NEW CARBOCYCLIC NUCLEOSIDE ANALOGUES BUILT ON A BICYCLO[2.2.2]OCTANE-2,2-DIMETHANOL TEMPLATE

Hubert HŘEBABECKÝ[1,*], Martin DRAČÍNSKÝ[2] and Antonín HOLÝ[3]

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic; e-mail: [1] hubert@uochb.cas.cz, [2] dracinsky@uochb.cas.cz, [3] holy@uochb.cas.cz

Received July 29, 2009
Accepted September 15, 2009
Published online September 21, 2009

(1*R**,4*S**,6*S**)-6-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanol (**22**) and (1*R**,4*R**,5*S**)-5-(6-chloro-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanol (**17**) were prepared from (1*R**,4*R**)-bicyclo[2.2.2]oct-5-ene-2,2-dimethanediyl dibenzoate (**7**) using two approaches. The first procedure consists in hydroboration of **7**, separation of obtained 6-*exo*-hydroxy derivative **8** and 5-*exo*-hydroxy derivative **9**, conversion of **8** and **9** to *endo*-hydroxy derivatives **12** and **13**, respectively, and the Mitsunobu reaction with 6-chloropurine. Only 5-(6-chloropurinyl) analogue **16** was obtained in an acceptable yield. The target analog **17** was prepared by reductive debenzoylation of **16**. The further reactions were hydroboration of **7**, treatment with hydroxylamine-*O*-sulfonic acid and debenzoylation. Chloropurine analogues **17** and **22** were built on the obtained 6-*exo*-amino- and 5-*exo*-aminobicyclo[2.2.2]-octane-2,2-dimethanols **18** and **19**, respectively. Compounds **17** and **22** were converted to adenine (**23**, **24**) and 6-(cyclopropylamino)purine analogues (**25**, **26**).

Keywords: Nucleosides; Carbocyclic nucleosides; Purines; Adenine; 6-Chloropurine; 6-(Cyclopropylamino)purine; Hydroboration; Mitsunobu reaction.

In carbocyclic nucleoside analogues, the furanose ring of natural nucleosides is substituted by a hydrocarbon ring of various size. This modification results in an increased resistance to enzymatic degradation. The search for new carbocyclic nucleosides accelerated since the natural products aristeromycin (**1**)[1] and neplanocin A (**2**)[2] were shown to exhibit interesting biological activities. Thereafter, a large number of carbocyclic analogues have been synthesized and tested[3]. U.S. Food and Drug Administration approved two of them: abacavir (Ziagen™; **3**)[2] for the treatment of HIV-1 infections and entecavir (Baraclude™; **4**)[3] for the treatment of chronic hepatitis B virus (HBV) infections (Chart 1).

Recently, a series of carbocyclic analogues containing bicycloalkanes, bicycloheteroalkanes or tricycloheteroalkanes with some activity against

doi:10.1135/cccc2009090

Coxsackie viruses was prepared in our laboratory[4]. *Coxsackie* viruses belong to the genus Enterovirus within the family of *Picornaviridae*. By their pathogenicity for suckling mice and antigenicity, they are classified as *Coxsackie* virus group A (A1–A22, A24) and *Coxsackie* virus group B (B1–B6). In most cases, *Coxsackie* viruses cause mild flu-like symptoms and go away without treatment. Occasionally, they can cause more serious infections, such as meningitis, encephalitis, myocarditis, pancreatitis, acute paralysis, or neonatal sepsis. Neonatal myocarditis in the first month of life may result in a severe and frequently fatal disease[5]. So far, U.S. Food and Drug Administration has not approved any compound for treatment of *Coxsackie* virus infections; therefore, only palliative but no curative treatment of these infections is available[6].

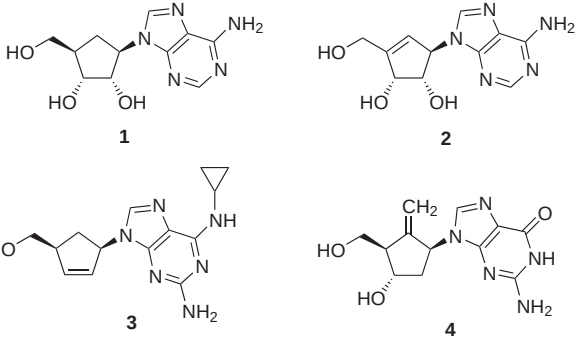
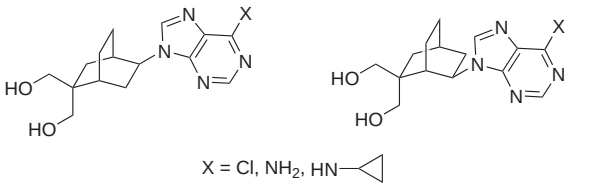


CHART 1



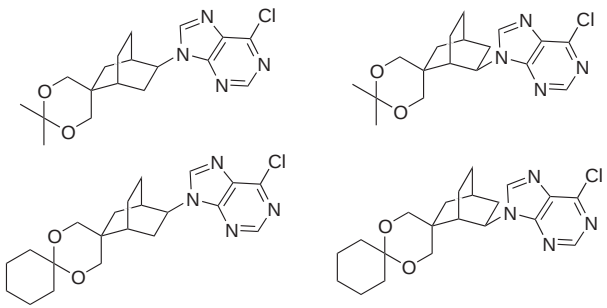
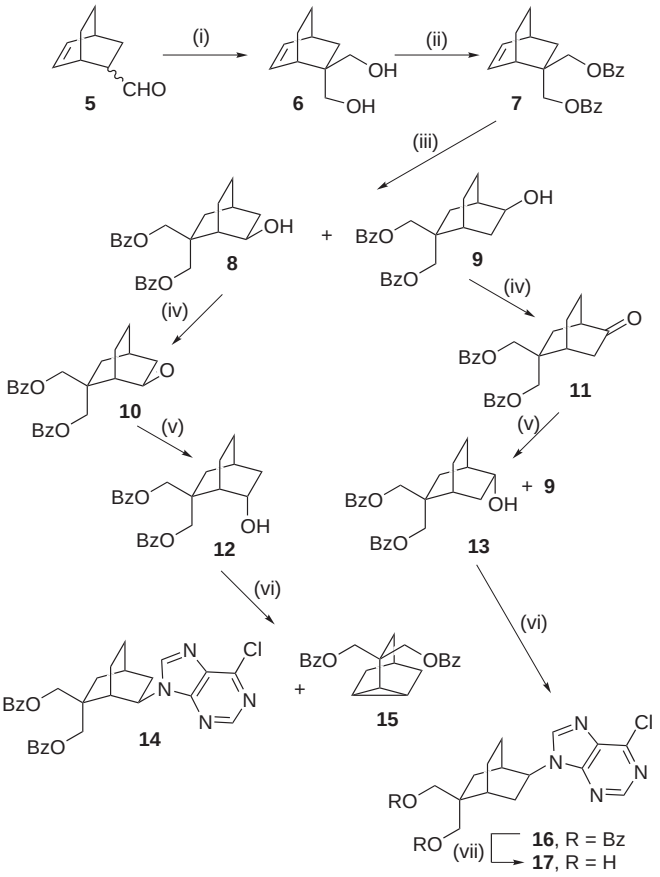


CHART 2

This paper describes synthesis of novel racemic nucleoside analogues containing bicyclo[2.2.2]octane-2,2-dimethanol as compounds with potential anti-coxsackievirus activity. The target compounds are shown in Chart 2.

Dibenzoate **7**, prepared from aldehyde **5**[7] by treatment with aqueous formaldehyde in aqueous sodium hydroxide and subsequent benzoylation of the obtained diol **6**, was used as the key starting material (Scheme 1).

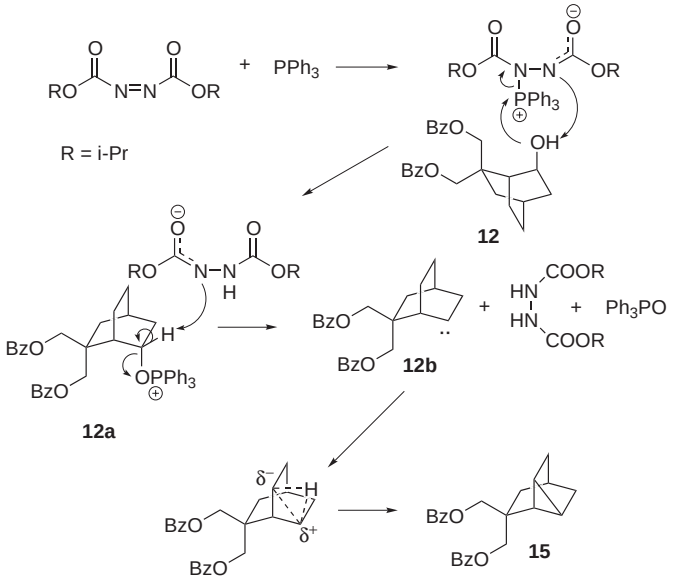


(i) 37% aq. CH_2O/25% aq. NaOH/THF, 53%; (ii) BzCl/pyridine, 91%; (iii) 1. BH_3·THF, 2. $NaBO_3 \cdot 4H_2O$, 33% of **8**, 46% of **9**; (iv) PDC/CH_2Cl_2, 93% of **10**, 94.5% of **11**; (v) $NaBH_4$/MeOH, 95% of **12**, 45% of **13**, 40.5% of **9**; (vi) 6-chloro-9*H*-purine, PPh_3, DIAD, THF, 1.3% of **14**, 85% of **15**, 45% of **16**; (vii) DIBAL-H/CH_2Cl_2, -78 °C, 46%

SCHEME 1

Hydroboration of dibenzoate **7** with the borane–tetrahydrofuran complex gave a mixture of hydroxy derivatives **8** (33%) and **9** (46%) which were separated by chromatography on silica gel. Oxidation of **8** and **9** with pyridinium dichromate (PDC) and subsequent reduction of the thus obtained ketones **10** (93%) and **11** (94.5%) with sodium borohydride led to the desired *endo*-hydroxy derivatives **12** (95%) and **13** (45%). Unfortunately, the borohydride reduction of ketone **11** did not proceed stereoselectively and *exo*-hydroxy derivative **9** was obtained as byproduct in 40.5% yield.

