SYNTHESIS OF NOVEL CONFORMATIONALLY LOCKED CARBOCYCLIC NUCLEOSIDES DERIVED FROM 3-(HYDROXYMETHYL)BICYCLO[2.2.1]HEPTANE-2,5-DIOL

Hubert HŘEBABECKÝ[1,*], Milena MASOJÍDKOVÁ[2], Martin DRAČÍNSKÝ[3] and Antonín HOLÝ[4]

Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, CZ-166 10 Prague 6, Czech Republic; e-mail: [1] hubert@uochb.cas.cz, [2] masojid@uochb.cas.cz, [3] dracinsky@uochb.cas.cz, [4] holy@uochb.cas.cz

Received April 11, 2006
Accepted May 5, 2006

The other autors (H. H., M. M. and M. D.) wish to dedicate this paper to Professor Antonín Holý on the occasion of his 70th birthday.

(1*R**,2*R**,3*R**,4*R**,5R*,6*S**)-3-Amino-5-(benzyloxy)-6-(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol (**18**) was prepared in seven easy steps from benzyl (1*R**,2*S**,3*S**,4*S**)-3-(benzyloxy)bicyclo-[2.2.1]hept-5-ene-2-carboxylate (**10**). Reaction of amine **18** with ethyl *N*-((2*E*)-3-ethoxy-methacryloyl)carbamate afforded 1-[(1*R**,2*R**,3*R**,4*R**,5*S**,6*R**)-6-(benzyloxy)-3-hydroxy-5-(hydroxymethyl)bicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**21**) and after deprotection by transfer hydrogenation, free thymine analogue **22**. The thymine derivative **21** was converted to 2,3′-anhydronucleoside **26**. Treatment of the benzyl derivative **18** with sodium in liquid ammonia led to amine **19**, which was used as key intermediate for the construction of (1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-(6-chloro-9*H*-purin-9-yl)-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol (**28**) and (1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-(2-amino-6-chloro-9*H*-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol (**33**). Ammonolysis of **28** led to 6-amino-9*H*-purine derivative **29**. 6-(Dimethylamino)-9*H*-purine analogue **30** and 6-(cyclopropylamino)-9*H*-purine analogues **31** and **34** were prepared by aminolysis of corresponding chloropurine derivatives.

Keywords: Azides; Amines; Cyclic sulfates; Nucleosides; Carbocyclic nucleosides; Purines; Adenine; Thymine; Antivirals; 6-(Dimethylamino)purine; 6-(Cyclopropylamino)purine.

The search for new modified nucleosides with potential biological activity remains an open promising field of research. The discovery of the antibiotic and antitumor activity of the natural carbocyclic nucleosides aristeromycin (**1**)[1] and neplanocin A (**2**)[2] stimulated the search for novel carbocyclic nucleoside analogues with biological activity. Carbocyclic nucleosides

doi:10.1135/cccc20060871

carbovir (**3**)[3] and the structurally related abacavir (Ziagen™) (**4**)[4] are prominent synthetic compounds with potent and selective inhibitory activity against HIV-1 replication and cytopathic effects in a variety of human T-lymphoblastoic cell lines (Chart 1).

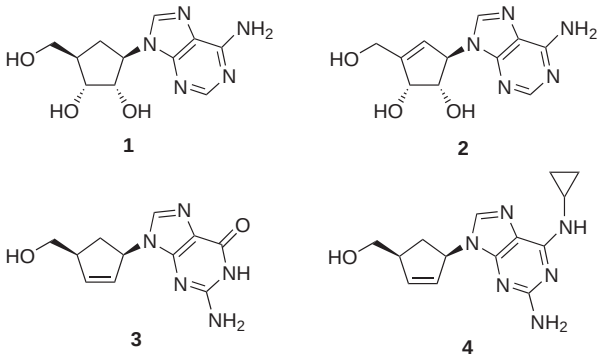


CHART 1

Synthesis of novel conformationally locked carbocyclic nucleosides with an oxabicyclo[2.2.1]heptane ring system (as precursors of carbocyclic locked nucleic acids) was recently described[5]. Bisphosphate of the 2-iodo-(6-methylamino)purine analogue containing this ring system displayed potent binding affinity at the human $P2Y_1$ receptor[6]. The bicyclo[2.2.1]-heptane (norbornane) ring, like oxabicyclo[2.2.1]heptane, is a conformationally locked carbapentofuranose and/or carbahexopyranose ring systems. Recently, we reported the synthesis of novel racemic conformationally locked carbocyclic purine nucleoside analogues derived from 5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol[7], 5,5- and 6,6-bis(hydroxymethyl)-bicyclo[2.2.1]heptan-2-ols[8], and analogues[9] with bicyclo[2.2.1]heptene or -heptane ring substituted with nucleobase at position 7. Nucleoside analogues **5**–**8** (Chart 2) exhibit certain activity in tests for anti-HIV-1 and anti-HIV-2 activity in human T-lymphocyte (CEM) cells.

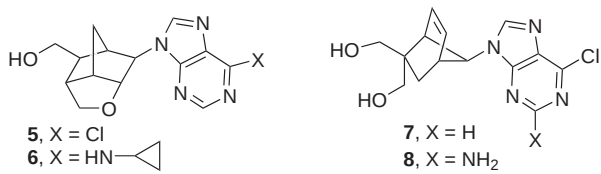


CHART 2

This study concerns syntheses of novel racemic carbocyclic nucleosides derived from racemic 3-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol. Chart 3 shows the target compounds which were synthesized from easily available methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (**9**)[10].

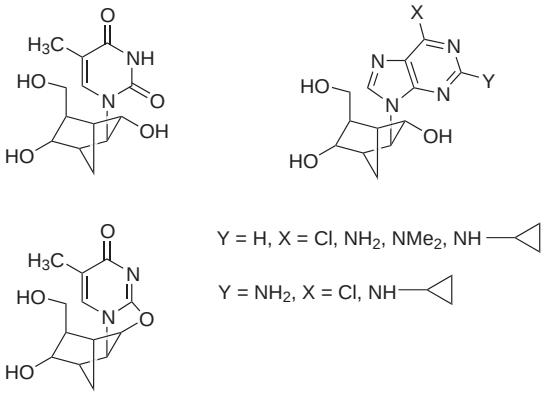


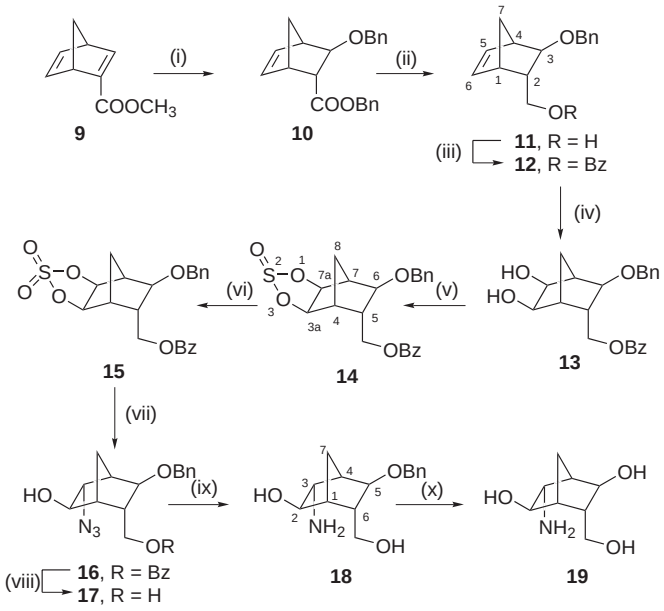
CHART 3

Addition of benzyl alcohol to the 2,3-double bond of carboxylate **9** performed in a mixture of benzyl alcohol, tetrahydrofuran, dimethylformamide, and sodium phenylmethoxide afforded benzyl ether **10** (65%) (Scheme 1). The analogous stereoselective addition of a variety of nucleophiles to several 2-acylnorbornadienes was studied by Baldwin and Tomesch[11]. Also treatment of the Diels–Alder reaction product of (*E*)-3-bromoacrylate of (*R*)-pantolactone and cyclopentadiene with sodium phenylmethoxide proceeds via elimination and addition[12].

Benzoate **10** was reduced with lithium aluminium hydride to hydroxymethyl derivative **11** (72%) which, after benzoylation afforded benzoate **12**. The unsaturated benzoate **12** was *cis*-hydroxylated with OsO_4 giving *cis*-diol **13** in the yield 88%. 4-Methylmorpholine oxide was used as donor of oxygen[13]. The diol **13** was treated with thionyl chloride in ether at room temperature to give a mixture of sulfites **14** (94%). The mixture of two stereoisomers with different orientation of the S=O bond, was not separated; the ratio of isomers (10:7) was determined by ^{1}H NMR spectroscopy. Sulfites **14** were converted to sulfate **15** (87%) following the procedure of Gao and Sharpless[14]. Treatment of sulfate **15** with lithium azide in dimethylformamide at 140 °C afforded, after hydrolysis with a mixture of tetrahydrofuran, sulfuric acid, and water, azido derivative **16** (76.5%), which was deprotected with methanolic sodium methoxide to give azide **17** (72%). Hydrogenation of azide **17** using palladium(II) hydroxide on carbon as

catalyst led to amine **18** (92%). Amine **19** was obtained by deprotection of the benzyl derivative **18** with sodium in liquid ammonia in a 78% yield.

Configuration of the key amine **19** was proven by NMR spectroscopy. Structural assignment of protons and carbon atoms was achieved using correlated homonuclear 2 D-COSY, 2 D-ROESY and heteronuclear ^{1}H, ^{13}C-2D-HSQC and ^{1}H, ^{13}C-2D-HMBC NMR spectra. From the spectra follows that the nucleophilic opening of cyclic sulfate **15** with azide proceeds stereospecifically in the position 7a. Also the recently described reaction[8] of cyclic sulfate (((3a*R**,4*R**,7*S**,7a*S**)-2,2-dioxohexahydro-2λ^{4}-4,7-methano-1,3,2-benzodioxathiole-5,5-diyl)dimethyl dibenzoate) with azide had a stereospecific course.

