}_{12}\text{H}_{15}\text{N}_5\text{O}_2$ (261.3) calculated: 55.16% C, 5.79% H, 26.80% N; found: 54.97% C, 5.77% H, 26.69% N. ESI MS, m/z (%): 285.1 (39) [M + Na + H], 284.1 (100) [M + Na], 262.2 (81) [M + H]. ^1H NMR: 1.12 ddd, 1 H, $J_{\text{gem}} = 12.6$, $J(3\text{ex},4) = 5.8$, $J(3\text{ex},2) = 3.8$ (H-3ex); 1.73 dd, 1 H, $J_{\text{gem}} = 12.6$, $J(3\text{en},2) = 8.5$ (H-3en); 1.92–2.02 m, 2 H (H-2 and H-6ex); 2.23 dd, 1 H, $J_{\text{gem}} = 13.1$, $J(6\text{en},5) = 8.4$ (H-6en); 3.11–3.20 m, 2 H (CH_2O); 4.49 d, 1 H, $J(4,3\text{ex}) = 5.7$ (H-4); 4.62 d, 1 H, $J(1,6\text{ex}) = 5.6$ (H-1); 4.76 bt, 1 H, $J(\text{OH},\text{CH}_2) = 5.3$ (OH); 4.78 dd, 1 H, $J(5,6\text{en}) = 8.4$, $J(5,6\text{ex}) = 3.3$ (H-5); 7.24 bs, 2 H (NH_2); 8.10 s, 1 H (H-8'); 8.14 s, 1 H (H-2'). ^{13}C NMR: 30.12 (C-3); 39.12 (C-6); 44.92 (C-2); 56.38 (C-5); 63.66 (CH_2O); 76.72 (C-1); 80.55 (C-4); 118.69 (C-5'); 138.46 (C-8'); 149.47 (C-4'); 152.59 (C-2'); 156.20 (C-6').

(1R*,2S*,4S*,6S*)-6-[6-(Dimethylamino)-9H-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**18c**) and

(1R*,2R*,4R*,5S*)-5-[6-(Dimethylamino)-9H-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**19c**)

A solution of chloropurine derivative **18a** and **19a** (140 mg, 0.5 mmol) in dimethylammonium dimethylcarbamate (2.5 ml) was left standing at room temperature overnight and then evaporated. The residue was chromatographed on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (95:15:8:7) and then crystallized from ether.

Compound 18c: Yield 114 mg (79%). M.p. 137–139 °C. For $\text{C}_{14}\text{H}_{19}\text{N}_5\text{O}_2$ (289.3) calculated: 58.12% C, 6.62% H, 24.21% N; found: 58.13% C, 6.64% H, 24.10% N. ESI MS, m/z (%): 291.2 (15) [M + 2 H], 290.2 (100) [M + H]. ^1H NMR: 1.08 m, 1 H (H-3ex); 1.64 dd, 1 H,

$J_{\text{gem}} = 11.9$, $J(3\text{en},2) = 8.5$ (H-3en); 1.92 dm, 1 H, $J_{\text{gem}} = 13.1$ (H-5ex); 2.06 m, 1 H (H-2); 2.25 dd, 1 H, $J_{\text{gem}} = 13.1$, $J(5\text{en},6) = 8.5$ (H-5en); 3.12–3.20 m, 2 H (CH₂O); 3.4 vbs, 6 H (CH₃); 4.34 s, 1 H (H-1); 4.73 t, 1 H, $J(4,3\text{ex}) = J(4,5\text{ex}) = 5.2$ (H-4); 4.78 t, 1 H, $J(\text{OH},\text{CH}_2) = 5.4$ (OH); 4.83 dd, 1 H, $J(6,5\text{en}) = 8.5$, $J(6,5\text{ex}) = 3.4$ (H-6); 8.09 s, 1 H (H-8'); 8.21 s, 1 H (H-2'). ¹³C NMR: 32.94 (C-3); 40.00 (C-5); 42.57 (C-2); 55.93 (C-6); 63.48 (CH₂O); 75.49 (C-4); 82.30 (C-1); 119.16 (C-5'); 137.24 (C-8'); 150.18 (C-4'); 151.94 (C-2'); 154.45 (C-6').