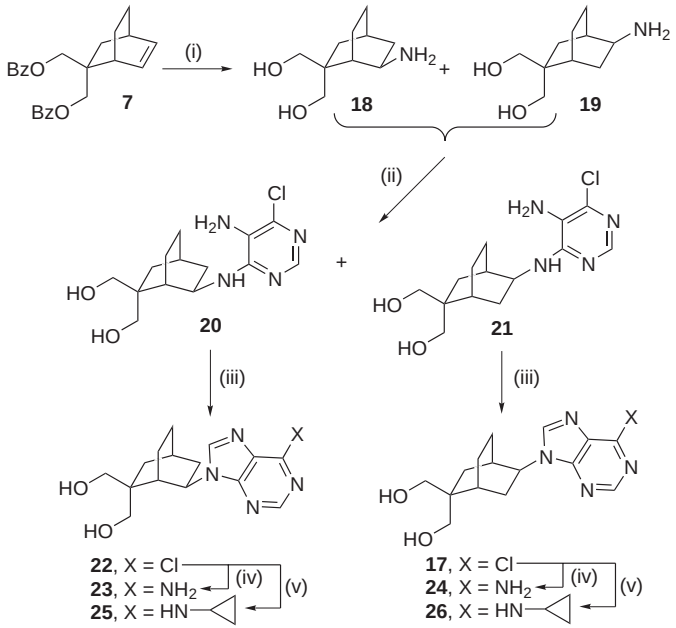
The Mitsunobu reaction[8] of **13** with 6-chloro-9*H*-purine afforded 6-chloropurine derivatives **16** (45%) which was deprotected with diisobutylaluminium hydride in dichloromethane at –78 °C giving the free chloropurine derivative **17** (46%). On the other hand, the main product of the Mitsunobu reaction of **12** was tricyclic derivative **15** (85%). The desired 6-chloropurine derivative **14** was obtained in a very low yield (1.3%). This unusual course of the Mitsunobu reaction could be explained as depicted in Scheme 2. The reaction of alcohol **12** with diisopropyl azodicarboxylate and triphenylphosphine affords activated alcohol **12a** (cf. ref.[9b] for the general mechanism of the Mitsunobu reaction). Subsequent treatment of **12a** with hydrazine-1,2-dicarboxylate anion leads to carbene **12b**. Bicyclo-



SCHEME 2

[2.2.2]octanyl carbene systems are prone to 1,2- and 1,3-migration of hydrogen (depending upon substitution) giving bicyclooctene and tricyclooctane derivatives, respectively[9]. Carbene **12b** afforded tricyclooctane derivative **15** due to 1,3-hydrogen migration.

It stands to reason that the Mitsunobu reaction is not suitable for this preparation of the target purine derivatives. Therefore, we made use of conversion of amines **18** and **19** for the preparation of 6-chloropurine analogues **17** and **22** (Scheme 3). The amines were prepared by modified procedure described by Rathke[10]. Bicycloalkene **7** was treated with a borane–tetrahydrofuran complex. The reaction of the thus obtained borane intermediate with hydroxylamine-*O*-sulfonic acid in diglyme at 100 °C and subsequent debenzoylation with methanolic sodium methoxide afforded a mixture of amines **18** and **19**. The attempts to separate these amines were unsuccessful. The mixture was used in the next reaction step. Conversion

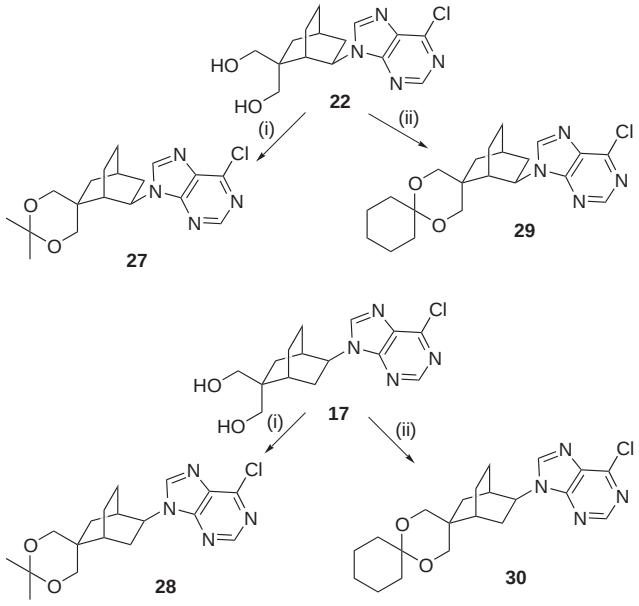


(i) 1. BH_3· THF/diglyme, 0 °C, r.t., 2. H_2N-OSO_3H, 100 °C, 3. MeONa/MeOH, 31% of a mixture of **18** and **19**; (ii) 4,6-dichloropyrimidin-5-amine/TEA/EtOH, 100 °C, 12% of **20**, 41% of **21**; (iii) 1. $CH(OEt)_3$/HCl, 2. THF/H_2O/HCl, 82% of **22**, 76% of **17**; (iv) NH_3 (l), 70 °C, 77% of **23**, 84% of **24**; (v) cyclopropylamine, r.t., 93% of **25**, 84% of **26**

SCHEME 3

of amines to the 6-chloropurine derivatives was performed by previously described procedures (ref.[4j] and references therein). Coupling of a mixture of amines **18** and **19** with 4,6-dichloropyrimidin-5-amine in ethanol in the presence of triethylamine gave pyrimidinylamino derivatives **20** (12%) and **21** (41%), respectively. Ring closure of **20** or **21** with triethyl orthoformate in the presence of concentrated hydrochloric acid afforded 6-chloropurine derivative **22** (82%) or **17** (76%). Ammonolysis of chloropurine derivatives **22** and **17** with liquid ammonia at 70 °C gave adenine derivatives **23** (77%) and **24** (84%), respectively. Aminolysis of **22** or **17** with cyclopropylamine led to cyclopropylamino derivative **25** (93%) or **26** (84%).

O,*O*′-Propane-2,2-diyl and *O*,*O*′-cyclohexane-1,1-diyl derivatives (**27**–**30**) were also prepared to determine the effect of this modification on antiviral activity. Propane-2,2-diyl derivatives **27** and **28** were easily prepared by treatment of chloropurine derivatives **22** and **17**, respectively, with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid. The same reaction of **22** and **17** with cyclohexanone under *p*-toluenesulfonic acid catalysis afforded cyclohexane-1,1-diyl derivatives **29** and **30**, respectively (Scheme 4).



(i) 2,2-dimethoxypropane/TsOH, r.t., 83% of **27**, 85% of **28**;
(ii) cyclohexanone/TsOH/1,4-dioxane, r.t., 79% of **29**, 83% of **30**

SCHEME 4

The structures of the prepared compounds were confirmed by NMR spectroscopy. Complete assignment of all ^{1}H and ^{13}C resonances is based on combination of ^{1}H, ^{13}C APT, H,H-COSY, H,C-HSQC, and H,C-HMBC experiments.

In conclusion, novel racemic carbocyclic nucleoside analogues of 6-chloropurine, adenine, and 6-(cyclopropylamino)purine derived from bicyclo[2.2.2]octane-2,2-dimethanol and their *O*,*O*′-propane-2,2-diyl and *O*,*O*′-cyclohexane-1,1-diyl derivatives were prepared. The target compounds were tested for the activity against *Coxsackie* virus (CVB3). Preliminary data showed that the 6-chloropurine analogues exhibit some activity. The antiviral activity will be discussed in detail in a separate paper.

EXPERIMENTAL

Melting points were determined on a Büchi melting point B-540 apparatus. NMR spectra (δ, ppm; *J*, Hz) were measured on Bruker Avance-500 instruments (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) in hexadeuterated dimethyl sulfoxide and the chemical shifts were referenced to the solvent signal (δ 2.50 and 39.70, respectively). Mass spectra were measured on an LTQ Orbitrap XL (Thermo Fischer Scientific) using electrospray ionization (ESI) and a GCT Premier (Waters) using EI. The elemental analyses were obtained on a Perkin–Elmer CHN Analyzer 2400, Series II Sys (Perkin–Elmer). Column chromatography and thin-layer chromatography (TLC) were performed using Silica gel 60 (Fluka) and Silufol Silica gel 60 F_{254} foils (Merck), respectively. Solvents were evaporated at 2 kPa and bath temperature 30–60 °C. The compounds were dried at 13 Pa and 50 °C.

