SYNTHESIS OF NOVEL RACEMIC CARBOCYCLIC NUCLEOSIDES DERIVED FROM 5,6-DISUBSTITUTED NORBORNENE

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Novel class of the carbocyclic nucleosides based on bicyclo[2.2.1]heptene/heptane was prepared by two approaches. Thymine analogues were synthesized starting from methyl (1*R**,4*S**)-bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate **1** by Michael addition of the thymine salt to the double bond as the key step. The yield and ratio of the isomers of this reaction depended on the used base (DBU, K_2CO_3). Purine nucleoside analogues were synthesized by the linear synthesis, the purine nucleobase was build-up on the amino group. The amino groups (*exo*/*endo* configuration) were introduced to the scaffold by the Curtius rearrangement. Norbornene analogues were converted to saturated and *cis*-hydroxylated nucleoside derivatives. [(1*R**,2*S**,3*S**,4*S**)-3-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol (**13a**) and [(1*R**,2*R**,3*R**,4*S**)-3-(6-chloro-9*H*-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol (**13b**) showed moderate activity against *Coxsackie* virus CVB3.

Keywords: Carbanucleosides; Carbocyclic nucleosides; Nucleosides; Norbornenes; Purines; *Coxsackie* virus; Michael addition; Amino alcohols; Curtius rearrangement.

Carbocyclic nucleosides are interesting group of compounds in which the endocyclic oxygen of the nucleoside sugar ring has been replaced by a methylene group[1]. This modification increases the enzymatic stability against phosporylases and also increases the absorption and penetration of this compound through the cell membrane due the enhanced lipophilicity. This group of compounds represents an extremely important class of potentially active therapeutic agents, e.g. abacavir[2] has been approved by the

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FDA as a drug for the treatment of HIV infections and entecavir[3] for the treatment of chronic hepatitis B virus infections.

In our ongoing research we have synthesized a series of the novel racemic conformationally-locked carbocyclic purine nucleoside analogues derived from 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-6-methanol[4], 4-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-9-methanol and their Pro-Tides[5], 5,5- and 6,6-bis(hydroxymethyl)-bicyclo[2.2.1]heptan-2-ols[6], 3-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol[7], 2- and 3-(hydroxymethyl)bicyclo[2.2.1]heptanes[8], 5- or 6-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol[9], 4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol and 4-oxatricyclo[4.3.1.$0^{3,7}$]decane-10-methanol[10], 7-oxabicyclo[2.2.1]-heptane-2-methanol[11] and analogues with a bicyclo[2.2.1]heptene or -heptane ring system substituted with nucleobase at position 7 with *syn*-configuration[12] and also *anti*-configuration[13].

This study concerns a synthesis of novel racemic conformationally locked nucleoside analogues containing bicyclo[2.2.1]hept-2-ene or heptane ring substituted with base and hydroxymethyl group at the 5,6-*trans* positions. Carbocyclic nucleosides with this unusual 1,2-positions of base and hydroxymethyl group were also descibed[14]. General formulae of target compounds are shown in Chart 1.

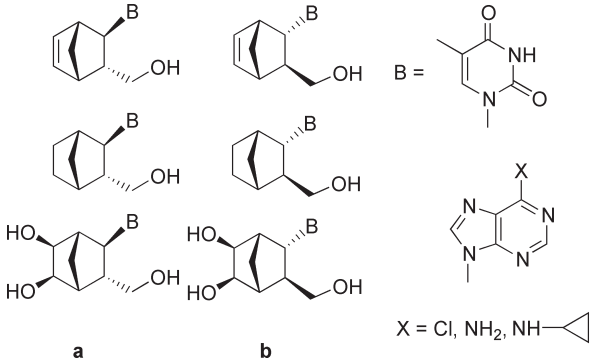
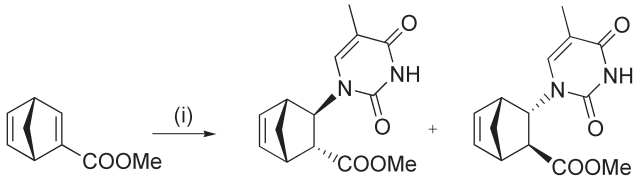


CHART 1

Synthetic strategy was originally based on Michael addition of the nucleobase to the activated double bond (see ref.[15] for acyclic nucleosides and ref.[16] for the carbocyclic nucleosides). Addition of thymine to ester **1** (ref.[17]) in the presence of the base (DBU, K_2CO_3) gave moderate yields of isomers **2a** and **2b** (Scheme 1). Only isomers with *trans*-configuration were observed in reaction mixture. These isomers were easily separated by column chromatography. The ratio of the *exo*-**2a** and *endo*-**2b** depended on the used base. In the case of DBU the ratio **2a**/**2b** was 3.5:1 (total yield

46%), whereas when potassium carbonate was used, the ratio was almost completely conversely – 1:2.5 (total yield 56%). However, this conjugate addition is not suitable for preparing purine nucleoside derivatives. Addition of adenine, N^6-benzoyl adenine and 6-chloropurine led to complicated reaction mixtures. In case of adenine (or protected adenine) addition, the pair (*exo*/*endo*) of the 3-substituted adenine derivatives was detected as a by-product. The same reaction with 6-chloropurine as a nucleobase gave pair of the 7-isomers followed the desired 9-isomers. The yields of these additions were also low and isolation of the pure isomers was not successful.