Compound 19c: Yield 116 mg (80%). M.p. 162–163.5 °C. For C₁₄H₁₉N₅O₂ (289.3) calculated: 58.12% C, 6.62% H, 24.21% N; found: 57.97% C, 6.64% H, 24.13% N. ESI MS, m/z (%): 291.2 (16) [M + 2 H], 290.2 (100) [M + H]. ¹H NMR: 1.12 ddd, 1 H, $J_{\text{gem}} = 12.6$, $J(3\text{ex},4) = 5.8$, $J(3\text{ex},2) = 3.8$ (H-3ex); 1.73 dd, 1 H, $J_{\text{gem}} = 12.6$, $J(3\text{en},2) = 8.6$ (H-3en); 1.92–1.99 m, 2 H (H-2 and H-6ex); 2.23 dd, 1 H, $J_{\text{gem}} = 13.2$, $J(6\text{en},5) = 8.5$ (H-6en); 3.11–3.20 m, 2 H (CH₂O); 3.4 vbs, 6 H (CH₃); 4.48 d, 1 H, $J(4,3\text{ex}) = 5.7$ (H-4); 4.62 d, 1 H, $J(1,6\text{ex}) = 5.7$ (H-1); 4.76 t, 1 H, $J(\text{OH},\text{CH}_2) = 5.3$ (OH); 4.80 dd, 1 H, $J(5,6\text{en}) = 8.4$, $J(5,6\text{ex}) = 3.3$ (H-5); 8.10 s, 1 H (H-8'); 8.20 s, 1 H (H-2'). ¹³C NMR: 30.15 (C-3); 38.47 (CH₃); 39.07 (C-6); 44.91 (C-2); 56.38 (C-5); 63.67 (CH₂O); 76.73 (C-1); 80.52 (C-4); 119.23 (C-5'); 137.30 (C-8'); 150.22 (C-4'); 151.90 (C-2'); 154.44 (C-6').

(1R*,2S*,4S*,6S*)-6-[6-(Cyclopropylamino)-9H-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**18d**) and

(1R*,2R*,4R*,5S*)-5-[6-(Cyclopropylamino)-9H-purin-9-yl]-7-oxabicyclo[2.2.1]heptane-2-methanol (**19d**)

A solution of chloropurine derivative **18a** or **19a** (140 mg, 0.5 mmol) in cyclopropylamine (2 ml) was left standing at room temperature overnight and then evaporated. The residue was chromatographed on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (90:15:11:9) and then crystallized from ether.

Compound 18d: Yield 125 mg (83%). M.p. 171–173 °C. For C₁₅H₁₉N₅O₂ (301.4) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.53% C, 6.43% H, 22.99% N. negESI MS, m/z (%): 623 (28) [2 × (M – H) + Na], 301.1 (17) [M], 300 (100) [M – H], 270 (25), 174.1 (43) [6-(cyclopropylamino)purine – H]. ¹H NMR: 0.59 m, 2 H, 0.71 m, 2 H, and 3.00 bs, 1 H (cyclopropyl); 1.08 m, 1 H (H-3ex); 1.64 dd, 1 H, $J_{\text{gem}} = 11.9$, $J(3\text{en},2) = 8.5$ (H-3en); 1.94 m, 1 H (H-5ex); 2.07 m, 1 H (H-2); 2.25 dd, 1 H, $J_{\text{gem}} = 13.1$, $J(5\text{en},6) = 8.5$ (H-5en); 3.12–3.20 m, 2 H (CH₂O); 4.35 s, 1 H (H-1); 4.73 t, 1 H, $J(4,3\text{ex}) = J(4,5\text{ex}) = 5.2$ (H-4); 4.77 t, 1 H, $J(\text{OH},\text{CH}_2) = 5.4$ (OH); 4.82 dd, 1 H, $J(6,5\text{en}) = 8.5$, $J(6,5\text{ex}) = 3.3$ (H-6); 7.91 bs, 1 H (NH); 8.09 s, 1 H (H-8'); 8.25 bs, 1 H (H-2'). ¹³C NMR: 6.63 (cyclopropyl CH₂); 32.97 (C-3); 40.02 (C-5); 42.54 (C-2); 55.93 (C-6); 63.50 (CH₂O); 75.50 (C-4); 82.38 (C-1); 119.02 (C-5'); 138.26 (C-8'); 149.78 (C-4'); 152.55 (C-2'); 155.76 (C-6').