(1*R**,4*R**)-Bicyclo[2.2.2]oct-5-ene-2,2-dimethanol (**6**)

A solution of bicyclo[2.2.2]oct-5-ene-2-carbaldehyde[7] (**5**; a mixture of *endo* and *exo* isomers, 43.58 g, 0.32 mol) in tetrahydrofuran (90 ml) was added to a stirred cool (0 °C) mixture of 37% aqueous formaldehyde (100 ml) and 25% aqueous sodium hydroxide (60 ml). The mixture was then stirred at 55 °C for 90 min, a formaldehyde solution (20 ml) and NaOH solution (10 ml) were added. The additions were repeated after 90 min. Stirring was continued for 90 min, the mixture was cooled and extracted with 4-methylpentan-2-one (2 × 200 ml). The combined extracts were dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ether afforded 16.61 g (31%) of compound **6**, m.p. 129–131 °C. Chromatography of mother liquors on silica gel (800 g) in ethyl acetate–toluene (4:1) and subsequent crystallization from ether gave another 11.7 g (22%) of the same compound. For $C_{10}H_{16}O_2$ (168.24) calculated: 71.39% C, 9.59% H; found: 71.51% C, 9.48% H. ESI MS, *m/z* (%): 289.3 (19), 288.3 (100), 191.1 (73) [M + Na], 169 (5) [M + H]. ^{1}H NMR: 0.85 dd, 1 H, J_{gem} = 12.8, *J*(3a,4) = 2.7 (H-3a); 0.89 dt, 1 H, J_{gem} = 12.9, *J*(3b,4) = *J*(3b,8a) = 2.9 (H-3b); 0.96 dddd, 1 H, J_{gem} = 12.7, *J*(7a,8a) = 12.0, *J*(7a,8b) = 5.6, *J*(7a,1) = 2.8 (H-7a); 1.15 tq, 1 H, J_{gem} = *J*(8a,7a) = 12.1, *J*(8a,7b) = *J*(8a,4) = *J*(8a,3b) = 3.3 (H-8a); 1.36 dddd, 1 H, J_{gem} = 12.3, *J*(8b,7b) = 9.6, *J*(8b,7a) = 5.6, *J*(8b,4) = 2.0 (H-8b); 1.77 ddt, 1 H, J_{gem} = 12.8, *J*(7b,8b) = 9.6, *J*(7b,8a) = *J*(7b,1) = 3.0 (H-7b); 2.39 m, 1 H (H-1); 2.43 m, 1 H (H-4); 3.01 dd, 1 H, J_{gem} = 10.1, *J*(CH_2,OH) = 5.2 and 3.18 dd, 1 H, J_{gem} = 10.1, *J*(CH_2,OH) = 5.5 and 3.29 dd, 1 H, J_{gem} =

10.5, $J(CH_2,OH)$ = 5.5 and 3.50 dd, 1 H, J_{gem} = 10.5, $J(CH_2,OH)$ = 4.9 (CH_2O); 4.28 t, 1 H, $J(OH,CH_2)$ = 5.3 and 4.37 t, 1 H, $J(OH,CH_2)$ = 5.2 (OH); 6.16 ddd, 1 H, $J(5,6)$ = 8.1, $J(5,4)$ = 6.4, $J(5,1)$ = 1.3 (H-5); 6.23 ddd, 1 H, $J(6,5)$ = 8.1, $J(6,1)$ = 6.6, $J(6,4)$ = 1.3 (H-6). ^{13}C NMR: 21.06 (C-7); 24.25 (C-8); 29.76 (C-4); 31.89 (C-1); 34.00 (C-3); 43.47 (C-2); 64.90 and 65.89 (CH_2O); 132.98 (C-5); 135.12 (C-6).

(1*R**,4*R**)-Bicyclo[2.2.2]oct-5-ene-2,2-dimethanediyl Dibenzoate (**7**)

Benzoyl chloride (19.7 ml, 170 mmol) was added at 0 °C to a stirred solution of alcohol **6** (11.78 g, 70 mmol) in pyridine (100 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 aqueous phase), and 10% sodium hydrogencarbonate solution (3 × 300 ml), then dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethanol afforded 24.04 g (91%) of benzoate **7**, m.p. 111–112 °C. For $C_{24}H_{24}O_4$ (376.46) calculated: 76.57% C, 6.43% H; found: 76.59% C, 6.47% H. ESI MS, *m/z* (%): 400.1 (25) [M + Na + H], 399.1 (100) [M + Na], 376.8 (30) [M + H]. ^{1}H NMR: 1.09–1.27 m, 3 H (H-3a, H-7a and H-8a); 1.33 dd, 1 H, J_{gem} = 13.2, $J(3b,4)$ = 2.4 (H-3b); 1.53 m, 1 H (H-8b); 1.84 m, 1 H (H-7b); 2.58 m, 1 H (H-4); 2.73 m, 1 H (H-1); 4.06 s, 2 H, 4.30 d, 1 H and 4.51 d, 1 H, J_{gem} = 11.3 (CH_2O); 6.30–6.37 m, 2 H (H-5 and H-6); 7.43–7.50 m, 4 H (H-3′); 7.60–7.65 m, 2 H (H-4′); 7.89–7.97 m, 4 H (H-2′). ^{13}C NMR: 20.90 (C-7); 23.61 (C-8); 29.34 (C-4); 32.46 (C-1); 33.83 (C-3); 41.11 (C-2); 67.50 and 68.53 (CH_2O); 128.95 and 129.00 (C-3′); 129.38 and 129.40 (C-2′); 129.78 and 129.80 (C-1′); 133.57 and 133.62 (C-4′); 133.88 (C-6); 134.11 (C-5); 165.77 and 165.81 (C=O).

(1*R**,4*S**,6*S**)-6-Hydroxybicyclo[2.2.2]octane-2,2-dimethanediyl Dibenzoate (**8**) and (1*R**,4*R**,5*S**)-5-Hydroxybicyclo[2.2.2]octane-2,2-dimethanediyl Dibenzoate (**9**)

A 1 M solution of borane in tetrahydrofuran (20 ml) was added dropwise under argon to a stirred solution of bicycloalkene **7** (11.29 g, 30 mmol) in tetrahydrofuran (20 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 and then a suspension of sodium perborate tetrahydrate (12.3 g, 80 mmol) in water (45 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, washed with water (100 ml), dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel (1 kg) in toluene–ethyl acetate (21:4).

8: Yield 4.0 g (34%). M.p. 93.5–95.5 °C (ethanol). For $C_{24}H_{26}O_5$ (394.47) calculated: 73.08% C, 6.64% H; found: 72.93% C, 6.72% H. ESI MS, *m/z* (%): 418.2 (28) [M + Na + H], 417.2 (100) [M + Na]. ^{1}H NMR: 1.21 dt, 1 H, J_{gem} = 13.6, $J(3a,4)$ = $J(3a,5b)$ = 1.6 (H-3a); 1.24–1.31 m, 2 H (H-3b and H-5a); 1.41–1.55 m, 3 H (H-7a and H-8); 1.67 m, 1 H (H-4); 1.85 q, 1 H, $J(1,6)$ = $J(1,7)$ = 2.8 (H-1); 1.93–2.03 m, 2 H (H-5b and H-7b); 4.11 m, 1 H (H-6); 4.26 d, 1 H, J_{gem} = 11.3, 4.34 d, 1 H, J_{gem} = 11.2, 4.40 d, 1 H, J_{gem} = 11.3 and 4.46 d, 1 H, J_{gem} = 11.2 (CH_2O); 4.59 d, 1 H, $J(OH,6)$ = 3.6 (OH); 7.43–7.48 m, 4 H (H-3′); 7.60–7.64 m, 2 H (H-4′); 7.90 m, 2 H and 7.93 m, 2 H (H-2′). ^{13}C NMR: 13.88 (C-7); 24.68 (C-8); 25.02 (C-4); 32.58 (C-3); 33.87 (C-1); 36.59 (C-5); 37.93 (C-2); 63.18 (C-6); 67.22 and 67.87 (CH_2O); 128.92 and 128.94 (C-3′); 129.30 and 129.39 (C-2′); 129.80 and 129.82 (C-1′); 133.57 (C-4′); 165.78 and 165.80 (COO).

9: Yield 5.5 g (46%) of thick sirup. For $C_{24}H_{26}O_5$ (394.47) calculated: 73.08% C, 6.64% H; found: 72.99% C, 6.78% H. ESI MS, *m/z* (%): 418.2 (25) [M + Na + H], 417.2 (100) [M + Na]. ^{1}H NMR: 1.23 ddd, 1 H, J_{gem} = 14.2, *J*(6a,5) = 3.8, *J*(6a,1) = 2.8 (H-6a); 1.29 dt, 1 H, J_{gem} = 14.1, *J*(3a,4) = *J*(3a,8b) = 2.7 (H-3a); 1.34 m, 1 H (H-8a); 1.39 dd, 1 H, J_{gem} = 14.2, *J*(3b,4) = 3.6 (H-3b); 1.47 m, 1 H (H-7a); 1.59 sextet, 1 H, *J*(4,3) = *J*(4,5) = *J*(4,8) = 3.1 (H-4); 1.71 m, 1 H (H-7b); 1.82 p, 1 H, *J*(1,6) = *J*(1,7) = 3.0 (H-1); 1.91 m, 1 H (H-8b); 2.18 ddt, 1 H, J_{gem} = 14.3, *J*(6b,5) = 9.6, *J*(6b,1) = *J*(6b,7b) = 3.3 (H-6b); 3.84 m, 1 H (H-5); 4.20 d, 1 H, J_{gem} = 11.2, 4.30 d, 1 H, J_{gem} = 11.2, 4.33 d, 1 H, J_{gem} = 11.2 and 4.44 d, 1 H, J_{gem} = 11.2 (CH_2O); 4.63 d, 1 H, *J*(OH,5) = 3.6 (OH); 7.43–7.48 m, 4 H (H-3′); 7.62 m, 2 H (H-4′); 7.91 m, 4 H (H-2′). ^{13}C NMR: 17.82 (C-8); 21.90 (C-7); 27.62 (C-1); 31.41 (C-3); 31.81 (C-4); 34.27 (C-6); 37.28 (C-2); 66.65 (C-5); 67.69 (CH_2O); 128.97 (C-3′); 129.36 (C-2′); 129.80 (C-1′); 133.58 (C-4′); 165.82 (COO).