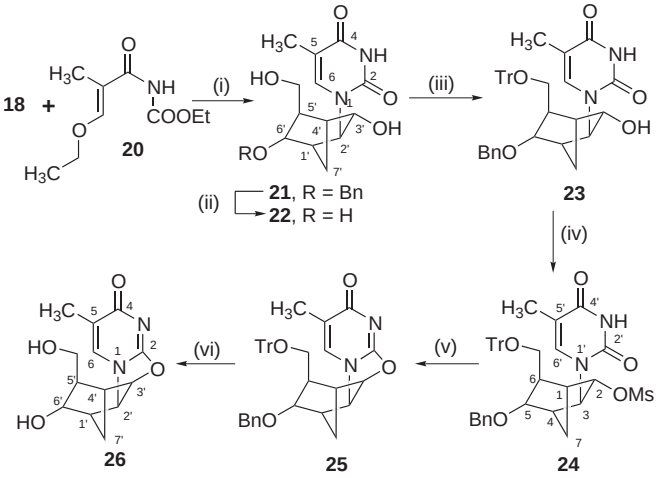


(i) NaH/benzyl alcohol/THF/DMF, 65%; (ii) LAH/THF, 72%; (iii) BzCl/pyridine, 96%; (iv) 4-methylmorpholine oxide/acetone/H_2O, 88%; (v) $SOCl_2$/ether, 94%; (vi) $NaIO_4$/$RuCl_3$/MeCN/CCl_4/H_2O, 87%; (vii) 1. LiN_3/DMF, 140 °C, 2. THF/H_2O/H_2SO_4, 76.5%; (viii) 0.1 M MeONa/MeOH, 72%; (ix) $Pd(OH)_2$/C, H_2, 92%; (x) Na/NH_3(l)

SCHEME 1

The reaction of amine **18** with *N*-acylcarbamate **20**[8] (Scheme 2) in 1,4-dioxane at 100 °C followed by treatment with Dowex 50 (H^+) afforded thymine derivative **21** (64%) and subsequent transfer hydrogenation[15], performed with 20% palladium(II) hydroxide on carbon in a refluxing mixture of ethanol and cyclohexene, afforded thymine analogue **22** (80%). Trityl-

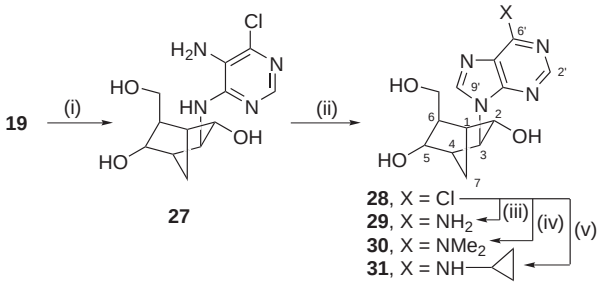
ation of thymine derivative **21**, followed by mesylation of the obtained trityl derivative **23** yielded mesyl derivative **24** (88%). Mesylate **24** was converted to the anhydro derivative **25** (84%) by the treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile. Compound **25** was deprotected with 20% palladium(II) hydroxide on carbon in a refluxing mixture of ethanol and cyclohexene to give anhydronucleoside analogue **26** (81%).



(i) 1. 1,4-dioxane, 100 °C, 2. Dowex 50 (H^+), 100 °C, 64%;
(ii) $Pd(OH)_2$/C, EtOH/cyclohexene, 80%; (iii) trityl chloride/pyridine, 82%;
(iv) mesyl chloride/pyridine, 88%; (v) DBU/MeCN, 60 °C,
84%; (vi) $Pd(OH)_2$/C, cyclohexene/ethanol, 81%

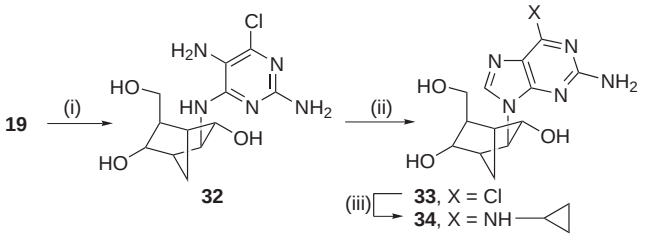
SCHEME 2

Conversion of amine **19** to the 6-chloropurine derivatives (Scheme 3) was performed by described procedures[7–9,15b,16]. Coupling of the amine with 4,6-dichloropyrimidin-5-amine or 4,6-dichloropyrimidine-2,5-diamine[16c] in ethanol (Scheme 4) in the presence of triethylamine gave pyrimidinylamino derivatives **27** (81%) or **32** (93%). Ring closure of **27** or **32** with triethyl orthoformate in the presence of hydrochloric acid gave 6-chloropurine derivative **28** (93%) or **33** (62%). The chloropurine **28** was ammonolysed with liquid ammonia at 70 °C to give adenine derivative **29** (73%). Treatment of **28** with dimethylammonium dimethylcarbamate afforded 6-(dimethylamino)purine derivative **30** (95%). Aminolysis of **28** or **33** with cyclopropylamine led to cyclopropylamino derivatives **31** (73%) and **34** (89%), respectively.



(i) 4,6-dichloropyrimidin-5-amine/TEA/EtOH, 100 °C, 81%; (ii) 1. $CH(OEt)_3$/HCl, 2. THF/H_2O/HCl, 93%; (iii) NH_3 (l), 73%; (iv) $Me_2NCOO^-Me_2NH^+$, 95%; (v) cyclopropylamine, 73%

SCHEME 3



(i) 4,6-dichloropyrimidin-2,5-diamine/TEA/EtOH, 100 °C, 93%; (ii) 1. $CH(OEt)_3$/HCl, 2. THF/H_2O/HCl, 62%; (iii) cyclopropylamine, 89%

SCHEME 4

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

In conclusion, novel racemic conformationally locked carbocyclic nucleoside analogues of adenine, 6-(dimethylamino)purine, 6-(cyclopropylamino)purine, and thymine derived from 3-(hydroxymethyl)bicyclo[2.2.1]-heptane-2,5-diol were prepared. The target compounds were tested for inhibition of cell growth of the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 240), human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2), human promyelocytic leukemia HL60 cells (ATCC CCL 240), and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). None of the compounds exhibited significant activity[17]. The compounds were also tested for anti-HIV-1 and anti-HIV-2 activity in human T-lymphocyte (CEM) cells. Preliminary data showed that only compound **32** exhibits a weak activity (EC_{50} > 63 μM and CC_{50} = 152 ± 2.53 μM)[18].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian Unity 500 and/or Bruker Arance-500 instruments (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) 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 with Xe, accelerating voltage 8 kV, thioglycerol; glycerol 3:1 mixture or bis(2-hydroxyethyl) disulfide were used as a matrix). Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol Silica gel 60 F_{254} foils (Merck). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; compounds were dried at 13 Pa and 50 °C.

Benzyl (1*R**,2*S**,3*S**,4*S**)-3-(Benzyloxy)bicyclo[2.2.1]hept-5-ene-2-carboxylate (**10**)

A dispersion of sodium hydride in mineral oil (60%; 11.22 g, 0.28 mol) was slowly added to a mixture of benzyl alcohol (70 ml), dimethylformamide (35 ml), and tetrahydrofuran (140 ml), cooled to 0 °C. The mixture was stirred at 0 °C for 20 min and then a solution of ester **9** (22.53 g, 0.15 mol) in tetrahydrofuran (100 ml) was added. The mixture was stirred at room temperature for 3 h, then neutralized with acetic acid and partitioned between ethyl acetate (800 ml) and water (350 ml). The organic layer was washed with water (2 × 350 ml), dried over anhydrous sodium sulfate and the solvent was evaporated. Chromatography of the residue on a silica gel (1 kg) column in petroleum ether–ethyl acetate (23:2) afforded 33.05 g (65%) of **10** (oil). For $C_{22}H_{22}O_3$ (334.4) calculated: 79.02% C, 6.63% H; found: 78.99% C, 6.73% H. FAB MS, *m/z* (%): 335 (1) [M + H], 91 (100). ^{1}H NMR: 1.54 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) = 1.7, J_{gem} = 8.6 (H-7b); 1.79 dt, 1 H, *J*(7a,1) = *J*(7a,4) = 1.6 (H-7a); 2.83 dd, 1 H, *J*(2,3) = 2.6, *J*(2,1) = 3.5 (H-2); 2.95 dqd, 1 H, *J*(4,1) = *J*(4,7a) = *J*(4,7b) = 1.7, *J*(4,3) = 0.6, *J*(4,5) = 3.3 (H-4); 3.06 m, 1 H, *J*(1,2) =3.5, *J*(1,5) = 0.5, *J*(1,4) = *J*(1,7a) = *J*(1,7b) = 1.7, *J*(1,6) = 2.7 (H-1); 3.76 ddd, 1 H, *J*(3,7b) = 1.8 (H-3); 4.54 s, 2 H (OCH_2Ph); 5.04 d, 1 H and 5.09 d, 1 H, J_{gem} = 12.4 (OCH_2Ph); 6.06 ddd, 1 H, *J*(5,6) = 5.6 (H-5); 6.09 brdd, 1 H (H-6); 7.25–7.40 m, 10 H (arom.). ^{13}C NMR: 43.62 (C-1); 46.54 (C-7); 47.16 (C-4); 52.37 (C-2); 65.73 (CH_2Ph); 70.70 (CH_2Ph); 82.38 (C-3); 134.55 (C-5); 137.70 (C-6); 127.51, 127.63, 2 C, 127.99, 2 C, 128.16, 128.35, 2 C, 128.61, 2 C, 136.41, and 138.68 (arom.); 172.59 (C=O).