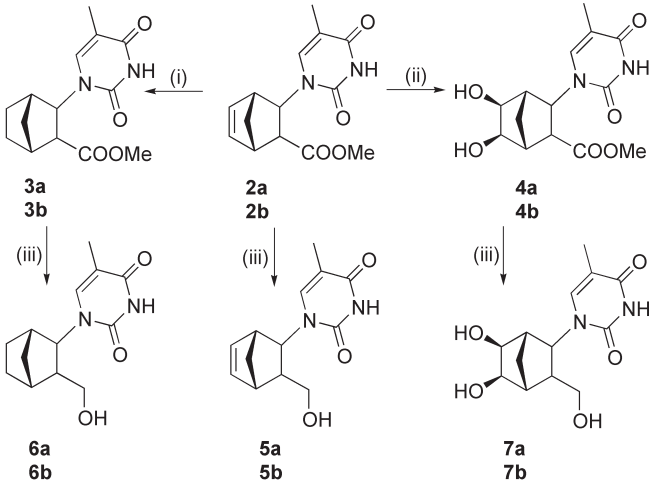
1 **2a** **2b**

(i) Method *A*: thymine, DBU, DMF, 75 °C, 35% of **2a**, 10% of **2b**, or method *B*: thymine, K_2CO_3, DMF, 75 °C, 16% of **2a**, 40% of **2b**

SCHEME 1

Target thymine nucleosides were prepared by standard reaction procedures (Scheme 2). Ester group on unsaturated esters **2a** and **2b** was reduced with lithium aluminium hydride (2.5 equivalents) in tetrahydrofurane to afford hydroxymethyl group (54% for **5a** and 69% for **5b**). Saturated nucleosides were prepared in simple two steps: the double bond was hydrogenated on palladium hydroxide (86% of **3a** and 84% of **3b**) and then the ester group was reduced to hydroxymethyl group with lithium aluminium hydride under the same conditions as for unsaturated compounds giving **6a** (55%) and **6b** (70%). The esters with two *cis*-hydroxy groups at the skeleton were prepared in excellent yields (98% of **4a** and 91% of **4b**) by osmium tetroxide catalyzed *cis*-hydroxylation in acetone–water mixture with *N*-methylmorpholine-*N*-oxide (NMMO) as a recovering agent for osmium catalytic cycle. Treatment of the *cis*-hydroxyesters **4a** and **4b** with lithium aluminium hydride led to *cis*-hydroxy nucleoside derivatives **7a** (39%) and **7b** (58%).

When the Michael addition strategy was abandoned, it was necessary to find a new route leading to the purine nucleosides. We have chosen Curtius rearrangement for the introduction of the amino function. The purine

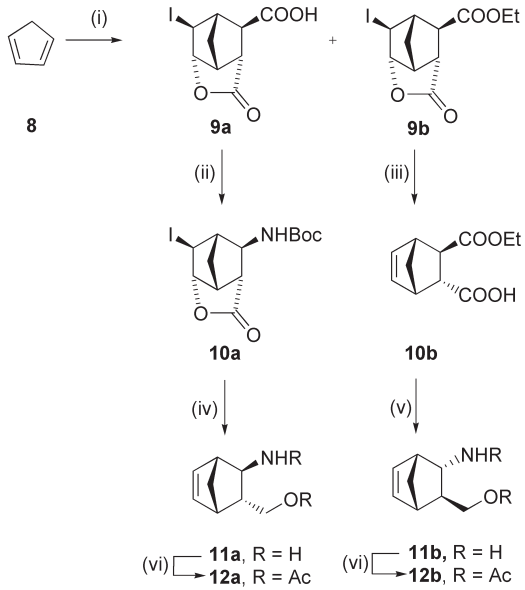


(i) H_2, $Pd(OH)_2/C$, MeOH, 86% of **3a**, 84% of **3b**; (ii) OsO_4, acetone-water, 98% of **4a**, 91% of **4b**; (iii) $LiAlH_4$, THF, r.t. 54% of **5a**, 69% of **5b**, 55% of **6a**, 70% of **6b**, 39% of **7a**, 58% of **7b**

SCHEME 2

nucleobase was then built up by standard procedures[12] at this amino function. The synthesis started by reaction of cyclopentadiene **8** and fumaric acid monoethyl ester (Scheme 3). The Diels–Alder adducts were treated with iodine and sodium bicarbonate in the presence of potassium iodide[18]. Two products were obtained – iodoacid **9a** (41%) and iodoester **9b** (31%). This step allowed the separation of these crucial intermediates by simple acid/base extraction. Both individuals were utilized for preparation of the isomeric aminoalcohols **11a** and **11b** in four steps. Iodoacid **9a** was firstly converted to Boc-protected amine **10a** (51%) by Curtius rearrangement. Double bond was restored with zinc in refluxing ethanol–water solution. Protected amino acid was immediately deprotected under acidic conditions and carboxylic acid was subsequently reduced with lithium aluminium hydride in THF to aminoalcohol **11a** (total yield of three steps from **10a** is 61%). Synthesis of the aminoalcohol **11b** was realized in the similar way, only the reaction sequence was different. Iodoester **9b** was firstly converted to acid **10b** by the zinc deiodolactonization (quantitative) and the carboxylic group was then degraded by the Curtius reaction. Boc-protected amine was not prepared in this case and the formed carbamic acid was directly decomposed to amino function under acidic conditions (reflux with aqueous 2 M HCl in THF). This amino acid intermediate was then reduced with