(1*R**,4*S**)-6-Oxobicyclo[2.2.2]octane-2,2-dimethanediyl Dibenzoate (**10**) and
(1*R**,4*R**)-5-Oxobicyclo[2.2.2]octane-2,2-dimethanediyl Dibenzoate (**11**)

A solution of alcohol **8** or **9** (3.94 g, 10 mmol) in dichloromethane (30 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 mixure 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 (250 g) in hexane–ethyl acetate (19:5) and crystallized from ethanol.

10: Yield 3.66 g (93%). M.p. 100–102 °C. For $C_{24}H_{24}O_5$ (392.46) calculated: 73.45% C, 6.16% H; found: 73.47% C, 6.21% H. ESI MS, *m/z* (%): 416.2 (22) [M + Na + H], 415.2 (100) [M + Na], 392.9 (19) [M + H]. ^{1}H NMR: 1.52 m, 1 H (H-3a); 1.60–1.73 m, 4 H (H-3b, H-7a and H-8); 2.10 m, 1 H (H-7b); 2.20 m, 1 H (H-4); 2.23–2.37 m, 2 H (H-5); 2.42 m, 1 H (H-1); 4.10 d, 1 H, J_{gem} = 11.3, 4.18 d, 1 H, J_{gem} = 11.3, 4.41 d, 1 H, J_{gem} = 11.6 and 4.49 d, 1 H, J_{gem} = 11.6 (CH_2O); 7.46–7.52 m, 4 H (H-3′); 7.62–7.68 m, 2 H (H-4′); 7.91 m, 2 H and 7.95 m, 2 H (H-2′). ^{13}C NMR: 18.49 (C-7); 23.10 (C-8); 27.60 (C-4); 32.44 (C-3); 38.60 (C-2); 43.30 (C-5); 45.92 (C-1); 66.03 and 68.73 (CH_2O); 128.98 and 129.06 (C-3′); 129.40 and 129.44 (C-2′); 129.56 and 129.58 (C-1′); 133.70 and 133.75 (C-4′); 165.67 and 165.74 (COO); 214.23 (C-6).

11: Yield 3.71 g (94.5%). M.p. 90–92 °C. For $C_{24}H_{24}O_5$ (392.46) calculated: 73.45% C, 6.16% H; found: 73.26% C, 6.15% H. ESI MS, *m/z* (%): 416.2 (23) [M + Na + H], 415.2 (100) [M + Na]. ^{1}H NMR: 1.59 m, 1 H (H-7a); 1.64 dt, 1 H, J_{gem} = 14.5, *J*(3a,4) = *J*(3a,8a) = 2.7 (H-3a); 1.74 m, 1 H (H-8a); 1.88 m, 1 H (H-8b); 1.97 m, 1 H (H-7b); 2.21 m, 1 H (H-4); 2.23 dd, 1 H, J_{gem} = 19.3, *J*(6a,1) = 2.9 (H-6a); 2.37 p, 1 H, *J*(1,7) = *J*(1,6) = 2.9 (H-1); 2.57 dt, 1 H, J_{gem} = 19.4, *J*(6b,1) = *J*(6b,7b) = 3.0 (H-6b); 4.25 d, 1 H, J_{gem} = 11.5, 4.37 d, 1 H, J_{gem} = 11.5, 4.41 d, 1 H, J_{gem} = 11.3 and 4.53 d, 1 H, J_{gem} = 11.3 (CH_2O); 7.44–7.49 m, 4 H (H-3′); 7.60–7.66 m, 2 H (H-4′); 7.91 m, 2 H and 7.94 m, 2 H (H-2′). ^{13}C NMR: 21.04 (C-7); 21.73 (C-8); 30.44 (C-3); 30.72 (C-1); 37.93 (C-2); 41.33 (C-6); 42.10 (C-4); 66.72 and 67.39 (CH_2O); 128.95 and 128.98 (C-3′); 129.43 (C-2′); 129.65 and 129.69 (C-1′); 133.66 (C-4′); 165.73 and 165.76 (COO); 215.10 (C-5).

(1*R**,4*S**,6*R**)-6-Hydroxybicyclo[2.2.2]octane-2,2-dimethanediyl Dibenzoate (**12**) and (1*R**,4*R**,5*R**)-5-Hydroxybicyclo[2.2.2]octane-2,2-dimethanediyl Dibenzoate (**13**)

Sodium borohydride (416 mg, 11 mmol) was added to a stirred solution of ketone **10** or **11** (3.92 g, 10 mmol) in methanol (40 ml) and tetrahydrofuran (15 ml) at 0 °C. The mixture was stirred at 0 °C for 40 min and then a saturated aqueous solution of ammonium chloride (50 ml) was slowly added. The mixture was extracted with ethyl acetate (200 ml), the ethyl acetate solution was dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (400 g) in toluene–ethyl acetate (21:4). In the case of compound **11**, 1.60 g (40.5%) of *exo*-derivative **9** was obtained. Compound **12** was crystallized from ethanol and compound **13** from ether–hexane mixture.

12: Yield 3.75 g (95%). M.p. 123–124 °C. For $C_{24}H_{26}O_5$ (394.47) calculated: 73.08% C, 6.64% H; found: 73.23% C, 6.68% H. ESI MS, *m/z* (%): 417.1 (100) [M + Na], 418 (26) [M + H + Na]. ^{1}H NMR: 1.24 dt, 1 H, J_{gem} = 13.7, *J*(3a,4) = *J*(3a,5b) = 2.7 (H-3a); 1.30–1.45 m, 4 H (H-5a, H-7a and H-8); 1.55 dm, 1 H, J_{gem} = 13.4 (H-3b); 1.72 m, 1 H (H-4); 1.80 m, 1 H (H-7b); 1.86 m, 1 H (H-1); 2.01 m, 1 H (H-5b); 3.93 m, 1 H (H-6); 4.25 d, 1 H, J_{gem} = 11.2, 4.42 d, 1 H, J_{gem} = 11.2, 4.47 d, 1 H, J_{gem} = 11.1, 4.80 d, 1 H, J_{gem} = 11.1 (CH_2O); 4.95 d, 1 H, *J*(OH,6) = 3.0 (OH); 7.46–7.52 m, 4 H (H-3′); 7.60–7.66 m, 2 H (H-4′); 7.91–7.95 m, 4 H (H-2′). ^{13}C NMR: 20.72 (C-7); 23.41 (C-8); 24.94 (C-4); 34.20 (C-3); 34.23 (C-1); 36.88 (C-5); 37.70 (C-2); 67.04 and 68.98 (CH_2O); 69.10 (C-6); 128.84 and 128.96 (C-3′); 129.26 and 129.30 (C-2′); 129.86 and 130.22 (C-1′); 133.31 and 133.55 (C-4′); 165.69 and 165.94 (C=O).

13: Yield 1.77 g (45%). M.p. 117–119 °C. For $C_{24}H_{26}O_5$ (394.47) calculated: 73.08% C, 6.64% H; found: 72.99% C, 6.61% H. ESI MS, *m/z* (%): 418.2 (20) [M + Na + H], 417.2 (100) [M + Na], 395.0 (10) [M + H]. ^{1}H NMR: 1.11 dt, 1 H, J_{gem} = 13.9, *J*(3a,4) = 3.0, *J*(3a,5) = 1.2 (H-3a); 1.29 m, 1 H (H-7a); 1.44 m, 1 H (H-8a); 1.55–1.60 m, 2 H (H-6a and H-8b); 1.61 m, 1 H (H-4); 1.68–1.74 m, 1 H (H-7b); 1.74 dt, 1 H, J_{gem} = 13.9, *J*(3b,4) = *J*(3b,8) = 2.7 (H-3b); 1.82 m, 1 H (H-6b); 1.83 m, 1 H (H-1); 3.79 m, 1 H (H-5); 4.27 d, 1 H, J_{gem} = 11.2, 4.41 d, 1 H, J_{gem} = 11.2, 4.43 d, 1 H, J_{gem} = 11.1 and 4.49 d, 1 H, J_{gem} = 11.1 (CH_2O); 4.72 d, 1 H, *J*(OH,5) = 3.1 (OH); 7.43–7.47 m, 4 H (H-3′); 7.59–7.63 m, 2 H (H-4′); 7.89 m, 2 H and 7.92 m, 2 H (H-2′). ^{13}C NMR: 20.97 (C-7); 22.38 (C-8); 26.42 (C-3); 27.17 (C-1); 31.51 (C-4); 33.93 (C-6); 37.41 (C-2); 66.49 (C-5); 67.37 and 67.84 (CH_2O); 128.92 and 128.93 (C-3′); 129.30 and 129.32 (C-2′); 129.83 and 129.87 (C-1′); 133.46 and 133.53 (C-4′); 165.83 and 165.84 (COO).

(1*R**,4*S**,6*S**)-6-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanediyl Dibenzoate (**14**) and Tricyclo[3.2.1.$0^{2,7}$]octane-3,3-dimethanediyl Dibenzoate (**15**)

A solution of diisopropyl azodicarboxylate (0.59 ml, 3 mmol) in tetrahydrofuran (5 ml) was added dropwise to a stirred suspension of compound **12** (788 mg, 2 mmol), 6-chloropurine (464 mg, 3 mmol), and triphenylphosphine (787 mg, 3 mmol) in tetrahydrofuran (15 ml). The mixture was then heated to reflux for 5 h and evaporated. Chromatography on silica gel (160 g) in toluene afforded 643 mg (85%) of tricyclic compound **15**. Subsequent elution with toluene–ethyl acetate gave 14 mg (1.3%) of compound **14**.