[(1*R**,2*R**,3*S**,4*S**)-3-(Benzyloxy)bicyclo[2.2.1]hept-5-en-2-yl]methanol (**11**)

A solution of benzyl ester **10** (30.1 g, 90 mmol) in tetrahydrofuran (150 ml) was added dropwise under stirring to a 1 M solution of lithium aluminium hydride in tetrahydrofuran (90 ml) under argon atmosphere. The mixture was refluxed for 2 h, cooled and ethyl acetate (20 ml) was added, followed after 15 min by water. The mixture was evaporated, the residue was extracted with ethyl acetate (3 × 150 ml) and the combined extracts were evaporated. Chromatography of the residue on a silica gel (1 kg) column in toluene–ethyl acetate (3:1) gave 14.92 g (72%) of compound **11**. For $C_{15}H_{18}O_2$ (230.3) calculated: 78.23% C, 7.88% H; found: 77.98% C, 7.92% H. FAB MS, *m/z* (%): 231 (4) [M + H], 91 (100). ^{1}H NMR: 1.52 dq, 1 H, *J*(7b,1) = *J*(7b,3) = *J*(7b,4) = 1.7, J_{gem} = 8.2 (H-7b); 1.73 dt, 1 H, *J*(7a,1) = *J*(7a,4) = 1.5 (H-7a); 1.93 m, 1 H (H-2); 2.77 m, 1 H (H-1); 2.85 m, 1 H (H-4); 3.02 m, 1 H (H-3); 3.10 ddd, 1 H, *J*(CH,2) = 8.8, *J*(CH,OH) = 5.3 and 3.28 ddd, 1 H, *J*(CH,2) = 6.8, *J*(CH,OH) = 5.2, J_{gem} = 10.6 (CH_2O); 4.50–4.53 m, 3 H (CH_2O**H**, CH_2Ph); 6.02 dd, 1 H, *J*(5,4) = 3.3, *J*(5,6) =

5.8 (H-5); 6.15 dd, 1 H, *J*(6,1) = 2.8 (H-6); 7.24–7.35 m, 5 H (arom.). ^{13}C NMR: 42.2.8 (C-1); 46.70 (C-7); 47.09 (C-4); 50.76 (C-2); 63.93 (CH_2O); 70.28 (CH_2Ph); 82.48 (C-3); 127.30, 127.46, 2 C, 128.29, 2 C, and 139.21 (arom.); 133.74 (C-5); 137.94 (C-3).

[(1*R**,2*R**,3*S**,4*S**)-3-(Benzyloxy)bicyclo[2.2.1]hept-5-en-2-yl]methyl Benzoate (**12**)

Benzoyl chloride (8.4 ml, 72 mmol) was added to a stirred and cooled solution of hydroxymethyl derivative **11** (13.82 g, 60 mmol) in pyridine (150 ml) and the mixture was left standing at room temperature overnight. Water (10 ml) was then added and, after 15 min, the solvent was evaporated. The residue was partitioned between ethyl acetate (500 ml) and water (250 ml). The organic phase was washed with water (250 ml), 5% hydrochloric acid (100 ml), 10% aqueous $KHCO_3$ (3 × 250 ml), dried over anhydrous sodium sulfate, and the solvent was evaporated. 19.26 g (96%) of benzoate **12** was obtained. An analytical sample was obtained by chromatography on a silica gel column in toluene–ethyl acetate (18:1) For $C_{22}H_{22}O_3$ (334.4) calculated: 79.02% C, 6.63% H; found: 78.99% C, 6.73% H. FAB MS, *m/z* (%): 335 (1) [M + H], 105 (100), 91 (98). ^{1}H NMR: 1.59 dm, 1 H, J_{gem} = 8.4 (H-7b); 1.79 dt, 1 H, *J*(7a,1) = *J*(7a,4) = 1.5 (H-7a); 2.27 tt, 1 H, *J*(2,1) = 3.1, *J*(2,3) = 2.8, *J*(2,CH_2) = 7.8 and 7.9 (H-2); 2.84 m, 1 H (H-1); 2.96 m, 1 H (H-4); 3.26 ddd, 1 H, *J*(3,2) = 2.5, *J*(3,4) = 0.6, *J*(3,7b) = 1.8 (H-3); 4.09 m, 2 H (CH_2O); 4.53 m, 2 H (CH_2Ph); 6.12 dd, 1 H, *J*(5,6) = 5.7, *J*(5,4) = 3.2 (H-5); 6.23 dd, 1 H, *J*(6,1) = 2.8 (H-6); 7.29 m, 5 H (arom. benzyl); 7.52 m, 2 H, 7.66 m, 1 H, and 7.99 m, 2 H (arom. benzoyl). ^{13}C NMR: 42.55 (C-1); 46.69 (C-7); 46.86 (C-2); 47.01 (C-4); 67.27 (CH_2O); 70.62 (CH_2Ph); 82.60 (C-3); 134.55 (C-5); 137.39 (C-6); 127.33, 127.36, 2 C, 128.23, 2 C, 128.79, 2 C,129.23, 2 C, 129.93, 133.35, and 138.79 (arom.); 165.73 (C=O).

[(1*R**,2*S**,3*S**,4*R**,5*S**,6*R**)-3-(Benzyloxy)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl]methyl Benzoate (**13**)

A mixture of the bicyclo[2.2.1]heptene derivative **12** (24.75 g, 74 mmol), acetone (1.5 l), water (150 ml), an aqueous solution of 4-methylmorpholine oxide (50%; 105 ml), and osmium tetroxide (75 mg) was stirred at room temperature overnight. The resulting solution was evaporated and the residue was partitioned between ethyl acetate (1 l) and water (500 ml). The aqueous layer was extracted with ethyl acetate (500 ml) and the collected acetate layers were washed with water (300 ml), dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethanol afforded 23.90 g (88%) of diol **13**, m.p. 99–100 °C. For $C_{22}H_{24}O_5$ (368.4) calculated: 71.72% C, 6.57% H; found: 71.61% C, 6.63% H. FAB MS, *m/z* (%): 369 [M + H]. ^{1}H NMR: 1.39 dpent, 1 H, *J*(7a,1) ~ *J*(7a,2) ~ *J*(7a,3) ~ *J*(7a,6) = 1.3, J_{gem} = 10.0 (H-7a); 1.76 dq, 1 H, *J*(7b,3) ~ *J*(7b,4) ~ *J*(7b,6) = 1.3 (H-7b); 2.09 tdd, 1 H, *J*(2,1) = 4.4, *J*(2,3) = 3.2, *J*(2,CH_2) = 8.0 (H-2); 2.18 brdq, 1 H, *J*(1,4) ~ *J*(1,7a) ~ *J*(1,7b) = 1.6 (H-1); 2.20 brs, 1 H (H-4); 3.21 brdd, 1 H, *J*(3,7b) = 1.1 (H-3); 3.53 brtd, 1 H, *J*(5,6) = 5.6, *J*(5,7a) = 1.2, *J*(5,OH) = 5.4 (H-5); 3.77 brtd, 1 H, *J*(6,7a) = 1.2, *J*(6,OH) = 4.9 (H-6); 4.23 dd, 1 H, *J*(CH,5) = 8.3 and 4.31 dd, 1 H, *J*(CH,5) = 7.8, J_{gem} = 11.2 (CH_2O); 4.40 d, 1 H and 4.48 d, 1 H, J_{gem} = 12.0 ($PhCH_2O$); 4.58 d, 1 H (5-OH); 4.69 d, 1 H (6-OH); 7.24 m, 5 H, 7.53 t, 2 H, 7.67 t, 1 H, and 7.98 d, 2 H (arom.). ^{13}C NMR: 30.39 (C-7); 44.55 (C-2); 46.51 (C-1); 48.80 (C-4); 63.86 (CH_2O); 67.75 (C-6); 69.99 (C-4); 70.16 ($PhCH_2O$); 81.29 (C-3); 127.45, 127.50, 2 C, 128.33, 2 C, and 138.81 (benzyl); 128.95, 2 C, 129.32, 2 C, 129.92, and 133.56 (benzoyl); 165.81 (C=O).

[(3a*R**,4*R**,5*S**, 6*S**,7*S**,7a*S**)-6-(Benzyloxy)-2-oxohexahydro-2λ^4-4,7-methano-1,3,2-benzodioxathiol-5-yl]methyl Benzoate (**14**)

Thionyl chloride (39 ml) was added to a stirred solution of diol **13** (22.11 g, 60 mmol) in ether (400 ml) and the mixture was stirred at room temperature for 3 h. The resulting solution was evaporated and a solution of the residue in ethyl acetate (800 ml) was washed with water (300 ml) and 10% aqueous sodium hydrogencarbonate (3 × 300 ml), dried over anhydrous sodium sulfate and the solvent was evaporated. The obtained product (23.37 g, 94%) was used in the next step without purification. An analytical sample was purified by crystallization from ether–petroleum ether. For $C_{22}H_{22}O_6S$ (414.5) calculated: 63.75% C, 5.35% H, 7.74% S; found: 63.70% C, 5.42% H, 7.77% S. FAB MS, *m/z* (%): 415 [M + H]. ^{1}H NMR: isomer A: 1.46 dq, 1 H, *J*(8b,4) = *J*(8b,6) = *J*(8b,7) = 1.6, J_{gem} = 11.1 (H-8b); 1.60 dm, 1 H (H-8a); 3.45 dd, 1 H, *J*(6,5) = 3.4 (H-6); 4.40 d, 2 H (CH_2O); 4.50 d, 1 H and 4.55 d, 1 H, J_{gem} = 11.9 (CH_2Ph); 5.07 dd, 1 H, *J*(7a,3a) = 5.5, *J*(7a,8a) = 1.5 (H-7a); 5.20 dd, 1 H, *J*(3a,8a) = 1.4 (H-3a); isomer B: 1.67 dm, 0.7 H, J_{gem} = 11.1 (H-8a); 2.17 dq, 0.7 H, *J*(8b,6) = 1.7 (H-8b); 3.35 dd, 0.7 H, *J*(6,5) = 3.3 (H-6); 4.24–4.33 m, 1.4 H (CH_2O); 4.50 d, 0.7 H and 4.56 d, 0.7 H, J_{gem} = 11.9 (CH_2Ph); 4.82 dd, 0.7 H, *J*(7a,3a) = 6.2, *J*(7a,8b) = 1.7 (H-7a); 4.98 dd, 0.7 H, *J*(3a,8b) = 1.4 (H-3a); isomer A + isomer B: 2.24–2.32 m, 1.7 H (H-5); 2.62–2.72 m, 3.4 H (H-7, H-4); 7.24–7.32 m, 8.5 H (arom. benzyl); 7.51–7.55 m, 3.4 H, 7.65–7.69 m, 1.7 H, and 7.96–8.01 m, 3.4 H (arom. benzoyl). ^{13}C NMR: isomer A: 29.64 (C-8); 41.57 (C-4); 45.41 (C-5); 45.68 (C-7); 63.11 (CH_2O); 70.59 (CH_2Ph); 78.96 (C-6); 82.90 (C-3a); 83.44 (C-7a); 129.28, 2 C and 129.78 (arom. benzoyl); 138.38 (arom. benzyl); 165.65 (C=O); isomer B: 30.04, 0.7 C (C-8); 41.85, 0.7 C (C-4); 45.38, 0.7 C (C-5); 46.01, 0.7 C (C-7); 63.21, 0.7 C (CH_2O); 70.54, 0.7 C (CH_2Ph); 79.19, 0.7 C (C-6); 87.08, 0.7 C (C-3a); 87.24, 0.7 C (C-7a); 129.29, 1.4 C and 129.73, 0.7 C (arom. benzoyl); 138.40, 0.7 C (arom. benzyl); 165.67, 0.7 C (C=O); isomer A + isomer B: 127.52, 1.7 C, 127.55, 3.4 C, and 128.30, 3.4 C (arom. benzyl); 128.86, 3.4 C and 133.49, 1.7 C (arom. benzoyl). The A:B ratio 10:7.