lithium aluminium hydride in THF to the aminoalcohol **11b** (total yield from **10b** is 67%). Both amines were used crude for the next step and the compounds were fully characterized as acetyl derivatives **12a** (80%) and **12b** (92%).

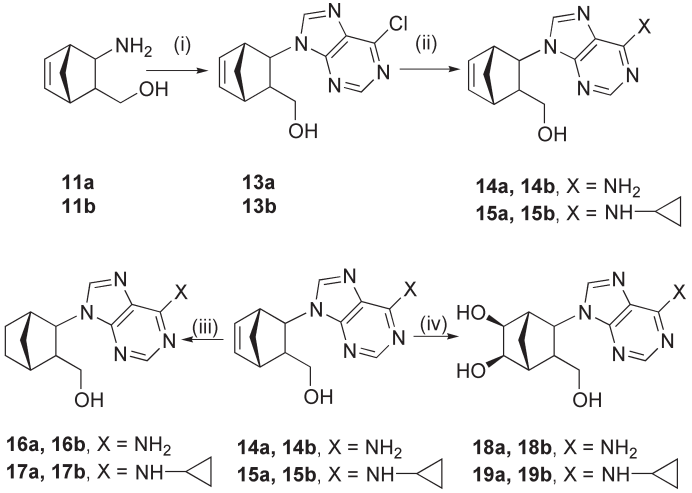


(i) 1. Fumaric acid monoethyl ester, dioxane 60 °C, 2. I_2, KI, Na_2CO_3, H_2O-$CHCl_3$, r.t., 31% of **9a**, 41% of **9b**; (ii) 1. ClCOOEt, Et_3N, acetone, 0 °C, NaN_3, H_2O-acetone, 0 °C, 3. benzene, *t*-BuOH, reflux, 51%; (iii) Zn, EtOH, reflux, quant.; (iv) 1. Zn, EtOH, reflux, 2. HCl, MeOH, 3. $LiAlH_4$, THF, reflux, 61%; (v) 1. ClCOOEt, Et_3N, acetone, 0 °C, 2. NaN_3, H_2O-acetone, 0 °C, tolulene, aq. HCl; 4. $LiAlH_4$, THF, reflux, 67%; (vi) Ac_2O, pyridine, r.t., 80% of **12a**, 92% of **12b**

SCHEME 3

The aminoalcohols **11a** and **11b** were used to build the target nucleoside analogues using standard and described synthetic procedure (Scheme 4). Amino group was coupled with 4,6-dichloropyrimidin-5-amine in ethanol in the presence of triethylamine and purine ring was closed with triethyl orthoformate in the presence of concentrated hydrochloric acid to give chloropurine derivatives **13a** (60%) and **13b** (55%). Ammonolysis of the chlorine atom with liquid ammonia at 75 °C led to adenine derivatives **14a** (83%) and **14b** (82%). Nucleophilic substitution of the chlorine atom with cyclopropylamine gave cyclopropylamino nucleosides **15a** (89%) and

15b (94%). Double bond in nucleosides **14** and **15** was utilized in two ways using the same methods as described above for preparation of saturated and *cis*-hydroxy thymine nucleosides (Scheme 4). As it was observed previously[13], it was not necessary to protect the free hydroxy group. Hydrogenation of the compounds **14** and **15** gave saturated compounds **16** and **17** and *cis*-hydroxylation of **14** and **15** led to diols **18** and **19**.



(i) 1. 4,6-dichloropyrimidin-5-amine, Et_3N, EtOH, 100 °C, 2. $CH(OEt)_3$, HCl, 3. HCl, THF-H_2O, 60% of **13a**, 55% of **13b**; (ii) NH_3 (l), 75 °C, 83% of **14a**, 82% of **14b**, or cyclopropylamine, MeOH, 89% of **15a**, 94% of **15b**; (iii) H_2, $Pd(OH)_2$/C, MeOH, 86% of **16a**, 78% of **16b**, 75% of **17a**, 78% of **17b**; (iv) OsO_4, NMMO, acetone-water, 62% of **18a**, 95% of **18b**, 85% of **19a**, 78% of **19b**

SCHEME 4

In conclusion, we have synthesized a novel series of carbocyclic nucleosides based on the norbornene or norbornane skeleton, in which the nucleobase and the hydroxymethyl group have a *trans*-1,2-relationship. We used two methodologies, direct addition of the nucleobase by conjugate addition for the thymine nucleosides and build-up strategy for purine nucleosides. 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 a considerable activity[19]. The compounds were also tested for anti-HIV-1

and anti-HIV-2 activity in human T-lymphocyte (CEM) cells and for the activity against *Coxsackie* virus (CVB3) in Vero cells. Preliminary data showed that only compounds **13a** and **13b** exhibit a weak activity (**13a**: EC_{50} = 20.2 μM, TC_{50} > 361 μM; **13b**: EC_{50} = 43.3 μM, TC_{50} > 361 μM) against *Coxsackie* virus (CVB3).

EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. NMR spectra (δ, ppm; *J*, Hz) were measured on a Bruker Avance II-600 and/or Bruker Avance II-500 instruments (600.1 or 500.0 MHz for ^{1}H and 150.9 or 125.7 MHz for ^{13}C) in hexadeuterodimethyl 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 (ionization with Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3:1 or bis-(2-hydroxyethyl) disulfide matrix) or LTQ Orbitrap XL (Thermo Fisher Scientific) for ESI. Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol Silica gel 60 F254 foils (Merck). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; the compounds were dried at 50 °C/13 Pa.

Methyl (1*R**,2*S**,3*S**,4*S**)-3-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (**2a**) and
Methyl (1*R**,2*R**,3*R**,4*S**)-3-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (**2b**)

Method A: A mixture of thymine (340 mg, 2.70 mmol), methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate **1** (600 mg, 4 mmol) and DBU (0.2 ml, 1.35 mmmol) in DMF (10 ml) was stirred at 75 °C for 72 h in an argon atmosphere, then AcOH (0.1 ml) was added and mixture was evaporated. The residue was adsorbed on silica gel and chromatographed on silica gel column (200 g) in ethyl acetate–toluene (20:1). Mixed fractions were re-chromatographed. It was obtained 260 mg (35%) of product **2a** and 75 mg (10%) of product **2b**. Analytical samples were obtained by crystallization from ethyl acetate.

Method B: A mixture of thymine (340 mg, 2.70 mmol), methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate **1** (600 mg, 4 mmol) and potassium carbonate (550 mg, 4 mmol) in DMF (10 ml) was stirred at 75 °C for 72 h in an argon atmosphere and mixture was evaporated. The residue was adsorbed on silica gel and chromatographed on silica gel column (200 g) in ethyl acetate–toluene (20:1). Mixed fractions were rechromatographed. It was obtained 120 mg (16%) of product **2a** and 292 mg (40%) of product **2b**.

Methyl (1R,2S*,3S*,4S*)-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate* (**2a**): M.p. 178–181 °C. ^{1}H NMR: 1.55 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) ~ 1.7, J_{gem} = 9.3 (H-7b); 1.79 brdt, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ 1.2 (H-7a); 1.79 d, 3 H, *J*(CH_3,6′) = 1.0 (CH_3); 3.01 brdq, 1 H, *J*(4,1) ~ 1.5, *J*(4,5) = 3.3 (H-4); 3.11 brt, 1 H, *J*(2,1) = 3.6, *J*(2,3) = 4.2 (H-2); 3.12 m, 1 H (H-1); 3.55 s, 3 H (OCH_3); 4.24 brdd, 1 H, *J*(3,4) < 1.0 (H-3); 6.13 dd, 1 H, *J*(6,1) = 2.6, *J*(6,5) = 5.6 (H-6); 6.30 dd, 1 H, *J*(5,4) = 3.3 (H-5); 7.68 q, 1 H (H-6′); 11.26 s, 1 H (NH). ^{13}C NMR: 12.30 (CH_3); 45.30 (C-1); 46.91 (C-4); 46.93 (C-7); 48.38 (C-2); 51.74 (OCH_3); 59.96 (C-3); 108.68 (C-5′); 136.25 (C-5); 136.80 (C-6); 137.56 (C-2′); 163.92 (C-4′); 172.94 (CO). FAB MS, *m/z* (rel.%): 277 (91) [M + H], 245 (20), 127 (61),

91 (100). For $C_{14}H_{16}N_2O_4$ (276.3) calculated: 60.86% C, 5.84% H, 10.14% N; found: 60.66% C, 5.81% H, 9.91% N.

Methyl (1R,2R*,3R*,4S*)-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate* (**2b**): M.p. 198–201 °C. ^{1}H NMR: 1.43 dq, 1 H, *J*(7b,1) = 1.8, *J*(7b,2) = *J*(7b,4) = 2.2, J_{gem} = 9.2 (H-7b); 1.71 brdt, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ 1.1 (H-7a); 1.73 d, 3 H, *J*(CH_3,6′) = 1.2 (CH_3); 2.59 dd, 1 H, *J*(2,3) = 4.8 (H-2); 3.04 m, 1 H (H-1); 3.13 m, 1 H (H-4); 3.64 s, 3 H (OCH_3); 5.10 dd, 1 H, *J*(3,4) = 3.4 (H-3); 6.14 dd, 1 H, *J*(5,4) = 2.2, *J*(5,6) = 5.6 (H-5); 6.49 dd, 1 H, *J*(6,1) = 3.2 (H-6); 7.22 q, 1 H (H-6′); 11.27 s, 1 H (NH). ^{13}C NMR: 12.28 (CH_3); 45.66 (C-4); 46.10 (C-7); 47.22 (C-1); 47.76 (C-2); 52.13 (OCH_3); 59.41 (C-3); 108.08 (C-5′); 133.64 (C-5); 137.74 (C-6′); 138.86 (C-6); 151.69 (C-2′); 163.88 (C-4′); 173.95 (CO). FAB MS, *m/z* (rel.%): 277 (100) [M + H], 245 (17), 127 (36), 91 (80). For $C_{14}H_{16}N_2O_4$ (276.3) calculated: 60.86% C, 5.84% H, 10.14% N; found: 60.74% C, 5.70% H, 9.96% N.