14: M.p. 211–212 °C. ESI MS, *m/z* (%): 555.2/553.2 (25/71) [M + Na], 533.1/531.1 (33/100) [M + H]. HR MS (ESI) calculated: 531.1794; found: 531.1796. ^{1}H NMR: 1.38 m, 1 H (H-7a); 1.46–1.50 m, 2 H (H-3); 1.60–1.68 m, 2 H (H-8a and H-7b); 1.92–2.00 m, 2 H (H-4 and H-8b); 2.29 m, 1 H (H-1); 2.35 m, 2 H (H-5); 4.35 d, 1 H, 4.54 d, 1 H, 4.58 d, 1 H and 4.66 d, 1 H, J_{gem} = 11.6 (CH_2O); 5.33 m, 1 H (H-6); 7.39 m, 2 H and 7.47 m, 2 H (H-3″); 7.58 m, 1 H

and 7.64 m, 1 H (H-4″); 7.84 m, 2 H and 8.03 m, 2 H (H-2″); 8.26 s, 1 H (H-2′); 9.10 s, 1 H (H-8′). ^{13}C NMR: 15.37 (C-7); 23.67 (C-8); 24.64 (C-4); 29.28 (C-5); 32.04 (C-1); 32.48 (C-3); 38.48 (C-2); 50.47 (C-6); 67.11 and 68.24 (CH_2O); 128.81 and 128.89 (C-3″); 129.35 and 129.64 (C-2″); 130.02 (C-1″); 131.62 (C-5′); 133.50 and 133.58 (C-4″); 146.52 (C-8′); 149.22 (C-6′); 151.12 (C-2′); 152.38 (C-4′); 165.80 and 165.98 (C=O).

15: M.p. 94–96 °C. For $C_{24}H_{24}O_4$ (376.46) calculated: 76.57% C, 6.43% H; found: 76.38% C, 6.41% H. ESI MS, *m/z* (%): 400.2 (24) [M + Na + 1], 399.1 (100) [M + Na]. ^{1}H NMR: 0.92 t, 1 H, *J*(2,1) = *J*(2,7) = 7.8 (H-2); 1.36–1.40 m, 4 H (H-1, H-4 and H-7); 1.58–1.66 m, 4 H (H-6 and H-8); 1.90 m, 1 H (H-5); 4.20–4.26 m, 4 H (CH_2O); 7.50 m, 4 H (H-3′); 7.64 m, 2 H (H-4′); 7.97 m, 4 H (H-2′). ^{13}C NMR: 15.52 (C-1 and C-7); 16.32 (C-2); 28.48 (C-5); 30.36 (C-6 and C-8); 33.58 (C-3); 35.71 (C-4); 69.48 (CH_2O); 128.99 (C-3′); 129.37 (C-2′); 129.83 (C-1′); 133.58 (C-4′); 165.87 (COO).

[(1*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-diyl]dimethanediyl Dibenzoate (**16**)

The reaction of compound **13** (788 mg, 2 mmol) with 6-chloro-9*H*-purine was performed as the reaction with alcohol **12**. Chromatography on silica gel (160 g) in ethyl acetate–hexane (1:1) and subsequent crystallization from ethanol afforded 482 mg (45%) of compound **16**, m.p. 147.5–149.5 °C. For $C_{29}H_{27}ClN_4O_4$ (531.02) calculated: 65.59% C, 5.13% H, 6.68% Cl, 10.55% N; found: 65.71% C, 5.10% H, 6.49% Cl, 10.36% N. ESI MS, *m/z* (%): 555.1/553.2 (22/61) [M + Na], 533.0/531.0 (34/100) [M + H]. ^{1}H NMR: 1.47–1.52 m, 2 H (H-8); 1.57 dd, 1 H, J_{gem} = 14.2, *J*(3a,4) = 3.4 (H-3a); 1.71 dt, 1 H, J_{gem} = 14.1, *J*(3b,4) = *J*(3b,8) = 2.7 (H-3b); 1.85–1.97 m, 2 H (H-7); 2.02 m, 1 H (H-4); 2.13 m, 1 H (H-1); 2.31 ddd, 1 H, J_{gem} = 14.9, *J*(6a,5) = 6.2, *J*(6a,1) = 2.7 (H-6a); 2.59 m, 1 H (H-6b); 4.37–4.56 m, 4 H (CH_2O); 5.08 m, 1 H (H-5); 7.45–7.49 m, 4 H (H-3″); 7.61–7.65 m, 2 H (H-4″); 7.93–7.96 m, 4 H (H-2″); 8.77 s, 1 H (H-2′); 9.00 s, 1 H (H-8′). ^{13}C NMR: 18.87 (C-8); 20.99 (C-7); 27.39 (C-1); 27.64 (C-6); 30.24 (C-4); 32.37 (C-3); 37.71 (C-2); 53.41 (C-5); 67.41 and 67.54 (CH_2O); 128.97 and 128.98 (C-3″); 129.40 (C-2″); 129.75 and 129.77 (C-1″); 131.56 (C-5′); 133.62 (C-4″); 146.25 (C-8′); 149.31 (C-6′); 151.51 (C-2′); 152.40 (C-4′); 165.80 and 165.85 (C=O).

(1*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanol (**17**)

A 1 M solution of DIBAL-H in dichloromethane (6 ml) was added dropwise to a solution of compound **16** (531 mg, 1 mmol) in dichloromethane (20 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 (0.5 ml) and methanol (80 ml) were added, and the mixture was filtered with a Celite pad. The filter was washed with methanol and the filtrate was evaporated. Chromatography of the residue on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (45:3:1:1) and subsequent crystallization from ethanol gave 149 mg (46%) of compound **17**, m.p. 236–238 °C. For $C_{15}H_{19}ClN_4O_2$ (322.80) calculated: 55.81% C, 5.93% H, 10.98% Cl, 17.36% N; found: 55.90% C, 5.90% H, 10.97% Cl, 17.21% N. ESI MS, *m/z* (%): 347.1/345.1 (16/52) [M + Na], 325.0/323.0 (31/100) [M + 1]. ^{1}H NMR: 1.13 dd, 1 H, J_{gem} = 13.9, *J*(3a,4) = 3.3 (H-3a); 1.28–1.43 m, 3 H (H-3b and H-8); 1.70–1.80 m, 3 H (H-1 and H-7); 1.83 m, 1 H (H-4); 2.10 ddd, 1 H, J_{gem} = 14.5, *J*(6a,5) = 6.3, *J*(6a,1) = 2.2 (H-6a); 2.47 m, 1 H (H-6b); 3.36–3.50 m, 4 H (CH_2O); 4.51 t, 1 H, *J*(OH,CH_2) = 5.2 (OH); 4.57 t, 1 H, *J*(OH,CH_2) = 5.1 (OH); 4.89 m, 1 H (H-5); 8.75 s, 1 H (H-2′); 8.97 s, 1 H (H-8′). ^{13}C NMR: 19.47 (C-8); 21.31 (C-7); 26.69

(C-1); 28.04 (C-6); 30.87 (C-4); 32.55 (C-3); 39.41 (C-2); 53.97 (C-5); 64.80 and 64.97 (CH_2O); 131.49 (C-5′); 146.18 (C-8′); 149.22 (C-6′); 151.44 (C-2′); 152.35 (C-4′).

(1*R**,4*S**,6*S**)-6-Aminobicyclo[2.2.2]octane-2,2-dimethanol (**18**) and (1*R**,4*R**,5*S**)-5-Aminobicyclo[2.2.2]octane-2,2-dimethanol (**19**) – a Mixture

A 1 M solution of borane in tetrahydrofuran (10 ml) was added dropwise under argon to a stirred solution of bicycloalkene **7** (9.41 g, 25 mmol) in diglyme (15 ml) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 20 min and at room temperature for 3 h. The mixture was cooled to 0 °C, excess of borane was decomposed by addition of water and tetrahydrofuran was evaporated (40 °C, water pump). A solution of hydroxylamine-*O*-sulfonic acid (3.17 g, 28 mmol) in diglyme (14 ml) was then added, the mixture was heated at 100 °C for 3 h and diglyme was evaporated (bath temperature 60 °C, 10 mbar). To a mixture of the residue, ethyl acetate (80 ml) and water (50 ml), solid potassium carbonate was added stepwise under stirring until the alkaline reaction of the water layer persists. The water phase was separated and washed with ethyl acetate (50 ml). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue was dissolved under stirring in 0.1 M methanolic sodium methoxide, the solution was kept at room temperature overnight and then neutralized with concentrated hydrochloric acid. Excess acid was neutralized with several drops of aqueous ammonia and the mixture was applied onto column with Dowex 50 (H^+, 100 ml). The column was washed with water (400 ml), methanol (400 ml) and then eluted with methanol–concentrated aqueous ammonia (4:1). The eluate was evaporated and the residue was chromatographed on a silica gel column (150 g) in 1,4-dioxane–concentrated aqueous ammonia (22:3) affording 1.44 g (31%) of a mixture of amines **18** an **19** as thick syrup. For $C_{10}H_{19}NO_2$ (185.27) calculated: 64.83% C, 10.34% H, 7.56% N; found: 64.51% C, 10.33% H, 7.49% N. HR MS (EI) for $C_{10}H_{19}NO_2$ [M] calculated: 185.1416; found: 185.1419.