[(3a*R**,4*R**,5*S**, 6*S**,7*S**,7a*S**)-6-(Benzyloxy)-2,2-dioxohexahydro-2λ^4-4,7-methano-1,3,2-benzodioxathiol-5-yl]methyl Benzoate (**15**)

To a stirred ice-cooled solution of sulfite **14** (8.29 g, 20 mmol) in acetonitrile (50 ml) and tetrachloromethane (25 ml), water (90 ml), sodium periodate (8.80 g) and ruthenium(III) chloride hydrate (25 mg) were added. The mixture was stirred at 0 °C for 20 min and at room temperature for 10 min. Additional sodium periodate (4.40 g) was then added, the mixture was stirred at room temperature for 30 min and then diluted with ethyl acetate (700 ml). The organic layer was separated, washed with water (3 × 200 ml), dried over anhydrous sodium sulfate, and evaporated. Crystallization of the residue from ethanol afforded 7.48 g (87%) of sulfate **15**, m.p. 154–155.5 °C. For $C_{22}H_{22}O_7S$ (430.5) calculated: 61.38% C, 5.15% H, 7.45% S; found: 61.09% C, 4.96% H, 7.41% S. ^{1}H NMR: 1.83 m, 1 H (CH_2); 2.35 tdd, 1 H, *J*(5,4) = 4.6, *J*(5,6) = 3.6, *J*(5,CH^aH) = *J*(5,CH^bH) = 8.1 (H-5); 2.78 brdq, 1 H, *J*(4,3a) ~ *J*(4,CH^aH) ~ *J*(4,CH^bH) = 1.5 (H-4); 2.85 m, 1 H (H-7); 3.43 brdq, 1 H, *J*(6,2) ~ *J*(6,CH^aH) ~ *J*(6,CH^bH) =1.2 (H-6); 4.34 d, 2 H (CH_2O); 4.48 d, 1 H and 4.56 d, 1 H, J_{gem} = 12.0 ($PhCH_2O$); 5.23 dq, 1 H, *J*(7a,7) ~ *J*(7a,6) ~ *J*(7a,CH^aH) = 1.0, *J*(7a,3a) = 5.4 (H-7a); 5.34 dq, 1 H, *J*(3a,4) ~ *J*(3a,CH^aH) ~ *J*(3a,CH^bH) = 1.0 (H-3a); 7.28 m, 5 H, 7.53 t, 2 H, 7.68 t, 1 H, and 7.98 d, 2 H (arom.). ^{13}C NMR: 30.07 (CH_2); 41.88 (C-4); 45.58 (C-7); 46.19 (C-5); 62.80 (CH_2O); 70.63 $PhCH_2O$); 78.18 (C-6); 83.19 (C-3a); 83.27 (C-7a); 127.67, 127.69, 2 C,

128.40, 2 C, and 138.25 (benzyl); 128.94, 2 C, 129.39, 2 C, 129.77, and 133.56 (benzoyl); 165.70 (C=O).

[(1*R**,2*S**,3*R**,4*R**,5*R**,6*R**)-5-Azido-3-(benzyloxy)-6-hydroxybicyclo[2.2.1]heptan-2-yl]-methyl Benzoate (**16**)

A solution of sulfate **15** (6.46 g, 15 mmol) and lithium azide (2.94 g, 60 mmol) in dimethylformamide (100 ml) was heated at 140 °C for 2 h and evaporated to dryness. A mixture of the residue, tetrahydrofuran (60 ml), sulfuric acid (3 ml) and water (3 ml) was stirred at room temperature overnight and then neutralized with sodium hydrogencarbonate. The mixture was partitioned between ethyl acetate (350 ml) and water (150 ml), the organic layer was separated, washed with water (2 × 100 ml), dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column (250 g) in toluene–ethyl acetate (4:1) gave 4.52 g (76.5%) of azide **16**. For $C_{22}H_{23}N_3O_4$ (393.5) calculated: 67.16% C, 5.89% H, 10.68% N; found: 66.91% C, 5.79% H, 10.57% N. FAB MS, *m/z* (%): 394 (0.5) [M + H], 105 (80), 91 (100). ^{1}H NMR: 1.63 dq, 1 H, *J*(7b,1) ~ *J*(7b,4) ~ *J*(7b,6) = 1.6, J_{gem} = 10.5 (H-7b); 1.75 dq, 1 H, *J*(7a,1) ~ *J*(7a,3) ~ *J*(7a,4) = 1.6 (H-7a); 2.22 tdd, 1 H, *J*(2,1) = 4.5, *J*(2,3) = 2.8, *J*(2,CH_2) = 8.2 (H-2); 2.23 m, 1 H (H-1); 2.61 dpent, 1 H, *J*(4,1) ~ *J*(4,7a) ~ *J*(4,7b) = 1.3, *J*(4,2) = 0.8, *J*(4,5) = 5.0 (H-4); 3.55 dd, 1 H, *J*(3,7a) = 1.6 (H-3); 3.60 m, 1 H (H-6); 3.78 ddd, 1 H, *J*(5,6) = 1.8 (H-5); 4.25 dd, 1 H, *J*(CH,2) = 8.2 and 4.37 dd, 1 H, *J*(CH,2) = 8.2, J_{gem} = 11.2 (CH_2O); 4.45 d, 1 H and 4.48 d, 1 H, J_{gem} = 12.0 (PhCH_2O); 5.26 d, 1 H, *J*(OH,6) = 3.7 (6-OH); 7.20–8.00 m, 10 H (arom.). ^{13}C NMR: 32.79 (C-7); 45.03 (C-2); 46.23 (C-1); 46.99 (C-4); 70.65 (PhCH_2O); 70.67 (C-3); 72.75 (C-5); 77.93 (C-6); 127.79, 127.85, 2 C, 128.60, 2 C, and 133.88 (benzyl); 129.13, 129.66, 130.17, 133.74, 133.77, and 133.79 (benzoyl); 166.10 (C=O).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-Azido-5-(benzyloxy)-6-(hydroxymethyl)-bicyclo[2.2.1]heptan-2-ol (**17**)

A solution of benzoate **16** (7.87 g, 20 mmol) in 0.1 M methanolic sodium methoxide (90 ml) was left standing at room temperature overnight and then neutralized with Dowex 50 (H^+). The resin was filtered off and washed with methanol. The collected filtrates were evaporated and the residue was diluted with ether (ca. 3 ml). The deposited crystalline product was filtered off and washed with ether. Azide **17** (4.17 g, 72%), m.p. 92.5–93.5 °C, was obtained. For $C_{15}H_{19}N_3O_3$ (289.3) calculated: 62.27% C, 6.62% H, 14.52% N; found: 62.08% C, 6.66% H, 14.55% N. ^{1}H NMR: 1.58 dq, 1 H, *J*(7b,1) ~ *J*(7b,2) ~ *J*(7b,4) = 1.6, J_{gem} = 10.2 (H-7b); 1.71 dq, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ *J*(7a,5) = 1.4 (H-7a); 1.90 brdddd, *J*(6,1) = 4.5, *J*(6,4) = 1.0, *J*(6,5) = 3.1, *J*(6,CH_2) = 7.5 and 8.8 (H-6); 2.18 dm, 1 H, *J*(1,6) = 4.5 (H-1); 2.50 dm, 1 H, *J*(4,3) = 5.1 (H-4); 3.34 dd, 1 H, *J*(5,6) = 3.1, *J*(5,7a) = 1.6 (H-5); 3.35 ddd, 1 H, *J*(CH,OH) = 5.0, *J*(CH,6) = 8.8 and 3,52 ddd, 1 H, *J*(CH,OH) = 4.6, *J*(CH,6) = 7.5, J_{gem} = 10.7 (CH_2O); 3.58 dt, 1 H, *J*(2,3) = *J*(2,7b) = 1.8, *J*(2,OH) = 4.0 (H-2); 3.72 dm, *J*(3,1) = 1.0, *J*(3,2) = 1.8 (H-3); 4.42 d, 1 H and 4.46 d, 1 H, J_{gem} = 12.2 (OCH_2Ph); 4.67 t, 1 H, *J*(OH,CH_2) = 4.8 (CH_2O**H**); 5.13 d, 1 H (2-OH); 7.25–7.35 m, 5 H (arom.). ^{13}C NMR: 32.57 (C-7); 45.06 (C-6); 45.72 (C-1); 50.33 (C-4); 59.69 (CH_2O); 69.97 (CH_2Ph); 70.65 (C-5); 72.305 (C-3); 77.80 (C-2); 127.42, 127.56, 2 C, 128.36, 2 C, and 139.04 (arom.).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-Amino-5-(benzyloxy)-6-(hydroxymethyl)-bicyclo[2.2.1]heptan-2-ol (**18**)