Compound 19d: Yield 119 mg (79%). M.p. 199–201 °C. For C₁₅H₁₉N₅O₂ (301.4) calculated: 59.79% C, 6.36% H, 23.24% N; found: 59.55% C, 6.51% H, 22.98% N. ESI MS, m/z (%): 324.1 (23), 302.2 (100) [M + H]. ¹H NMR: 0.59 m, 2 H, 0.71 m, 2 H, and 3.02 bs, 1 H (cyclopropyl); 1.13 ddd, 1 H, $J_{\text{gem}} = 12.6$, $J(3\text{ex},4) = 5.7$, $J(3\text{ex},2) = 3.9$ (H-3ex); 1.74 dd, 1 H, $J_{\text{gem}} = 12.6$, $J(3\text{en},2) = 8.5$ (H-3en); 1.92–2.02 m, 2 H (H-2 and H-6ex); 2.23 dd, 1 H, $J_{\text{gem}} = 13.1$, $J(6\text{en},5) = 8.4$ (H-6en); 3.11–3.22 m, 2 H (CH₂O); 4.49 d, 1 H, $J(4,3\text{ex}) = 5.7$ (H-4); 4.62 d, 1 H, $J(1,6\text{ex}) = 5.3$ (H-1); 4.75 t, 1 H, $J(\text{OH},\text{CH}_2) = 5.3$ (OH); 4.79 dd, 1 H, $J(5,6\text{en}) = 8.4$, $J(5,6\text{ex}) = 3.3$ (H-5); 7.87 bs, 1 H (NH); 8.09 s, 1 H (H-8'); 8.23 bs, 1 H (H-2'). ¹³C NMR: 6.66 (cyclopropyl CH₂); 24.30 (cyclopropyl CH); 30.12 (C-3); 39.10 (C-6); 44.91 (C-2); 56.37

(C-5); 63.66 (CH₂O); 76.73 (C-1); 80.55 (C-4); 119.06 (C-5'); 138.29 (C-8'); 148.92 (C-4'); 152.47 (C-2'); 155.74 (C-6').

6-Chloro-9-[(1R*,2S*,4S*,6R*)-6-(chloromethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-9H-purine (**20**) and

6-Chloro-9-[(1R*,2S*,4R*,5S*)-5-(chloromethyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-9H-purine (**21**)

Thionyl chloride (0.13 ml, 1.8 mmol) was added to a solution of hydroxymethyl derivative **18a** or **19a** (140 mg, 0.5 mmol) in hexamethylphosphoramide (1.8 ml). The solution was heated to 80 °C for 2.5 h and then poured into a saturated solution of sodium hydrogen-carbonate (10 ml). The resulting mixture was extracted with ethyl acetate (10 ml) and the extract was washed with water (2 × 5 ml), dried over anhydrous sodium sulfate, and evaporated. The residue was crystallized from ethyl acetate.