Methyl (1*R**,2*R**,3*R**,4*S**)-3-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[2.2.1]heptane-2-carboxylate (**3a**) and
Methyl (1*R**,2*S**,3*S**,4*S**)-3-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[2.2.1]heptane-2-carboxylate (**3b**)

A mixture of unsaturated ester **2** (280 mg, 1 mmol) and palladium on charcoal (100 mg) in methanol (30 ml) was stirred in atmosphere of hydrogen for 5 h. The catalyst was filtered off and washed with methanol and filtrate was evaporated. The residue was chromatographed on silica gel (10 g) in ethyl acetate–toluene (10:1).

Methyl (1R,2R*,3R*,4S*)-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)bicyclo[2.2.1]-heptane-2-carboxylate* (**3a**): Yield 246 mg (86%) as a foam. ^{1}H NMR: 1.25 dddd, 1 H, *J*(5en,7a) = 2.2, *J*(5en,6ex) = 4.6, *J*(5en,6en) = 8.8, J_{gem} = 12.2 (H-5en); 1.28 ttd, 1 H, *J*(6ex,2) = 1.7, *J*(6ex,1) = 4.5, *J*(6ex,5ex) = 12.2 (H-6ex); 1.36 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) = 1.6, J_{gem} = 10.6 (H-7b); 1.41 dddd, 1 H, *J*(6en,7a) = 1.8, *J*(6en,5ex) = 4.4 (H-6en); 1.62 tt, 1 H, *J*(5ex,4) = 4.5 (H-5ex); 1.75 brdpent, 1 H, *J*(7a,1) ~ *J*(7a,4) = 1.7 (H-7a); 1.78 d, 3 H, *J*(CH_3,6′) = 1.1 (CH_3); 2.43 brdq, 1 H, *J*(4,1) = 4.5 (H-4); 2.54 brtq, 1 H, *J*(1,2) = 4.5 (H-1); 2.99 brdt, 1 H, *J*(2,3) = 5.0 (H-2); 3.61 s, 3 H (OCH_3); 4.37 dd, 1 H (H-3); 7.61 q, 1 H (H-6′); 11.23 s, 1 H (NH). ^{13}C NMR: 12.30 (CH_3); 23.56 (C-6); 27.35 (C-5); 37.54 (C-7); 40.03 (C-1); 41.00 (C-4); 51.72 (C-2); 53.15 (OCH_3); 61.21 (C-3); 108.43 (C-5′); 137.50 (C-6′); 151.33 (C-2′); 163.91 (C-4′); 172.63 (CO). FAB MS, *m/z* (rel.%): 279 (100) [M + H], 247 (15), 153 (10), 127 (54), 121 (30). For $C_{14}H_{18}N_2O_4$ (278.3) calculated: 60.42% C, 6.52% H, 10.07% N; found: 60.29% C, 6.63% H, 9.84% N.

Methyl (1R,2S*,3S*,4S*)-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)bicyclo[2.2.1]-heptane-2-carboxylate* (**3b**): Yield 236 mg (84%). M.p. 212–215 °C (ethyl acetate). ^{1}H NMR: 1.25 dddd, 1 H, *J*(5en,7a) = 2.0, *J*(5en,6ex) = 4.3, *J*(5en,6en) = 8.8, J_{gem} = 12.2 (H-5en); 1.30 dq, 1 H, *J*(7b,1) ~ *J*(7b,2) ~ *J*(7b,4) = 1.7, J_{gem} = 10.7 (H-7b); 1.42 tddd, 1 H, *J*(5ex,3) = 1.7, *J*(5ex,4) = 4.4, *J*(5ex,6en) = 4.9, *J*(5ex,6ex) = 12.0 (H-5ex); 1.57 brdpent, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ *J*(7a,4) ~ 1.5 (H-7a); 1.60 m, 2 H (H-6en, H-6ex); 1.79 d, 3 H, *J*(CH_3,6′) = 1.0 (CH_3); 2.49 m (H-1); 2.51 m, 1 H (H-4); 2.84 dd, 1 H, *J*(2,3) = 6.0 (H-2); 3.61 s, 3 H (OCH_3); 4.81 dd, 1 H, *J*(3,4) = 3.9 (H-3); 7.51 q, 1 H (H-6′); 11.29 s, 1 H (NH). ^{13}C NMR: 12.22 (CH_3); 21.00 (C-5); 27.96 (C-6); 36.17 (C-7); 40.20 (C-4); 41.41 (C-1); 47.32 (C-2); 52.07 (OCH_3); 60.46 (C-3); 108.18 (C-5′); 138.33 (C-6′); 151.69 (C-2′); 163.86 (C-4′); 173.98 (CO). FAB MS, *m/z* (rel.%): 279 (100) [M + H], 247 (23), 153 (10), 127 (29), 121 (44). For $C_{14}H_{18}N_2O_4$ (278.3) calculated: 60.42% C, 6.52% H, 10.07% N; found: 60.29% C, 6.54% H, 9.97% N.