Hydrogen was bubbled through a stirred mixture of azide 17 (2.89 g, 10 mmol), methanol (30 ml), and palladium(II) hydroxide on carbon (20% Pd, 85 mg) for 4 h. The catalyst was filtered off and washed with methanol. The collected filtrates and washings were evaporated. Crystallization of the residue from ether–petroleum ether afforded 2.42 g (92%) of **18**, m.p. 118–119.5 °C. For $C_{15}H_{21}NO_3$ (263.3) calculated: 68.42% C, 8.04% H, 5.32% N; found: 68.23% C, 8.09% H, 5.23% N. FAB MS, *m/z* (%): 264 (100) [M + H], 239 (47), 91 (71). ^{1}H NMR: 1.44 dq, 1 H, *J*(7b,1) = *J*(7b,4) = *J*(7b,2) = 1.7, J_{gem} = 9.6 (H-7b); 1.62 dm, 1 H (H-7a); 1.83 m, 1 H (H-6); 2.06 brd, 1 H, *J*(1,6) = 4.6 (H-1); 2.19 brd, 1 H, *J*(4,3) = 4.2 (H-4); 2.86 m, 1 H (H-3); 3.29 brs, 1 H (H-2); 3.32 brs, 2 H (NH_2); 3.47 dd, 1 H, *J*(CH,6) = 8.6 and 3.57 dd, 1 H, *J*(CH,6) = 6.8, J_{gem} = 10.7 (CH_2O); 3.63 m, 1 H (H-5); 4.41 brs, 1 H (2-OH); 4.38 d, 1 H and 4.46 d, 1 H, J_{gem} = 12.2 (CH_2Ph); 7.23–7.34 m, 5 H (arom.). ^{13}C NMR: 33.44 (C-7); 46.80 (C-1); 47.52 (C-4); 50.82 (C-6); 59.79 (CH_2O); 62.12 (C-3); 69.72 (CH_2Ph); 75.46 (C-2); 77.74 (C-5); 127.19, 127.42, 2 C, 128.25, 2 C, and 139.53 (arom.).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-Amino-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol (**19**)

Sodium (506 mg, 22 mmol) was added to a stirred solution of protected amine **18** (2.63 g, 10 mmol) in NH_3 (l, 50 ml) at –75 °C. The mixture was stirred at –75 °C for 1 h, then NH_4Cl (1.1 g) was added and ammonia was evaporated. The residue was applied onto a column filled with Dowex 50 (H^+) (200 ml). The column was eluted with water (800 ml), methanol (800 ml), and 3.5 M methanolic NH_3. The fractions containing amine (TLC, detection with a solution $KMnO_4$ in acetone) were collected and evaporated. Crystallization of the residue from ethanol afforded (1.35 g, 78%) of amine **19**, m.p. 184–187 °C. For $C_8H_{15}NO_3$ (173.2) calculated: 55.47% C, 8.73% H, 8.09% N; found: 55.19% C, 8.77% H, 7.92% N. FAB MS, *m/z* (%): 174 [M + H]. ^{1}H NMR: 1.47 dm, 1 H, J_{gem} = 9.5 (H-7b); 1.54 dm, 1 H (H-7a); 1.65 m, 1 H (H-6); 1.88 m, 1 H (H-4); 1.99 m, 1 H (H-1); 2.76 m, 1 H (H-3); 3.27 brs, 3 H (H-2, NH_2); 3.42 dd, 1 H, *J*(CH,6) = 9.4 and 3.57 dd, 1 H, *J*(CH,6) = 6.1, J_{gem} = 10.7 (CH_2O); 3.65 brs, 1 H (H-5); 4.19 brd, 1 H, *J*(OH,5) = 4.6 (5-OH); 4.28 brd, 1 H, *J*(OH,2) = 3.9 (2-OH). ^{13}C NMR: 32.95 (C-7); 46.79 (C-1); 50.64 (C-4); 53.21 (C-6); 59.57 (CH_2O); 62.46 (C-3); 68.32 (C-5); 75.39 (C-2).

1-[(1*R**,2*R**,3*R**,4*R**,5*S**,6*R**)-6-(Benzyloxy)-3-hydroxy-5-(hydroxymethyl)-bicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**21**)

A solution of amine **18** (1.32 g, 5 mmol) and *N*-acylcarbamate **20** (1.01 g, 5 mmol) in 1,4-dioxane (45 ml) was heated at 100 °C for 3 h. Dowex 50 (H^+) (15 ml) was washed with 1,4-dioxane and then added to the mixture. The mixture was heated at 100 °C for 3 h, the resin was filtered off, washed with methanol and the collected filtrates were evaporated. Crystallization of the residue from ethyl acetate afforded 1.20 g (64%) of thymine derivative **21**, m.p. 198–199 °C. For $C_{20}H_{24}N_2O_5$ (372.4) calculated: 64.50% C, 6.50% H, 7.52% N; found: 64.19% C, 6.59% H, 7.31% N. FAB MS, *m/z* (%): 373 (15) [M + H], 265 (15), 91 (100). ^{1}H NMR: 1.57 dm, 1 H, J_{gem} = 10.3 (H-7b´); 1.79 dm, 1 H (H-7a´); 1.83 m, 1 H (H-5´); 2.22 m, 1 H (H-4´); 2.65 m, 1 H (H-1´); 3.17 dd, 1 H, *J*(6´,5´) = 4.4, *J*(6´,7a´) = 1.4 (H-6´); 3.60–3.64 m, 2 H (CH_2O); 4.05 t, 1 H, *J*(2´,1´) = *J*(2´,3´) = 3.9 (H-2´); 4.31 m, 1 H (H-3´); 4.33 d, 1 H and

4.42 d, 1 H, J_{gem} = 12.1 (CH_2Ph); 4.87 t, 1 H, *J*(OH,CH_2) = 4.5 (CH_2O**H**); 4.98 d, 1 H, *J*(OH,3′) = 4.4 (3′-OH); 7.19–7.28 m, 5 H (CH_2Ph); 7.54 q, 1 H, *J*(6,CH_3) = 1.0 (H-6); 11.27 brs, 1 H (NH). ^{13}C NMR: 33.28 (C-7′); 45.18 (C-1′); 47.27 (C-4′); 51.47 (C-5′); 59.53 (CH_2O); 67.76 (C-3′); 68.20 (C-2′); 70.11 (CH_2Ph); 74.97 (C-6′); 107.91 (C-5); 127.41, 127.76, 2 C, 128.25, 2 C, and 138.44 (arom.); 139.08 (C-6); 151.84 (C-2); 163.82 (C-4).

1-[(1*R**,2*R**,3*R**,4*R**,5*S**,6*R**)-3,6-Dihydroxy-5-(hydroxymethyl)-bicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**22**)

Palladium(II) hydroxide on carbon (20% Pd, 100 mg) was added to a solution of protected compound **21** (186 mg, 0.5 mmol) in a mixture of ethanol–cyclohexene (1:1, 8 ml) and the mixture was refluxed under argon for 6 h. The catalyst was filtered off with a Celite pad, washed with methanol and the filtrates were evaporated. Crystallization of the residue from ethanol afforded 90 mg (59%) of **22**. Chromatography of the mother liquors on silica gel in ethyl acetate–acetone–ethanol–water (30:5:4:3) followed by crystallization from ethanol gave another 32 mg (21%) of the product, m.p. 212–214 °C. For $C_{13}H_{18}N_2O_5 \cdot 0.5C_2H_5OH$ (306.9) calculated: 54.80% C, 7.39% H, 9.13% N; found: 54.89% C, 7.20% H, 9.00% N. FAB MS, *m/z* (%): 283 [M + H]. ^{1}H NMR: 1.61 brd, 1 H, J_{gem} = 10.0 (H-7b′); 1.65 brddt, 1 H, *J*(5′,4′) = *J*(5′,6′) = 3.9, *J*(5′,CH_2) = 7.1 and 8.6 (H-5′); 1.72 brd, 1 H (H-7a′); 1.78 s, 3 H (CH_3); 2.17 brd, 1 H, *J*(4′,5′) = 4.0, *J*(4′,7a′) ~ *J*(4′,7b′) = 1.0 (H-4′); 2.30 brd, 1 H, *J*(1′,2′) = 3.8, *J*(1′,7a′) ~ *J*(1′,7b′) = 1.0 (H-1′); 3.36 brt, 1 H, *J*(6′,7a′) = 1.0, *J*(6′,OH) = 3.8 (H-6′); 3.64 ddd, 1 H, *J*(CH,OH) = 4.5, *J*(CH,5′) = 8.6 and 3.68 ddd, 1 H, *J*(CH,OH) = 4.5, *J*(CH,5′) = 7.1, J_{gem} = 11.0 (CH_2O); 4.01 t, 1 H, *J*(2′,1′) = *J*(2′,3′) = 3.8 (H-2′); 4.29 brt, 1 H, *J*(3′,7b′) = 1.5, *J*(3′,OH) = 3.9 (H-3′); 4.65 d, 1 H (6′-OH); 4.86 t, 1 H, *J*(OH, CH_2) = 4.5 (CH_2O**H**); 4.88 d, 1 H (3′-OH); 7.33 s, 1 H (H-6); 11.34 brs, 1 H (NH). ^{13}C NMR: 12.34 (CH_3); 32.995 (C-7′); 47.55 (C-4′); 49.10 (C-1′); 53.30 (C-5′); 67.33 (C-6′); 68.02 (C-2′); 68.46 (C-3′); 107.76 (C-5); 139.58 (C-6); 152.11 (C-2); 163.91 (C-4).