(1*R**,4*S**,6*S**)-6-[(5-Amino-6-chloropyrimidin-4-yl)amino]bicyclo[2.2.2]octane-2,2-dimethanol (**20**) and (1*R**,4*R**,5*S**)-5-[(5-Amino-6-chloropyrimidin-4-yl)amino]-bicyclo[2.2.2]octane-2,2-dimethanol (**21**)

A mixture of amines **18** and **19** (1.48 g, 8 mmol), 4,6-dichloropyrimidin-5-amine (1.31 g, 8 mmol), and triethylamine (2.4 ml) in ethanol (24 ml) was heated in a pressure vessel at 100 °C for 7 days and, after cooling, evaporated. Crystallization of the residue from methanol afforded 980 mg of **21**. Chromatography of the mother liquors on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (45:3:1:1) gave 304 mg of **20** and 150 mg of **21**, both after crystallization from methanol.

20: Yield 304 mg (12%). M.p. 201–202 °C. For $C_{14}H_{21}ClN_4O_2$ (312.80) calculated: 53.76% C, 6.77% H, 11.33% Cl, 17.91% N; found: 53.69% C, 6.78% H, 11.33% Cl, 17.70% N. ESI MS, *m/z* (%): 337.1/335.1 (35/100) [M + Na], 315.1/313.1 (28/86) [M + 1]. ^{1}H NMR: 0.97 ddd, 1 H, J_{gem} = 13.7, *J*(3a,4) = 3.6, *J*(3a,5a) = 2.6 (H-3a); 1.07 dt, 1 H, J_{gem} = 13.7, *J*(3b,4) = *J*(3b,8b) = 2.4 (H-3b); 1.32–1.40 m, 2 H (H-5a and H-8a); 1.49–1.56 m, 2 H (H-7a and H-8b); 1.63–1.71 m, 3 H (H-1, H-4 and H-7b); 2.00 m, 1 H (H-5b); 3.32 dd, 1 H, J_{gem} = 10.5, *J*(CH_2,OH) = 4.4, 3.46 dd, 1 H, J_{gem} = 10.5, *J*(CH_2,OH) = 4.9, 3.51 dd, 1 H, J_{gem} = 10.7, *J*(CH_2,OH) = 4.8 and 3.58 dd, 1 H, J_{gem} = 10.7, *J*(CH_2,OH) = 6.2 (CH_2O); 4.34–4.41 m, 3 H (H-6 and OH); 5.19 bs, 2 H (NH_2); 6.56 d, 1 H, *J*(NH,6) = 6.4 (NH); 7.68 s, 1 H (H-2′). ^{13}C NMR: 15.54

(C-7); 25.38 (C-4); 25.44 (C-8); 30.35 (C-1); 32.72 (C-3); 33.59 (C-5); 40.33 (C-2); 45.46 (C-6); 64.50 and 64.52 (CH_2O); 123.86 (C-5′); 136.67 (C-6′); 145.68 (C-2′); 151.58 (C-4′).

21: Yield 1.03 g (41%). M.p. 253–255 °C (decomp.). For $C_{14}H_{21}ClN_4O_2$ (312.80) calculated: 53.76% C, 6.77% H, 11.33% Cl, 17.91% N; found: 53.49% C, 6.73% H, 11.23% Cl, 17.64% N. ESI MS, *m/z* (%): 337.1/335.1 (13/39) [M + Na], 315.1/313.1 (32/100) [M + 1]. ^{1}H NMR: 1.00 dd, 1 H, J_{gem} = 13.8, *J*(3a,4) = 3.1 (H-3a); 1.12 dt, 1 H, J_{gem} = 13.8, *J*(3b,4) = *J*(3b,8b) = 2.9 (H-3b); 1.20–1.28 m, 2 H (H-6a and H-8a); 1.41 m, 1 H (H-7a); 1.61 m, 1 H (H-1); 1.68–1.74 m, 3 H (H-4, H-7b and H-8b); 2.24 m, 1 H (H-6b); 3.33–3.44 m, 4 H (CH_2O); 4.10 m, 1 H (H-5); 4.42 t, 1 H, *J*(OH,CH_2) = 5.2 (OH); 4.45 t, 1 H, *J*(OH,CH_2) = 5.2 (OH); 5.18 bs, 2 H (NH_2); 6.46 d, 1 H, *J*(NH,5) = 6.7 (NH); 7.69 s, 1 H (H-2′). ^{13}C NMR: 19.37 (C-8); 22.08 (C-7); 26.62 (C-1); 28.95 (C-4); 31.06 (C-6); 32.52 (C-3); 39.28 (C-2); 48.90 (C-5); 65.01 and 65.19 (CH_2O); 123.75 (C-5′); 136.80 (C-6′); 145.82 (C-2′); 151.64 (C-4′).

(1*R**,4*S**,6*S**)-6-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanol (**22**) and
(1*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanol (**17**)

Concentrated hydrochloric acid (2 ml) was added to a stirred mixture of compound **20** or **21** (782 mg, 2.5 mmol) and triethyl orthoformate (40 ml), the mixture was stirred at room temperature for 5 days and then evaporated. The residue was dissolved in a mixture of tetrahydrofuran (15 ml) and 0.5 M hydrochloric acid (15 ml), the mixture was left at room temperature for 4 h and then neutralized with solid sodium hydrogencarbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (4 × 20 ml). The combined organic layers were dried over anhydrous sodium sulfate, evaporated and the residue was crystallized from ethanol.

17: Yield 617 mg (76%). This compound was identical with that prepared by reductive debenzoylation of **16**.

22: Yield 663 mg (82%). M.p. 195.5–197 °C. For $C_{15}H_{19}ClN_4O_2$ (322.80) calculated: 55.81% C, 5.93% H, 10.98% Cl, 17.36% N; found: 55.77% C, 6.05% H, 11.05% Cl, 17.19% N. ESI MS, *m/z* (%): 347.1/345.0 (35/100) [M + Na], 325.0/322.9 (10/33) [M + H]. ^{1}H NMR: 0.98 dm, 1 H, J_{gem} = 13.7 (H-3a); 1.22 m, 1 H (H-7a); 1.30 dt, 1 H, J_{gem} = 13.7, *J*(3b,4) = *J*(3b,8b) = 2.6 (H-3b); 1.44 m, 1 H (H-8a); 1.60 m, 1 H (H-7b); 1.79–1.82 m, 3 H (H-1, H-4 and H-8a); 2.16–2.27 m, 2 H (H-5); 3.34 m, 1 H, 3.49 dd, 1 H, J_{gem} = 10.7, *J*(CH_2,OH) = 4.8, 3.61 dd, 1 H, J_{gem} = 10.6, *J*(CH_2,OH) = 5.0 and 3.69 dd, 1 H, J_{gem} = 10.6, *J*(CH_2,OH) = 4.8 (CH_2O); 4.47 t, 1 H, *J*(OH,CH_2) = 5.1 (OH); 4.58 t, 1 H, *J*(OH,CH_2) = 5.1 (OH); 5.24 m, 1 H (H-6); 8.77 s, 1 H (H-2′); 8.97 s, 1 H (H-8′). ^{13}C NMR: 15.60 (C-7); 24.22 (C-8); 25.10 (C-4); 30.15 (C-5); 32.51 (C-3); 32.52 (C-1); 40.36 (C-2); 51.14 (C-6); 64.51 and 64.63 (CH_2O); 131.47 (C-5′); 146.58 (C-8′); 149.18 (C-6′); 151.49 (C-2′); 152.42 (C-4′).

(1*R**,4*S**,6*S**)-6-(6-Amino-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanol (**23**) and
(1*R**,4*R**,5*S**)-5-(6-Amino-9*H*-purin-9-yl)bicyclo[2.2.2]octane-2,2-dimethanol (**24**)

A solution of chloropurine derivative **22** or **17** (161 mg, 0.5 mmol) in liquid ammonia (15 ml) was heated in an autoclave at 75 °C for 48 h and then ammonia was evaporated. The residue was crystallized from water.

23: Yield 124 mg (77%). M.p. 239–241 °C. For $C_{15}H_{23}N_5O_3 \cdot H_2O$ (321.38) calculated: 56.06% C, 7.21% H, 21.79% N; found: 56.26% C, 7.17% H, 21.73% N. ESI MS, *m/z* (%): 327.3 (16) [M + Na + H], 326.3 (100) [M + Na], 304.3 (34) [M + H]. ^{1}H NMR: 0.99 m, 1 H (H-3a); 1.22–1.30 m, 2 H (H-3b and H-7a); 1.42 m, 1 H (H-8a); 1.56 m, 1 H (H-7b); 1.72–1.83 m,

3 H (H-1, H-4 and H-8b); 2.08–2.21 m, 2 H (H-5); 3.34 dd, 1 H, J_{gem} = 10.6, J(CH_2,OH) = 5.4, 3.48 dd, 1 H, J_{gem} = 10.6, J(CH_2,OH) = 5.1, 3.61 dd, 1 H, J_{gem} = 10.7, J(CH_2,OH) = 5.0 and 3.68 dd, 1 H, J_{gem} = 10.7, J(CH_2,OH) = 5.6 (CH_2O); 4.46 t, 1 H, J(OH,CH_2) = 5.3 (OH); 4.58 t, 1 H, J(OH,CH_2) = 5.3 (OH); 5.04 m, 1 H (H-6); 7.19 bs, 2 H (NH_2); 8.12 bs, 1 H (H-2′); 8.40 s, 1 H (H-8′). ^{13}C NMR: 15.48 (C-7); 24.51 (C-8); 25.25 (C-4); 30.08 (C-5); 32.53 (C-1); 32.64 (C-3); 40.43 (C-2); 49.62 (C-6); 64.44 and 64.50 (CH_2O); 119.46 (C-5′); 139.81 (C-8′); 149.96 (C-4′); 152.48 (C-2′); 156.18 (C-6′).