Methyl (1*R**,2*R**,3*R**,4*S**,5*S**,6*R**)-5,6-Dihydroxy-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[2.2.1]heptane-2-carboxylate (**4a**) and Methyl (1*R**,2*S**,3*S**,4*S**,5*S**,6*R**)-5,6-Dihydroxy-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[2.2.1]heptane-2-carboxylate (**4b**)

Ester **2** (250 mg, 0.90 mmol) was dissolved in mixture of acetone (25 ml) and water (2.5 ml). Solution of NMMO (50%, 1.6 ml) and aqueous solution of osmium tetroxide (30 µl, 20%) was added and the reaction mixture was stirred at r.t. for 3 h and taken down. The product was isolated by column chromatography on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (105:15:3:2).

Methyl (1R,2R*,3R*,4S*,5S*,6R*)-5,6-dihydroxy-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)bicyclo[2.2.1]heptane-2-carboxylate* (**4a**): Yield 275 mg (98%). M.p. 206–209 °C (ethanol). ^{1}H NMR: 1.33 brdpent, 1 H, *J* (7a,1) ~ *J*(7a,4) ~ *J*(7a,5) ~ *J*(7a,6) ~ 1.5, J_{gem} = 10.9 (H-7a); 1.77 d, 3 H, *J*(CH_3,6′) = 1.1 (CH_3); 1.87 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) = 1.7 (H-7b); 2.23 brq, 1 H, *J*(4,1) = 1.6 (H-4); 2.31 brdq, 1 H, *J*(1,2) = 4.6 (H-1); 2.97 dd, 1 H, *J*(2,3) = 5.3 (H-2); 3.61 s, 3 H (OCH_3); 3.65 m, 2 H (H-5, H-6); 4.30 dd, 1 H (H-3); 4.79 d, 1 H, *J*(OH,5) = 4.5 (OH-5); 4.83 d, 1 H, *J*(OH,6) = 4.5 (OH-6); 7.58 brq, 1 H (H-6′); 11.23 s, 1 H (NH). ^{13}C NMR: 12.25 (CH_3); 31.45 (C-7); 46.36 (C-2); 48.50 (C-1); 49.96 (C-5); 51.88 (OCH_3); 57.77 (C-3); 68.86 (C-6); 71.87 (C-5); 108.65 (C-5′); 137.48 (C-6′); 151.32 (C-2′); 163.89 (C-4′); 173.13 (CO). FAB MS, *m/z* (rel.%): 311 (32) [M + H], 279 (10), 153 (10), 127 (100). For $C_{14}H_{18}N_2O_6$ (310.3) calculated: 54.19% C, 5.85% H, 9.03% N; found: 53.94% C, 6.00% H, 8.86% N.

Methyl (1R,2S*,3S*,4S*,5S*,6R*)-5,6-dihydroxy-3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)bicyclo[2.2.1]heptane-2-carboxylate* (**4b**): Yield 255 mg (91%). M.p. 219–221 °C (ethanol). ^{1}H NMR: 1.33 brdpent, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ *J*(7a,5) ~ *J*(7a,6) ~ 1.5, J_{gem} = 10.6 (H-7a); 1.78 dq, 1 H, *J*(7b,1) ~ *J*(7b,2) ~ *J*(7b,4) ~ 1.7 (H-7b); 1.79 d, 3 H, *J*(CH_3,6′) = 1.1 (CH_3); 2.25 brq, 1 H, *J*(1,4) ~ 1.2, *J*(1,6) < 1.0 (H-1); 2.34 brdq, 1 H, *J*(4,3) = 4.0 (H-4); 2.82 dd, 1 H, *J*(2,3) = 6.5 (H-2); 3.62 s, 3 H (OCH_3); 3.66 brdt, 1 H, *J*(5,6) ~ *J*(5,OH) ~ 5.2 (H-5); 3.96 brtt, 1 H, *J*(6,OH) ~ 5.0 (H-6); 4.63 dd, 1 H (H-3); 4.71 d, 1 H (OH-6); 4.83 d, 1 H (OH-5); 7.47 brq, 1 H (H-6′); 11.24 s, 1 H (NH). ^{13}C NMR: 12.19 (CH_3); 29.90 (C-7); 43.79 (C-2); 47.16 (C-4); 48.17 (C-1); 52.20 (OCH_3); 58.78 (C-3); 67.25 (C-5); 71.98 (C-6); 108.46 (C-5′); 138.44 (C-6′); 151.67 (C-2′); 163.82 (C-4′); 173.58 (CO). FAB MS, *m/z* (rel.%): 311 (100) [M + H], 293 (21), 127 (80). For $C_{14}H_{18}N_2O_6$ (310.3) calculated: 54.19% C, 5.85% H, 9.03% N; found: 54.10% C, 5.93% H, 8.65% N.