1-{(1*R**,2*R**,3*R**,4*R**,5*S**,6*R**)-6-(Benzyloxy)-3-hydroxy-5-[(trityloxy)methyl]-bicyclo[2.2.1]heptan-2-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**23**)

A solution of thymine derivative **21** (931 mg, 2.5 mmol) and trityl chloride (864 mg, 3.1 mmol) in pyridine (20 ml) was heated to 100 °C for 1 h and then pyridine was evaporated. A solution of the residue in ethyl acetate (70 ml) was washed with water (2 × 30 ml), dried over anhydrous sodium sulfate and concentrated to a small volume (ca. 7 ml). Deposited crystalline compound **23** (1.26 g, 82%), m.p. 181–182 °C, was filtered off. For $C_{39}H_{38}N_2O_5$ (614.8) calculated: 76.20% C, 6.23% H, 4.56% N; found: 75.94% C, 6.31% H, 4.39% N. FAB MS, *m/z* (%): 615 [M + H]. ^{1}H NMR: 1.51 d, 3 H, *J*(CH_3,6) = 1.2 (CH_3); 1.64 dm, 1 H, J_{gem} = 10.5 (H-7b′); 1.80 dm, 1 H (H-7a′); 2.11 m, 1 H (H-5′); 2.34 m, 1 H (H-4′); 2.79 m, 1 H (H-1′); 2.90–2.95 m, 2 H (H-6′, CH^aHO);3.11 dd, 1 H, *J*(CH,5′) = 7.1, J_{gem} = 9.5 (CH^bHO); 3.74 m, 1 H (H-3′); 3.90 t, 1 H, *J*(2′,3′) = *J*(2′,1′) = 3.9 (H-2′); 4.31 d, 1 H and 4.42 d, 1 H, J_{gem} = 12.2 (CH_2Ph); 4.99 d, 1 H (3′-OH); 6.67 q, 1 H (H-6); 7.11–7.13 m, 2 H and 7.17–7.21 m, 3 H (arom. benzyl); 7.26 m, 3 H, 7.32 m, 6 H, and 7.38 m, 6 H (arom. trityl); 11.25 brs, 1 H (NH). ^{13}C NMR: 12.25 (CH_3); 32.79 (C-7′); 44.80 and 46.09 (C-1′, C-4′); 48.78 (C-5′); 61.89 (CH_2O); 68.25 and 68.39 (C-2′, C-3′); 69.96 (CH_2Ph); 76.28 (C-6′); 86.27 (CPh_3); 108.35 (C-5); 137.79 (C-6); 151.68 (C-2); 163.55 (C-4); 127.12, 3 C, 127.95, 6 C, 128.29, 6 C, and 143.77, 3 C (arom. trityl); 127.36, 127.55, 2 C, 128.18, 2 C, and 138.20 (arom. benzyl).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-5-(Benzyloxy)- 3-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-6-[(trityloxy)methyl]bicyclo[2.2.1]heptan-2-yl Mesylate (**24**)

Mesyl chloride was added to a stirred solution of trityl derivative **23** (922 mg, 1.5 mmol) in pyridine (10 ml) at 0 °C and the solution was left standing at room temperature overnight. Then water was added (ca. 5 ml) and, after 10 min, the solvent was evaporated. The residue was partitioned between ethyl acetate (50 ml) and water (15 ml). The organic layer was separated and washed with water (2 × 15 ml), dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ether gave 911 mg (88%) of mesylate **24**, m.p. 167–168 °C. For $C_{40}H_{40}N_2O_7S$ (692.8) calculated: 69.34% C, 5.82% H, 4.04% N, 4.63% S; found: 69.17% C, 5.73% H, 3.93% N, 4.65% S. FAB MS, m/z: 693 [M + H]. ^{1}H NMR: 1.54 d, 3 H, J(CH_3,6) = 1.1 (CH_3); 1.75 brs, 2 H (2 × H-7); 2.16 m, 1 H (H-6); 2.74–2.80 m, 2 H (H-1, H-4); 3.12 s, 3 H (CH_3SO_2); 3.08–3.21 m, 3 H (H-5, CH_2O); 4.26 t, 1 H, J(3,2) = J(3,4) = 3.7 (H-3); 4.28d, 1 H and 4.37 d, 1 H, J_{gem} = 12.2 (CH_2Ph); 5.13 brd, 1 H (H-2); 6.94 q, 1 H (H-6′); 7.08–7.11 m, 2 H and 7.18–7.22 m, 3 H (arom. benzyl); 7.26 m, 3 H, 7.32 m, 6 H, and 7.37–7.41 m, 6 H (trityl); 11.25 brs, 1 H (NH). ^{13}C NMR: 12.12 (CH_3); 32.60 (C-7); 38.16 (CH_3SO_2); 45.28 and 45.60 (C-1, C-4); 48.87 (C-6); 61.35 (CH_2O); 66.42 (C-3); 70.06 (CH_2Ph); 75.42 (C-5); 78.31 (C-2); 86.55 (CPh_3); 109.17 (C-5′); 138.60 (C-6′); 151.34 (C-2′); 163.52 (C-4′); 127.17, 3 C, 127.99, 6 C, 128.28, 6 C, and 143.68, 3 C (arom. trityl); 127.46, 127.55, 2 C, 128.21, 2 C, and 137.99 (arom. benzyl).

2,3′-Anhydro-1-{(1*R**,2*R**,3*S**,4*R**,5*S**,6*R**)-6-(benzyloxy)-3-hydroxy-5-[(trityloxy)methyl]-bicyclo[2.2.1]heptan-2-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**25**)

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.3 ml, 2 mmol) was added to a stirred suspension of mesylate **24** (693 mg, 1 mmol) in acetonitrile (10 ml) and the resulting solution was heated at 60 °C for 1 h. The solution was then concentrated to a third of the original volume, diluted with ethyl acetate (60 ml), washed with water (3 × 10 ml), dried over anhydrous sodium sulfate, and evaporated. Crystallization of the residue from ethanol afforded 501 mg (84%) of **25**, m.p. 216–218 °C. For $C_{39}H_{36}N_2O_4$ (596.7) calculated: 78.50% C, 6.08% H, 4.69% N; found: 78.38% C, 6.12% H, 4.59% N. FAB MS, *m/z* (%): 597 (23) [M + H], 243 (100), 91 (94). ^{1}H NMR: 1.46 dm, 1 H, J_{gem} = 11.2 (H-7b′); 1.77 m, 1 H (H-7a′); 1.78 d, 3 H, J(CH_3,6) = 1.3 (CH_3); 2.19 m, 1 H (H-5′); 2.75 m, 1 H (H-4′); 2.85 dd, 1 H, J(6′,5′) = 3.9, J(6′,7a′) = 1.5 (H-6′); 2.91 brd, 1 H, J(1′,2′) = 5.2 (H-1′); 3.03 t, 1 H, J(CH,5′) = 9.5 and 3.21 dd, 1 H, J(CH,5′) = 4.3, J_{gem} = 9.5 (CH_2O); 4.43 s, 2 H (CH_2Ph); 4.65 dd, 1 H, J(2′,1′) = 5.2, J(2′,3′) = 10.2 (H-2′); 5.07 ddd, 1 H, J(3′,4′) = 4.6 J(3′,5′) = 1.2 (H-3′); 7.19–7.31 m, 20 H (arom.); 7.59 q, 1 H (H-6). ^{13}C NMR: 13.78 (CH_3); 33.96 (C-7′); 43.04 (C-4′); 44.15 (C-1′); 50.88 (C-5′); 60.16 (C-2′); 63.25 (CH_2O); 70.12 (CH_2Ph); 78.68 (C-6′); 81.66 (C-3′); 86.08 (CPh3); 116.69 (C-5); 132.83 (C-6); 160.39 (C-2); 170.92 (C-4); 126.95, 3 C, 127.80, 6 C, 128.30, 6 C, and 143.75, 3 C (arom. trityl); 127.46, 127.59, 2 C, 128.19, 2 C, and 138.19 (arom. benzyl).

2,3′-Anhydro-1-[(1*R**,2*R**,3*S**,4*R**,5*S**,6*R**)-3,6-dihydroxy-5-(hydroxymethyl)-bicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**26**)

Palladium(II) hydroxide on carbon (20% Pd, 150 mg) was added to a mixture of benzyl derivative **25** (597 mg, 1 mmol) in ethanol (7 ml) and cyclohexene (7 ml), the mixture was refluxed under argon for 9 h and then evaporated. The residue was extracted with methanol

(20 ml), the catalyst was then filtered off, washed with methanol and the combined filtrates were evaporated. The residue was triturated with ether. Crystallization of the residue from aqueous ethanol gave 222 mg (81%) of compound **26**, m.p. 141–143 °C (hydrate), 255–257 °C. For $C_{13}H_{16}N_2O_4 \cdot 0.5H_2O$ (273.3) calculated: 57.13% C, 6.27% H, 10.25% N; found: 57.30% C, 6.45% H, 10.03% N. FAB MS, *m/z*: 265 [M + H]. ^{1}H NMR: 1.39 dq, 1 H, *J*(7a′,1′) ~ *J*(7a′,4′) ~ *J*(7a′,6′) = 1.5, J_{gem} = 11.0 (H-7a′); 1.78 dt, 1 H, *J*(7b′,1′) ~ *J*(7b′,4′) = 1.6 (H-7b′); 1.80 d, 3 H, *J*(CH_3,6) = 1.0 (CH_3); 1.94 dddt, 1 H, *J*(5′,3′) = 1.3, *J*(5′,4′) = *J*(5′,6′) = 3.8, *J*(5′,CH_2) = 7.9 and 9.0 (H-5′); 2.57 dq, 1 H, *J*(1′,2′) = 5.0, *J*(1′,4′) ~ *J*(1′,7a′) ~ *J*(1′,7b′) = 1.2 (H-1′); 2.74 ddq, 1 H, *J*(4′,1′) ~ *J*(4′,7a′ ~ *J*(4′,7b′) = 1.4, *J*(4′,3′) = 4.8 (H-4′); 2.98 brd, 1 H, *J*(6′,7a′) = 1.5 (H-6′); 3.39 ddd, 1 H, *J*(CH,OH) = 4.5, *J*(CH,5′) = 7.0 and 3.45 ddd, 1 H, *J*(CH,OH) = 4.5, *J*(CH,5′) = 9.0, J_{gem} = 11.0 (CH_2O); 4.48 brt, 1 H (CH_2O**H**); 4.67 dd, 1 H, *J*(2′,3′) = 10.1 (H-2′); 4.89 brs, 1 H (6′-OH); 5.13 ddd, 1 H (H-3′); 7.73 brq, 1 H (H-6). ^{13}C NMR: 13.80 (CH_3); 33.655 (C-7′); 42.19 (C-4′); 47.99 (C-1′); 56.09 (C-5′); 60.72 (C-2′); 69.73 (C-6′); 82.32 (C-3′); 116.62 (C-5); 133.72 (C-6); 160.79 (C-4); 171.56 (C-2).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-6-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol (**27**) and (1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-[(2,5-Diamino-6-chloropyrimidin-4-yl)amino]-6-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol (**32**)