Compound 20: Yield 115 mg (77%). M.p. 193–195 °C. For C₁₂H₁₂Cl₂N₄O (299.2) calculated: 48.18% C, 4.04% H, 23.70% Cl, 18.73% N; found: 47.91% C, 3.91% H, 23.95% Cl, 18.48% N. ESI MS, *m/z* (%): 316.4 (56), 303.1/301.1/299.1 (10/40/67) [M + H]. ¹H NMR: 1.31 dtd, 1 H, *J*_{gem} = 12.2, *J*(5'ex,4') = *J*(5'ex,6') = 4.9, *J*(5'ex,3'ex) = 2.6 (H-5'ex); 1.85 dd, 1 H, *J*_{gem} = 12.2, *J*(5'en,6') = 8.4 (H-5'en); 2.07 dm, 1 H, *J*_{gem} = 13.3 (H-3'ex); 2.32 dd, 1 H, *J*_{gem} = 13.3, *J*(3'en,2') = 8.5 (H-3'en); 2.44 m, 1 H (H-6'); 3.44 dd, 1 H, *J*_{gem} = 10.7, *J*(CH₂,6') = 7.2 and 3.51 dd, 1 H, *J*_{gem} = 10.7, *J*(CH₂,6') = 8.7 (CH₂Cl); 4.52 s, 1 H (H-1'); 4.84 t, 1 H, *J*(4',3'ex) = *J*(4',5'ex) = 5.1 (H-4'); 5.04 dd, 1 H, *J*(2',3'en) = 8.4, *J*(2',3'ex) = 3.3 (H-2'); 8.63 s, 1 H (H-8); 8.78 s, 1 H (H-2). ¹³C NMR: 35.38 (C-5'); 39.25 (C-3'); 42.61 (C-6'); 47.47 (CH₂Cl); 56.74 (C-2'); 76.14 (C-4'); 82.63 (C-1'); 130.92 (C-5); 145.20 (C-8); 149.17 (C-6); 151.64 (C-2); 151.83 (C-4).

Compound 21: Yield 123 mg (82%). M.p. 162–163 °C. For C₁₂H₁₂Cl₂N₄O (299.2) calculated: 48.18% C, 4.04% H, 23.70% Cl, 18.73% N; found: 47.90% C, 3.99% H, 23.95% Cl, 18.46% N. ESI MS, *m/z* (%): 303.2/301.1/299.0 (13/68/100) [M + H], 288.3 (50). ¹H NMR: 1.36 dm, 1 H, *J*_{gem} = 13.1 (H-6'ex); 1.96 dd, 1 H, *J*_{gem} = 13.0, *J*(6'en,5') = 8.5 (H-6'en); 2.15 dddd, 1 H, *J*_{gem} = 13.5, *J*(3'ex,4') = 5.7, *J*(3'ex,2') = 3.1, *J*_{l.r.} = 0.9 (H-3'ex); 2.26 m, 1 H (H-5'); 2.34 dd, 1 H, *J*_{gem} = 13.5, *J*(3'en,2') = 8.4 (H-3'en); 3.43 dd, 1 H, *J*_{gem} = 10.7, *J*(CH₂,5') = 7.0 and 3.52, dd, 1 H, *J*_{gem} = 10.7, *J*(CH₂,5') = 9.0 (CH₂Cl); 4.66 d, 1 H, *J*(4',3'ex) = 5.7 (H-4'); 4.69 d, 1 H, *J*(1',6'ex) = 5.8 (H-1'); 4.98 dd, 1 H, *J*(2',3'en) = 8.4, *J*(2',3'ex) = 3.1 (H-2'); 8.64 s, 1 H (H-8); 8.77 s, 1 H (H-2). ¹³C NMR: 32.04 (C-6'); 38.31 (C-3'); 45.04 (C-5'); 47.64 (CH₂Cl); 57.01 (C-2'); 77.56 (C-4'); 80.50 (C-1'); 130.92 (C-5); 145.26 (C-8); 149.13 (C-6); 151.60 (C-2); 151.85 (C-4).