24: Yield 130 mg (84%). M.p. 275–278 °C. For $C_{15}H_{21}N_5O_2 \cdot 1/3H_2O$ (309.44) calculated: 58.24% C, 7.06% H, 22.64% N; found: 58.22% C, 7.05% H, 22.51% N. ESI MS, *m/z* (%): 305.3 (17) [M + 2 H], 304.2 (100) [M + H]. ^{1}H NMR: 1.11 dd, 1 H, J_{gem} = 13.9, J(3a,4) = 3.3 (H-3a); 1.30 dt, 1 H, J_{gem} = 13.8, J(3b,4) = J(3b,8) = 2.9 (H-3b); 1.29–1.46 m, 2 H (H-8); 1.66–1.83 m, 4 H (H-1, H-4 and H-7); 2.02 ddd, 1 H, J_{gem} = 14.5, J(6a,5) = 6.4, J(6a,1) = 2.4 (H-6a); 2.41 ddt, 1 H, J_{gem} = 14.5, J(6b,5) = 11.2, J(6b,1) = J(6b,7) = 3.3 (H-6b); 3.39 m, 1 H, 3.42 dd, 1 H, J_{gem} = 10.7, J(CH_2,OH) = 5.5, 3.46 dd, 1 H, J_{gem} = 10.4, J(CH_2,OH) = 4.9 and 3.48 dd, 1 H, J_{gem} = 10.6, J(CH_2,OH) = 5.0 (CH_2O); 4.48 t, 1 H, J(OH,CH_2) = 5.2 (OH); 4.54 t, 1 H, J(OH,CH_2) = 5.2 (OH); 4.73 m, 1 H (H-5); 7.18 bs, 2 H (NH_2); 8.11 s, 1 H (H-2′); 8.39 s, 1 H (H-8′). ^{13}C NMR: 19.44 (C-8); 21.47 (C-7); 26.72 (C-1); 28.18 (C-6); 31.02 (C-4); 32.68 (C-3); 39.42 (C-2); 52.54 (C-5); 64.86 and 65.01 (CH_2O); 119.40 (C-5′); 139.40 (C-8′); 149.93 (C-4′); 152.44 (C-2′); 156.19 (C-6′).

(1*R**,4*S**,6*S**)-6-[6-(Cyclopropylamino)-9*H*-purin-9-yl]bicyclo[2.2.2]octane-2,2-dimethanol (**25**) and (1*R**,4*R**,5*S**)-5-[6-(Cyclopropylamino)-9*H*-purin-9-yl]bicyclo[2.2.2]octane-2,2-dimethanol (**26**)

A solution of chloropurine derivative **22** or **17** (161 mg, 0.5 mmol) in cyclopropylamine (2 ml) was left standing at room temperature overnight and then evaporated. The residue was crystallized from water.

25: Yield 160 mg (93%). M.p. 204–206 °C. For $C_{18}H_{25}N_5O_2$ (343.43) calculated: 62.95% C, 7.34% H, 20.39% N; found: 62.70% C, 7.53% H, 20.28% N. negESI MS, *m/z* (%): 343.0 (17) [M], 342.0 (100) [M – 1]. ESI MS, *m/z* (%): 366.2 (44) [M + Na], 344.2 (100) [M + H]. ^{1}H NMR: 0.60 m, 2 H and 0.71 m, 2 H (CH_2 of cyclopropane); 0.99 dm, 1 H, J_{gem} = 13.6 (H-3a); 1.23 m, 1 H (H-7a); 1.26 dt, 1 H, J_{gem} = 13.7, J(3b,4) = J(3b,8b) = 2.6 (H-3b); 1.42 m, 1 H (H-8a); 1.55 m, 1 H (H-7b); 1.73 m, 1 H (H-1); 1.75–1.82 m, 2 H (H-4 and H-8b); 2.09–2.20 m, 2 H (H-5); 3.00 bs, 1 H (CH of cyclopropane); 3.33 dd, 1 H, J_{gem} = 10.6, J(CH_2,OH) = 5.3, 3.47 dd, 1 H, J_{gem} = 10.6, J(CH_2,OH) = 5.0, 3.61 dd, 1 H, J_{gem} = 10.6, J(CH_2,OH) = 5.0 and 3.68 dd, 1 H, J_{gem} = 10.6, J(CH_2,OH) = 5.5 (CH_2O); 4.47 t, 1 H, J(OH,CH_2) = 5.3 (OH); 4.59 t, 1 H, J(OH,CH_2) = 5.3 (OH); 5.05 m, 1 H (H-6); 7.87 bs, 1 H (NH); 8.23 bs, 1 H (H-2′); 8.40 s, 1 H (H-8′). ^{13}C NMR: 6.61 (CH_2 of cyclopropane); 15.47 (C-7); 23.90 (CH of cyclopropane); 24.51 (C-8); 25.26 (C-4); 30.05 (C-5); 32.53 (C-1); 32.65 (C-3); 40.44 (C-2); 49.61 (C-6); 64.40 and 64.46 (CH_2O); 119.85 (C-5′); 139.64 (C-8′); 149.36 (C-4′); 152.39 (C-2′); 155.74 (C-4′).

26: Yield 145 mg (84%). M.p. 250.5–252.5 °C. For $C_{18}H_{25}N_5O_2$ (343.43) calculated: 62.95% C, 7.34% H, 20.39% N; found: 62.62% C, 7.32% H, 20.11% N. ^{1}H NMR: 0.60 m, 2 H and 0.71 m, 2 H (CH_2 of cyclopropyl); 1.11 dd, 1 H, J_{gem} = 13.9, J(3a,4) = 3.1 (H-3a); 1.26–1.44 m, 3 H (H-3b and H-8); 1.65–1.83 m, 4 H (H-1, H-4 and H-7); 2.02 m, 1 H (H-6a); 2.41 m, 1 H (H-6b); 2.99 bs, 1 H (CH of cyclopropyl); 3.38–3.51 m, 4 H (CH_2O); 4.49 t, 1 H, J(OH,CH_2) = 5.1 (OH); 4.54 t, 1 H, J(OH,CH_2) = 5.2 (OH); 4.75 m, 1 H (H-5); 7.88 bs, 1 H (NH); 8.22 bs, 1 H (H-2′); 8.40 s, 1 H (H-8′). ^{13}C NMR: 6.67 (CH_2 of cyclopropyl); 19.43

(C-8); 21.46 (C-7); 26.71 (C-1); 28.15 (C-6); 31.03 (C-4); 32.68 (C-3); 39.43 (C-2); 52.20 (C-5); 64.78 and 64.93 (CH_2O); 119.79 (C-5′); 139.22 (C-8′); 149.31 (C-4′); 152.34 (C-2′); 155.75 (C-6′).

(1*R**,4*S**,6*S**)-6-(6-Chloro-9*H*-purin-9-yl)-*O*,*O*′-(propane-2,2-diyl)bicyclo[2.2.2]octane-2,2-dimethanol (**27**) and (1*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)-*O*,*O*′-(propane-2,2-diyl)bicyclo[2.2.2]octane-2,2-dimethanol (**28**)

p-Toluenesulfonic acid monohydrate (50 mg) was added to a stirred mixture of 6-chloropurine derivative **22** or **17** (161 mg, 0.5 mmol) and 2,2-dimethoxypropane (5 ml), and the mixture was stirred at room temperature for 5 h. The resulting suspension was diluted with ethyl acetate (15 ml), washed with saturated aqueous sodium hydrogencarbonate, dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from methanol.

27: Yield 151 mg (83%). M.p. 151.5–153 °C. For $C_{18}H_{23}ClN_4O_2$ (362.86) calculated: 59.58% C, 6.39% H, 9.77% Cl, 15.44% N; found: 59.34% C, 6.40% H, 9.80% Cl, 15.30% N. ESI MS, *m/z* (%): 387.2/385.2 (7/22) [M + Na], 365.2/363.1 (33/100) [M + 1]. ^{1}H NMR: 1.30 s, 3 H and 1.33 s, 3 H (CH_3); 1.31–1.54 m, 5 H (H-3, H-7 and H-8a); 1.82 m, 1 H (H-8b); 1.87 m, 1 H (H-4); 1.91 m, 1 H (H-1); 2.20–2.24 m, 2 H (H-5); 3.58 dd, 1 H, J_{gem} = 11.6, $J_{l.r.}$ = 1.1, 3.73 d, 1 H, J_{gem} = 11.6, 3.80 dd, 1 H, J_{gem} = 11.6, $J_{l.r.}$ = 1.0 and 3.93 d, 1 H, J_{gem} = 11.6 (CH_2O); 5.09 m, 1 H (H-6); 8.78 s, 1 H (H-2′); 9.01 s, 1 H (H-8′). ^{13}C NMR: 15.00 (C-7); 23.20 and 24.85 (CH_3); 23.75 (C-8); 25.20 (C-4); 29.89 (C-5); 33.18 (C-1); 33.57 (C-2); 34.06 (C-3); 50.38 (C-6); 67.88 and 68.14 (CH_2O); 97.38 (O-C-O); 131.48 (C-5′); 146.50 (C-8′); 149.25 (C-6′); 151.57 (C-2′); 152.37 (C-4′).