A solution of amine **19** (520 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (492 mg, 3 mmol) or 4,6-dichloropyrimidine-2,5-diamine (537 mg, 3 mmol), and triethylamine (0.9 ml) in ethanol (9 ml) was heated in a pressure vessel at 100 °C for 6 days and, after cooling, evaporated. The residue was chromatographed on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (180:30:23:4).

(1R,2R*,3R*,4R*,5R*,6S*)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol* (**27**): Yield after crystallization from propan-2-ol 735 mg (81%), m.p. 228–229 °C. For $C_{12}H_{17}ClN_4O_3$ (300.8) calculated: 47.92% C, 5.70% H, 11.79% Cl, 18.63% N; found: 47.72% C, 5.68% H, 11.97% Cl, 18.49% N. FAB MS, *m/z* (%): 313/311 (36/100) [M + H]. ^{1}H NMR: 1.56 dm, 1 H, J_{gem} = 9.9 (H-7b); 1.70 m, 2 H (H-7a, H-6); 2.13 m, 1 H (H-1); 2.40 m, 1 H (H-4); 3.31 td, 1 H, *J*(5,7b) = 1.4, *J*(5,6) = *J*(5,OH) = 4.7 (H-5); 3.55 m, 1 H and 3.63 m, 1 H (CH_2O); 3.74 m, 2 H (H-2, H-3); 4.36 d, 1 H, *J* = 4.7 (OH); 4.37 t, 1 H, *J*(OH,CH_2) = 5.0 (CH_2O**H**); 4.68 d, 1 H, *J* = 4.0 (OH); 5.18 s, 2 H (NH_2); 6.52 d, 1 H, *J*(NH,3) = 4.9 (NH); 7.75 s, 1 H (H-2′). ^{13}C NMR: 32.34 (C-7); 45.90 (C-1); 47.99 (C-4); 53.57 (C-6); 59.39 (CH_2O); 63.27 (C-3); 69.13 (C-5); 71.79 (C-2); 123.90 (C-5′); 136.91 (C-6′); 145.56 (C-2′); 152.08 (C-4′).

(1R,2R*,3R*,4R*,5R*,6S*)-3-[(2,5-Diamino-6-chloropyrimidin-4-yl)amino]-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol* (**32**): Yield after crystallization from ethanol 884 mg (93%), m.p. 250 °C (dec). For $C_{12}H_{18}ClN_5O_3$ (315.8) calculated: 45.65% C, 5.75% H, 11.23% Cl, 22.18% N; found: 45.38% C, 5.74% H, 11.28% Cl, 21.94% N. FAB MS, *m/z* (%): 318/316 (33/100) [M + H], 215 (35), 149 (31). ^{1}H NMR: 1.57 dm, 1 H, J_{gem} = 9.8 (H-7b); 1.66 dm, 1 H (H-7a); 1.70 m, 1 H (H-6); 2.11 m, 1 H (H-1); 2.38 m, 1 H (H-4); 3.41 brt, 1 H, *J*(5,6) = 3.4, *J*(5,OH) = 3.7 (H-5); 3.51 m, 1 H and 3.61 m, 1 H (CH_2O); 3.66 m, 1 H (H-3); 3.69 m, 1 H (H-2); 4.01 brs, 2 H (NH_2); 4.37 d, 1 H, *J*(OH,2) = 4.6 (2-OH); 4.41 t, 1 H, *J*(OH,CH_2) = 5.2 (CH_2O**H**); 4.54 d, 1 H (5-OH); 5.64 brs, 2 H (NH_2); 6.23 d, 1 H, *J*(NH,3) = 5.4 (NH). ^{13}C NMR: 32.38 (C-7); 46.02 (C-1); 48.05 (C-4); 53.27 (C-6); 59.50 (CH_2O); 62.71 (C-3); 68.94 (C-5); 72.22 (C-2); 113.59 (C-5′); 141.22 (C-6′); 155.31 and 155.74 (C-2′, C-4′).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-(6-Chloro-9*H*-purin-9-yl)-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol (**28**)

Concentrated hydrochloric acid (1.4 ml) was added to a stirred mixture of compound **27** (602 mg, 2 mmol) and triethyl orthoformate (30 ml), the resulting solution was set aside at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (20 ml). To the stirred solution, 0.5 M hydrochloric acid (20 ml) was added, the mixture was stirred at room temperature for 3 h and then neutralized with solid sodium hydrogencarbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (4 × 15 ml). The collected organic phases were dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethanol gave 580 mg (93%) of chloropurine derivative **28**, m.p. 225–226 °C. For $C_{13}H_{15}ClN_4O_3$ (310.7) calculated: 50.25% C, 4.87% H, 11.41% Cl, 18.03% N; found: 50.06% C, 4.90% H, 11.64% Cl, 17.86% N. FAB MS, *m/z* (%): 303/301 (36/100) [M + H]. ^{1}H NMR: 1.74 m, 2 H (H-7b, H-6); 1.89 dm, 1 H, J_{gem} = 9.9 (H-7a); 2.29 m, 1 H (H-1); 2.73 m, 1 H (H-4); 3.09 td, 1 H, *J*(5,7b) = 0.9, *J*(5,6) = *J*(5,OH) = 3.5 (H-5); 3.63 m, 2 H (CH_2O); 4.40 t, 1 H, *J*(3,2) = *J*(3,4) = 3.7 (H-3); 4.57 d, 1 H (5-OH); 4.67 t, 1 H, *J*(OH,CH_2) = 4.7 (CH_2O**H**); 4.80 m, 1 H (H-2); 5.21 d, 1 H, *J*(OH,2) = 4.2 (2-OH); 8.80 s, 1 H and 8.83 s, 1 H (H-2´, H-8´). ^{13}C NMR: 32.49 (C-7); 46.98 (C-1); 49.23 (C-4); 53.14 (C-6); 59.34 (CH_2O); 67.17 (C-3); 68.03 (C-5); 68.83 (C-2); 131.31 (C-5´); 146.66 (C-8´); 149.29 (C-4´); 151.54 (C-2´);152.75 (C-6´).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-(6-Amino-9*H*-purin-9-yl)-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol (**29**)

A solution of chloropurine derivative **28** (211 mg, 0.7 mmol) in liquid ammonia (15 ml) was heated in an autoclave at 70 °C for 48 h and then ammonia was evaporated. Crystallization of the residue from water gave 148 mg (73%) of adenine derivative **29**, m.p. 164–165.5 °C. For $C_{13}H_{17}N_5O_3$ (291.3) calculated: 53.60% C, 5.88% H, 24.04% N; found: 53.35% C, 5.86% H, 23.83% N. FAB MS, *m/z* (%): 292 (100) [M + H], 181 (29), 136 (44). ^{1}H NMR: 1.67–1.76 m, 2 H (H-7b, H-6); 1.85 brd, 1 H, J_{gem} = 9.8 (H-7a); 2.26 brd, 1 H, *J*(1,6) = 2.8 (H-1); 2.60 m, 1 H (H-1); 3.12 brt, 1 H, *J*(5,6) = 3.7 (H-5); 3.62–3.68 m, 2 H (CH_2O); 4.28 t, 1 H, *J*(3,2) = *J*(3,4) = 4.8 (H-3); 4.54 d, 1 H, *J*(5,OH) = 4.5 (5-OH); 4.63 t, 1 H, *J*(OH,CH_2) = 4.8 (CH_2O**H**); 4.66 brs, 1 H (H-2); 5.13 d, 1 H, *J*(OH,2) = 4.2 (2-OH); 7.20 brs, 2 H (NH_2); 8.15 s, 1 H (H-2´); 8.23 s, 1 H (H-8´). ^{13}C NMR: 32.62 (C-7); 46.81 (C-1); 49.37 (C-4); 53.48 (C-6); 59.39 (CH_2O); 66.27 (C-3); 68.19 (C-5); 68.91 (C-2); 119.31 (C-5´); 139.88 (C-8´); 150.48 (C-4´); 152.52 (C-2´); 156.17 (C-6´).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-[6-(Dimethylamino)-9*H*-purin-9-yl]-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol (**30**)

Compound **28** (155 mg, 0.5 mmol) was dissolved under stirring in dimethylammonium dimethylcarbamate (2 ml), the solution was left standing at room temperature for 5 h and then evaporated. Crystallization of the residue from water afforded 152 mg (95%) of **30**, m.p. 240–242 °C. For $C_{15}H_{21}N_5O_3$ (319.4) calculated: 56.41% C, 6.63% H, 21.93% N; found: 56.25% C, 6.72% H, 21.84% N. FAB MS, *m/z* (%): 320 (100) [M + H], 164 (35). ^{1}H NMR: 1.68–1.76 m, 2 H (H-7b, H-6); 1.86 dm, 1 H, J_{gem} = 10.2 (H-7a); 2.27 m, 1 H (H-1); 2.60 m, 1 H (H-4); 3.11 td, 1 H, *J*(5,7b) = 1.4, *J*(5,6) = 4.3, *J*(5,OH) = 4.5 (H-5); 3.46 brs, 6 H (CH_3); 3.64 m, 2 H (CH_2O); 4.30 t, 1 H, *J*(3,2) = *J*(3,4) = 3.8 (H-3); 4.51 d, 1 H (5-OH); 4.62 t, 1 H,