Reduction of the Methyl Esters **2**, **3** and **4**. General Procedure

Solution of methyl ester **2**, **3** or **4** (1 mmol) in anhydrous THF (10 ml) was added dropwise to a 1 M solution of $LiAlH_4$ in THF (2.5 ml, 2.5 equiv.) at r.t. in an argon atmosphere. Reaction mixture was stirred at r.t. for 4 h. After adding ethyl acetate (5 ml), ethanol (5 ml) and water (5 ml), reaction mixture was filtered through diatomaceous earth and residual solids were washed with hot water–ethanol (1:1). Glacial AcOH (3 ml) and CH_2Cl_2 (10 ml) were added to the residual solids. This mixture was filtered, combined filtrates were evaporated and the crude product was purified by column chromatography on silica gel (35 g).

1-[(1R,2R*,3R*,4S*)-3-(Hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**5a**): Chromatography in ethyl acetate–acetone–ethanol–water (100:15:6:4) afforded 134 mg (54%) of **5a** as an oily residue, which slowly crystallized upon standing in acetone–methanol (10:1) in refrigerator. M.p. 200–203 °C (decomp.). ^{1}H NMR: 1.54 dq, 1 H,

J(7b,1) ~ *J*(7b,2) ~ *J*(7b,4) ~ 1.6, J_{gem} = 9.2 (H-7b); 1.79 d, 3 H, *J*(CH_3,6′) = 1.0 (CH_3); 1.80 brdq, 1 H, *J* ~ 1.2 (3 ×) (H-7a); 2.22 dddd, 1 H, *J*(3,4) = 3.3, *J*(3,2) = 4.9, *J*(3,CHa) = 6.2, *J*(3,CHb) = 8.8 (H-3); 2.76 brdq, 1 H, *J*(1,4) = 1.5, *J*(1,7a) = 1.8, *J*(1,6) = 3.2 (H-1); 2.93 m, 1 H (H-4); 3.10 ddd, 1 H, *J*(CHa,OH) = 5.2, J_{gem} = 10.8 (CHa); 3.42 ddd, 1 H, *J*(CHb,OH) = 5.2 (CHb); 3.67 dd, 1 H (H-2); 4.56 t, 1 H (OH); 6.21 dd, 1 H, *J*(5,4) = 2.7, *J*(5,6) = 5.6 (H-5); 6.27 brdd, 1 H, *J*(6,7a) = 0.7 (H-6); 7.67 q, 1 H (H-6′); 11.25 s, 1 H (NH). ^{13}C NMR: 12.31 (CH_3); 43.13 (C-3); 46.53 (C-7); 47.48 (C-4); 47.55 (C-1); 59.09 (C-2); 64.28 (OCH_2); 108.82 (C-5′); 136.25 (C-6); 137.27 (C-5); 137.71 (C-6′); 151.88 (C-2′); 163.83 (C-4′). FAB MS, *m/z* (rel.%): 249 (67) [M + H], 201 (20), 127 (64), 91 (100). For $C_{13}H_{16}N_2O_4$ (248.3) calculated: 62.89% C, 6.20% H, 11.28% N; found: 62.64% C, 6.50% H, 10.92% N.

1-[(1R,2S*,3S*,4S*)-3-(Hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**5b**): Chromatography in ethyl acetate–acetone–ethanol–water (100:15:6:4) afforded 170 mg (68.5%) of **5b** as an oily residue, which slowly crystallized upon standing in acetone–methanol (10:1) in refrigerator. M.p. 209–211 °C. ^{1}H NMR: 1.34 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) ~ 2.0, J_{gem} = 9.0 (H-7b); 1.68 brdt, 1 H, *J*(7a,1) ~*J*(7a,4) ~ 1.5 (H-7a); 1.72 d, 3 H, *J*(CH_3,6′) = 1.2 (CH_3); 1.83 brdddd, 1 H, *J*(3,2) = 4.8, *J*(3,CHa) = 6.2, *J*(3,CHb) = 7.6 (H-3); 2.78 m, 1 H, *J*(4,1) = 2.0, *J*(4,5) = 3.1 (H-4); 2.91 m, 1 H (H-1); 3.49 ddd, 1 H, *J*(CHa,OH) = 5.1, J_{gem} = 10.6 (CHa); 3.56 ddd, 1 H, *J*(CHb,OH) = 5.1 (CHb); 4.63 dd, 1 H, *J*(2,1) = 3.4 (H-2); 4.77 t, 1 H (OH); 5.97 dd, 1 H, *J*(6,1) = 2.8, *J*(6,5) = 5.7 (H-6); 6.51 dd, 1 H (H-5); 7.16 q, 1 H (H-6′); 11.23 brs, 1 H (NH). ^{13}C NMR: 12.36 (CH_3); 44.33 (C-4); 45.38 (C-1); 45.81 (C-7); 46.30 (C-3); 58.02 (C-2); 63.91 (OCH_2); 104.62 (C-5′); 132.34 (C-6); 139.59 (C-5); 137.61 (C-6′); 151.77 (C-2′); 163.85 (C-4′). FAB MS, *m/z* (rel.%): 249 (67) [M + H], 201 (20), 127 (27), 91 (100). For $C_{13}H_{16}N_2O_4 \cdot 1/4H_2O$ (252.8) calculated: 61.77% C, 6.58% H, 11.08% N; found: 61.89% C, 6.81% H, 10.65% N.