28: Yield 154 mg (85%). M.p. 199–201 °C. For $C_{18}H_{23}ClN_4O_2$ (362.86) calculated: 59.58% C, 6.39% H, 9.77% Cl, 15.44% N; found: 59.41% C, 6.39% H, 9.83% Cl, 15.28% N. ESI MS, *m/z* (%): 365.1/363.1 (31/100) [M + 1]. ^{1}H NMR: 1.33 dd, 1 H, J_{gem} = 14.0, J(3a,4) = 3.3 (H-3a); 1.35 s, 3 H and 1.35 s, 3 H (CH_3); 1.33–1.43 m, 2 H (H-8); 1.47 dt, 1 H, J_{gem} = 14.0, J(3b,4) = J(3b,8b) = 2.9 (H-3b); 1.70–1.81 m, 2 H (H-7); 1.89 m, 1 H (H-4); 1.94 m, 1 H (H-1); 2.18 ddd, 1 H, J_{gem} = 14.7, J(6a,5) = 6.4, J(6a,1) = 2.6 (H-6a); 2.41 ddt, 1 H, J_{gem} = 14.7, J(6b,5) = 11.2, J(6b,1) = J(6b,7) = 3.3 (H-6b); 3.59 d, 1 H, J_{gem} = 11.5, 3.62 d, 1 H, J_{gem} = 11.6, 3.72 d, 1 H, J_{gem} = 11.5 and 3.77 d, 1 H, J_{gem} = 11.6 (CH_2O); 4.89 m, 1 H (H-5); 8.77 s, 1 H (H-2′); 8.98 s, 1 H (H-8′). ^{13}C NMR: 19.08 (C-8); 20.39 (C-7); 23.52 and 24.66 (CH_3); 26.83 (C-6); 27.05 (C-1); 30.87 (C-4); 32.65 (C-2); 33.77 (C-3); 53.57 (C-5); 67.82 and 68.02 (CH_2O); 97.32 (O-C-O); 131.54 (C-5′); 146.25 (C-8′); 149.28 (C-6′); 151.51 (C-2′); 152.36 (C-4′).

(1*R**,4*S**,6*S**)-6-(6-Chloro-9*H*-purin-9-yl)-*O*,*O*′-(cyclohexane-1,1-diyl)bicyclo[2.2.2]octane-2,2-dimethanol (**29**) and (1*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)-*O*,*O*′-(cyclohexane-1,1-diyl)bicyclo[2.2.2]octane-2,2-dimethanol (**30**)

p-Toluenesulfonic acid monohydrate (50 mg) was added to a solution of 6-chloropurine derivative **22** or **17** (161 mg, 0.5 mmol) in 1,4-dioxane (2 ml) and cyclohexanone (1 ml), the mixture was stirred at room temperature for 1 h and then diluted with ethyl acetate (10 ml). The mixture was washed with saturated aqueous sodium hydrogencarbonate, dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from methanol.

29: Yield 159 mg (79%). M.p. 174.5–177 °C. For $C_{21}H_{27}ClN_4O_2$ (402.93) calculated: 62.60% C, 6.75% H, 8.80% Cl, 13.91% N; found: 62.67% C, 6.73% H, 8.83% Cl, 13.81% N. ESI MS, *m/z* (%): 427.2/425.2 (34/100) [M + Na], 405.1/403.1 (20/61) [M + H]. ^{1}H NMR: 1.28–1.54 m, 11 H (H-3, H-7, H-8a, H-3″, H-4″ and H-5″); 1.58–1.78 m, 4 H (H-2″ and H-6″);

1.81 m, 1 H (H-8a); 1.86–1.89 m, 2 H (H-1 and H-4); 2.20–2.25 m, 2 H (H-5); 3.58 bd, 1 H, J_{gem} = 11.5, 3.73 d, 1 H, J_{gem} = 11.5, 3.82 bd, 1 H, J_{gem} = 11.6 and 3.93 d, 1 H, J_{gem} = 11.5 (CH_2O); 5.08 m, 1 H (H-6); 8.78 s, 1 H (H-2′); 9.01 s, 1 H (H-8′). ^{13}C NMR: 15.02 (C-7); 22.49 and 22.51 (C-3″ and C-5″); 23.75 (C-8); 25.25 (C-4); 25.50 (C-4″); 29.91 (C-5); 31.18 and 33.71 (C-2″ and C-6″); 33.42 (C-1); 33.76 (C-2); 34.38 (C-3); 50.41 (C-6); 67.31 and 67.48 (CH_2O); 97.26 (C-1″); 131.51 (C-5′); 146.54 (C-8′); 149.27 (C-6′); 151.60 (C-2′); 152.40 (C-4′).

30: Yield 168 mg (83%). M.p. 186–188 °C. For $C_{21}H_{27}ClN_4O_2$ (402.93) calculated: 62.60% C, 6.75% H, 8.80% Cl, 13.91% N; found: 62.55% C, 6.74% H, 8.92% Cl, 13.79% N. ESI MS, *m/z* (%): 427.2/425.2 (18/55) [M + Na], 405.1/403.1 (32/100) [M + H]. ^{1}H NMR: 1.31–1.46 m, 9 H (H-3a, H-8, H-3″, H-4″ and H-5″); 1.48 dt, 1 H, J_{gem} = 14.2, *J*(3b,4) = *J*(3b,8) = 2.7 (H-3b); 1.62–1.66 m, 2 H (H-2″ and H-6″); 1.68–1.81 m, 4 H (H-7, H-2″ and H-6″); 1.89 m, 1 H (H-4); 1.94 m, 1 H (H-1); 2.17 ddd, 1 H, J_{gem} = 14.6, *J*(6a,5) = 6.3, *J*(6a,1) = 2.6 (H-6a); 2.42 ddt, 1 H, J_{gem} = 14.5, *J*(6b,5) = 11.3, *J*(6b,1) = *J*(6b,7) = 3.1 (H-6b); 3.59 d, 1 H, J_{gem} = 11.6, 3.62 d, 1 H, J_{gem} = 11.7, 3.72 d, 1 H, J_{gem} = 11.5 and 3.77 d, 1 H, J_{gem} = 11.5 (CH_2O); 4.88 m, 1 H (H-5); 8.76 s, 1 H (H-2′); 8.97 s, 1 H (H-8′). ^{13}C NMR: 19.07 (C-8); 20.40 (C-7); 22.48 (C-3″ and C-5″); 25.49 (C-4″); 26.83 (C-6); 27.17 (C-1); 30.88 (C-4); 31.97 and 32.96 (C-2″ and C-6″); 32.86 (C-2); 33.95 (C-3); 53.59 (C-5); 67.09 and 67.28 (CH_2O); 97.18 (C-1″); 131.54 (C-5′); 146.21 (C-8′); 149.27 (C-6′); 151.49 (C-2′); 152.35 (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 the Academy of Sciences of the Czech Republic (1QS400550501), and Gilead Sciences, Inc. (Foster City, CA, USA).

REFERENCES

1. a) Shealy Y. F., Clayton J. D.: *J. Am. Chem. Soc.* **1966**, *88*, 3885; b) KusakaT., Yamamoto H., Shibata M., Masayuki M., Kishi T., Mizuno K.: *J. Antibiotics* **1968**, *21*, 255; c) Kishi T., Muroi M., Kusaka T., Nishikawa M., Kamiya K., Mizuno K.: *Chem. Pharm. Bull.* **1972**, *20*, 940.
2. a) Yaginuma S., Muto N., Tsujino M., Sudate Y., Hayashi M., Otani M.: *J. Antibiot.* **1981**, *34*, 359; b) Hayashi M., Yaginuma S., Yoshioka H., Nakatsu K.: *J. Antibiot.* **1981**, *34*, 675.
3. 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.
4. 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.: *17th International Roundtable on Nucleosides, Nucleotides and Nucleic Acids*, Conference Book

IRT, p. 217. 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) Šála M., Hřebabecký H., Dračínský M., De Palma A., Neyts J., Holý A.: *Antiviral Res.* **2007**, *74*, A52; i) Hřebabecký H., Dračínský M., Holý A.: *Collect. Czech. Chem. Commun.* **2008**, *73*, 44; j) Hřebabecký H., Dračínský M., De Palma A. M., Neyts J., Holý A.: *Collect. Czech. Chem. Commun.* **2009**, *74*, 469; k) Hřebabecký H., Dračínský M., De Palma A. M., Neyts J., Holý A.: *Collect. Czech. Chem. Commun.* **2009**, *74*, 487; l) De Palma A. M., Holý A., Hřebabecký H., Neyts J., Šála M.: PCT WO 2008/131501 A2.

5. Yin-Murphy M., Almond J. W. in: *Medicinal Microbiology* (S. Baron, Ed.), 4th ed., Sect. 2, http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mmed.chapter.2833. University of Texas, Medical Branch at Galveston 1996.
6. De Palma A. M., Vliegen I., De Clercq E., Neyts J.: *Med. Res. Rev.* **2008**, *28*, 823.
7. Krantz A., Lin C. Y.: *J. Am. Chem. Soc.* **1973**, *95*, 5662.
8. a) Kumara Swamy K. C., Bhuvan Kumar N. N., Balaraman E., Pavan Kumar K. V. P.: *Chem. Rev.* **2009**, *109*, 2551; b) Tsunoda T., Kaku H., Ito S.: TCIMAIL No. 123, 2005, http://www.tciamerica.com/tcimail/backnumber/article/123drE.pdf.
9. Creary X., Butchko M. A.: *J. Am. Chem. Soc.* **2001**, *123*, 1569.
10. Rathke M. W., Inoue N., Varma K. R., Brown H. C.: *J. Am. Chem. Soc.* **1966**, *88*, 2870.