J(OH,CH_2) = 4.7 (CH_2O**H**); 4.63 m, 1 H (H-2); 5.11 d, 1 H, *J*(OH,2) = 4.2, 8.23 s, 1 H and 8.24 s, 1 H (H-2´, H-8´). ^{13}C NMR: 32.61 (C-7); 38.02, 2 C (2 × CH_3); 46.82 (C-1); 49.16 (C-4); 53.45 (C-6); 59.32 (CH_2O); 66.14 (C-3); 68.07 (C-5); 68.92 (C-2);119.82 (C-5´); 138.54 (C-8´); 151.21 (C-4´); 151.78 (C-2´); 154.42 (C-6´).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol (**31**)

A solution of chloropurine **28** (155 mg, 0.5 mmol) in cyclopropylamine (2 ml) was kept at room temperature overnight and then was evaporated. Chromatography of the residue on a silica gel (15 g) column in ethyl acetate–acetone–ethanol–water (90:15:12:8) afforded, after crystallization from ethanol, 121 mg (73%) of compound **31**, m.p. 245.5–247 °C. For $C_{16}H_{21}N_5O_3$ (331.4) calculated: 57.99% C, 6.39% H, 21.13% N; found: 57.72% C, 6.44% H, 20.90% N. FAB MS, *m/z*: 332 [M + H]. ^{1}H NMR: 0.62 m, 2 H, 0.73 m, 2 H, and 3.08 brs, 1 H (cyclopropyl); 1.70 dm, 1 H, J_{gem} = 10.1 (H-7b); 1.74 m, 1 H (H-6); 1.85 dm, 1 H (H-7a); 2.26 m, 1 H (H-1); 2.61 m, 1 H (H-4); 3.12 td, 1 H, *J*(5,7b) = 1.3, *J*(5,6) = 4.3, *J*(5,OH) = 4.5 (H-5); 3.64 m, 2 H (CH_2OH); 4.29 t, 1 H, *J*(3,2) = *J*(3,4) = 3.9 (H-3); 4.51 d, 1 H (5-OH); 4.60 t, 1 H, *J*(OH,CH_2) = 4.9 (CH_2O**H**); 4.66 m, 1 H (H-2); 5.11 d, 1 H, *J*(OH,2) = 4.2 (2-OH); 7.81 brd, 1 H, *J* = 3.6 (NH); 8.22 s, 1 H and 8.25 s, 1 H (H-2´, H-8´). ^{13}C NMR: 6.55, 2 C and 24.08 (cyclopropyl); 32.55 (C-7); 46.77 (C-1); 49.31 (C-4); 53.43 (C-6); 59.35 (CH_2O); 66.23 (C-3); 68.15 (C-5); 68.89 (C-2); 119.63 (C-5´); 139.63 (C-8´); 150.12 (C-6´); 152.33 (C-2´); 155.71 (C-4´).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-(2-Amino-6-chloro-9*H*-purin-9-yl)-6-(hydroxymethyl)-bicyclo[2.2.1]heptane-2,5-diol (**33**)

A mixture of triethyl orthoformate (45 ml), pyrimidine derivative **32** (622 mg, 2 mmol), and concentrated hydrochloric acid (1.9 ml) was stirred at room temperature for 4 days and then evaporated. The residue was dissolved in tetrahydrofuran (25 ml). To the stirred solution, 0.5 M hydrochloric acid (25 ml) was added, the mixture was stirred 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 × 15 ml). The collected organic layers were dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from water afforded 404 mg (62%) compound **33**, m.p. 256 °C (dec). For $C_{13}H_{16}ClN_5O_3$ (325.8) calculated: 47.93% C, 4.95% H, 10.88% Cl, 21.50% N; found: 47.70% C, 4.88% H, 10.70% Cl, 21.30% N. FAB MS, *m/z* (%): 328/326 (36/100) [M + H]. ^{1}H NMR: 1.68–1.75 m, 2 H (H-6, H-7b); 1.80 dm, 1 H, J_{gem} = 10.1 (H-7a); 2.25 m, 1 H (H-1); 2.57 m, 1 H (H-4); 3.18 td, 1 H, *J*(5,7b) = 1.5, *J*(5,6) = 4.2, *J*(5,OH) = 4.3 (H-5); 3.63 m, 2 H (CH_2O); 4.16 t, 1 H, *J*(3,2) = *J*(3,4) = 3.8 (H-3); 4.54 d, 1 H (5-OH); 4.55 brs, 1 H (H-2); 4.64 t, 1 H, *J*(OH,CH_2) = 4.8 (CH_2O**H**); 5.10 d, 1 H, *J*(OH,2) = 4.1 (2-OH); 6.91 brs, 2 H (NH_2); 8.23 s, 1 H (H-8´). ^{13}C NMR: 32.58 (C-7); 46.89 (C-1); 48.90 (C-4); 53.16 (C-6); 59.34 (CH_2O); 66.24 (C-3); 68.01 (C-5); 69.06 (C-2); 123.75 (C-5´); 141.95 (C-8´); 149.58 (C-4´); 154.96 (C-6´); 159.82 (C-2´).

(1*R**,2*R**,3*R**,4*R**,5*R**,6*S**)-3-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-6-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol (**34**)

A solution of chloropurine **33** (163 mg, 0.5 mmol) in cyclopropylamine (2 ml) was left standing at room temperature overnight and then was evaporated. Crystallization of the residue from water gave 154 mg (89%) of compound **33**, m.p. 240–243 °C. For $C_{16}H_{22}N_6O_3$ (346.4) calculated: 55.48% C, 6.40% H, 24.26% N; found: 55.19% C, 6.43% H, 23.98% N. FAB MS, *m/z* (%): 347 (100) [M + H], 191 (45). ^{1}H NMR: 0.56–0.69 m, 4 H and 3.05 brs, 1 H (cyclopropyl); 1.68 dm, 1 H, J_{gem} = 10.0 (H-7b); 1.74 m, 1 H (H-6); 1.79 dm, 1 H (H-7a); 2.24 m, 1 H (H-1); 2.52 m, 1 H (H-4); 3.22 td, 1 H, *J*(5,7b) = 1.2, *J*(5,6) = *J*(5,OH) = 4.2 (H-5); 3.60 m, 2 H (CH_2O); 4.08 t, 1 H, *J*(3,2) = *J*(3,4) = 3.8 (H-3); 4.40 m, 1 H (H-2); 4.54 d, 1 H (5-OH); 4.57 t, 1 H, *J*(OH,CH_2) = 5.1 (CH_2O**H**); 5.06 d, 1 H, *J*(OH,2) = 4.0 (2-OH); 5.85 brs, 2 H (NH_2); 7.23 brs, 1 H (NH); 7.75 s, 1 H (H-8´). ^{13}C NMR: 6.57, 2 C, and 24.01 (cyclopropyl); 32.65 (C-7); 46.44 (C-1); 48.86 (C-4); 53.42 (C-6); 59.34 (CH_2O); 65.62 (C-3); 68.29 (C-5); 69.46 (C-2); 113.90 (C-5´); 135.80 (C-8´); 152.28 (C-4´); 156.06 (C-6´); 160.19 (C-2′).

The cytostatic activity was studied by Dr I. Votruba from the Institute and the antiviral activity was tested by Dr J. Balzarini (Rega Institute, Katholieke Universiteit Leuven, Belgium). Their contribution is gratefully acknowledged. 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) and the Grant Agency of the Czech Republic (grant No. 203/05/0132).

REFERENCES

1. Kusaka T., Yamamoto H., Shibata M., Muroi M., Kishi T., Mizuno K.: *J. Antibiot.* **1968**, *21*, 255.
2. Yaginuma S., Muto N., Tsujino M., Sudate Y., Hayashi M., Otani M.: *J. Antibiot.* **1981**, *34*, 359.
3. a) Vince R., Hua M.: *J. Med. Chem.* **1990**, *33*, 17; b) Parker W. B., Shaddix S. C., Bowdon B. J., Rose L. M., Vince R., Shannon W. N., Bennett L. L.: *Antimicrob. Agents Chemother.* **1993**, *37*, 1004.
4. 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.
5. Kim H. S., Jacobson K. A.: *Org. Lett.* **2003**, *5*, 1665.
6. 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.
7. Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 103.
8. Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 519.
9. Šála M., Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2006**, *71*, 635.
10. Adam W., DeLucchi O., Pasquato L., Will B.: *Chem. Ber.* **1987**, *120*, 531.
11. Baldwin S. W., Tomesch J. C.: *J. Org. Chem.* **1974**, *39*, 2382.

12. Linz G., Weetman J., Hady A. F. A., Helmchen G.: *Tetrahedron Lett.* **1989**, *30*, 5599.
13. VanRheenen V., Kelly R. C., Cha D. Y.: *Tetrahedron Lett.* **1976**, 1973.
14. Gao Y., Sharpless K. B.: *J. Am. Chem. Soc.* **1988**, *110*, 7538.
15. a) Tippie M. A., Martin J. C., Smee D. F., Mathews T. R., Verheyden J. P. H.: *Nucleosides Nucleotides* **1984**, *3*, 525; b) Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 435; c) Šála M., Hřebabecký H., Masojídková M., Holý A.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 918.
16. a) Greenberg S. M., Ross L. O., Robins R. K.: *J. Org. Chem.* **1959**, *24*, 1314; b) Bhushan R. S., Vince R.: *Bioorg. Med. Chem.* **2002**, *10*, 2325; c) Legraverend M., Boumchita H., Bisagni E: *Synthesis* **1990**, 587.
17. Votruba I.: Unpublished results.
18. Balzarini J.: Unpublished resuts.