The authors are indebted to Ms J. Sklenářová for excellent technical assistance and to the staff of the Analytical Laboratory of the Institute for elemental analyses. This study, a part of the research project Z4 055 0506, was supported by the Ministry of Education, Youth and Sports of the Czech Republic (Centre for New Antivirals and Antineoplastics No. 1M0508), the Programme of Targeted Projects of Academy of Sciences of the Czech Republic (1QS400550501), and Gilead Sciences, Inc. (Foster City, CA, U.S.A.).

REFERENCES

1. a) Borthwick A. D., Biggadike K.: *Tetrahedron* **1992**, 48, 571; b) Agrofoglio L., Suhas E., Farese A., Condom R., Challand S. R., Earl R. A., Guedj R.: *Tetrahedron* **1994**, 50, 10611; c) Crimmins M. T.: *Tetrahedron* **1998**, 54, 9229; d) Schneller S. W.: *Curr. Top. Med. Chem.* **2002**, 2, 1087; e) Rodríguez J. B., Comin M. J.: *Mini Rev. Med. Chem.* **2003**, 3, 95; f) Simons C., Wu Q., Htar T. T.: *Curr. Top. Med. Chem.* **2005**, 5, 1191; g) Agrofoglio L.: *Curr. Org. Chem.* **2006**, 10, 333.
2. a) Crimmins M. T., King B. W.: *J. Org. Chem.* **1996**, 61, 4192; b) Daluge S. M., Good S. S., Faletto M. B., Miller W. H., StClair M. H., Boone L. R., Tisdale M., Parry N. R., Reardon J. E., Dornsife R. E., Averett D. R., Krenitski T. A.: *Antimicrob. Agents Chemother.* **1997**, 41, 1082; c) Hervey P. S., Perry C. M.: *Drugs* **2000**, 60, 447.
3. Bisacchi G. S., Chao S. T., Bachard C., Daris J. P., Innaimo S., Jacobs G. A., Kocy O., Lapointe P., Martel A., Merchant Z., Slusarchyk W. A., Sundeen J. E., Young M. G., Colonna R., Zahler B.: *Bioorg. Med. Chem. Lett.* **1997**, 7, 127.
4. a) Kim H. S., Jacobson K. A.: *Org. Lett.* **2003**, 5, 1665; b) Ohno M., Costanzi S., Kim H. S., Kempeneers V., Vastmans K., Herdewijn P., Maddileti S., Gao Z.-G., Harden T. K., Jacobson K. A.: *Bioorg. Med. Chem.* **2004**, 12, 5619.
5. a) Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2005**, 70, 103; b) Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2005**, 70, 519; c) Šála M., Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2006**, 71, 635; d) Šála M., Hřebabecký H., Dračínský M., Holý A.: *Conference Book IRT-17th International Roundtable on Nucleosides, Nucleotides and Nucleic Acids*, p. 217. DCB University of Bern, Bern 2006; e) Hřebabecký H., Masojídková M., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2006**, 71, 871; f) Hřebabecký H., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2007**, 71, 1331; g) Dejmek M., Hřebabecký H., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2007**, 72, 1523; h) Hřebabecký H., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2008**, 73, 44; i) Hřebabecký H., Dračínský M., De Palma A. M., Neyts J., Holý A.: *Collect. Czech. Chem. Commun.* **2008**, 73, 469.
6. Šála M., Hřebabecký H., Dračínský M., De Palma A., Neyts J., Holý A.: *Antiviral Res.* **2007**, 74, A52.
7. De Palma A. M., Vliegen I., De Clercq E., Neyts J.: *Med. Res. Rev.* **2008**, 28, 823.
8. Kappe O. C., Murphree S. S., Padwa A.: *Tetrahedron* **1997**, 53, 14179.
9. a) Mitsunobu O.: *Synthesis* **1981**, 1; b) Martin S. F., Dodge J. A.: *Tetrahedron* **1995**, 51, 2029.