1-[(1R,2S*,3S*,4S*)-3-(Hydroxymethyl)bicyclo[2.2.1]hept-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**6a**): Chromatography in ethyl acetate–toluene–acetone–ethanol–water (85:20:15:3:2) yielded 138 mg (55%) of **6a** as a viscous oil, slowly crystallized from acetone–methanol (10:1). M.p. 197–199 °C. ^{1}H NMR: 1.26 dq, 1 H, *J*(7b,1) ~ *J*(7b,2) ~ *J*(7b,3) ~ *J*(7b,4) = 1.5, J_{gem} = 10.6 (H-7b); 1.32 ttd, 1 H, *J*(5ex,3) = 1.3 *J*(5ex,4) ~ *J*(5ex,6en) ~ 4.2, *J*(5ex,6ex) ~ J_{gem} = 12.2 (H-5ex); 1.47 dddd, 1 H, *J*(5en,7a) = 2.0, *J*(5en,6ex) = 4.4, *J*(5en,6en) = 8.9, J_{gem} = 12.2 (H-5en); 1.54 tt, 1 H, *J*(6ex,1) = 4.5 (H-6ex); 1.75 brdpent, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ *J*(7a,6en) ~ 1.7 (H-7a); 1.79 d, 3 H, *J*(CH_3,6′) = 1.1 (CH_3); 2.12 m, 1 H (H-3); 2.16 brdq, 1 H, *J*(1,4) =1.5 (H-1); 2.37 brtq, 1 H, *J*(4,7b) ~ 1.3, *J*(4,3) = 4.0 (H-4); 3.38 ddd, 1 H, *J*(CHa,OH) = 5.0, *J*(CHa,3) = 8.9, J_{gem} = 10.7 (CHa); 3.55 ddd, 1 H, *J*(CHb,OH) = 5.2, *J*(CHb,3) = 6.2 (CHb); 3.76 dd, 1 H, *J*(2,3) = 6.1 (H-2); 4.48 t, 1 H (OH); 7.61 q, 1 H (H-6′); 11.20 s, 1 H (NH). ^{13}C NMR: 12.31 (CH_3); 21.33 (C-5); 28.88 (C-6); 37.16 (C-7); 37.72 (C-4); 42.32 (C-1); 50.93 (C-3); 61.00 (OCH_2); 61.11 (C-2); 108.78 (C-5′); 137.69 (C-6′); 151.62 (C-2′); 163.80 (C-4′). FAB MS, *m/z* (rel.%): 251 (100) [M + H], 127 (30). For $C_{13}H_{18}N_2O_4$ (250.3) calculated: 62.38% C, 7.25% H, 11.19% N; found: 62.11% C, 7.31% H, 10.97% N.

1-[(1R,2R*,3R*,4S*)-3-(Hydroxymethyl)bicyclo[2.2.1]hept-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**6b**): Chromatography in ethyl acetate–toluene–acetone–ethanol–water (85:15:15:6:4) yielded 175 mg (70%) of **6b** as a viscous oil, slowly crystallized from acetone. M.p. 178–180 °C. ^{1}H NMR: 1.20 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) = 1.7, J_{gem} = 10.4 (H-7b); 1.21 dddd, 1 H, *J*(6en,7a) = 2.0 *J*(6en,5ex) = 4.2, *J*(6en,5en) = 9.0, J_{gem} = 12.2 (H-6en); 1.35 m, 1 H (H-6ex); 1.56 m, 2 H (H-5en, H-5en); 1.61 brdpent, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ *J*(7a,5en) ~ 1.5 (H-7a); 1.81 d, 3 H, *J*(CH_3,6′) = 1.0 (CH_3); 1.94 brqd, 1 H, *J*(3,2) ~ *J*(3,CH_2) ~ 7.0 (H-3); 2.18 m, 1 H (H-4); 2.16 brtq, 1 H, *J*(1,4) ~ 1.0, *J*(1,2) ~ *J*(1,6ex) ~ 4.0 (H-1); 3.20 ddd, 1 H,

J(CHa,OH) = 5.5, *J*(CHa,3) = 6.6, J_{gem} = 10.5 (CHa); 3.34 ddd, 1 H, *J*(CHb,OH) = 4.6, *J*(CHb,3) = 7.6 (CHb); 4.21 ddd, 1 H, *J*(2,6ex) = 1.8 (H-2); 4.48 dd, 1 H, *J*(OH,CHa) = 5, *J*(OH,CHb) = 4.6 (OH); 7.50 brq, 1 H (H-6′); 11.24 s, 1 H (NH). ^{13}C NMR: 12.30 (CH_3); 21.40 (C-6); 28.30 (C-5); 35.79 (C-7); 38.55 (C-4); 40.61 (C-1); 44.88 (C-3); 61.15 (C-2); 63.86 (OCH_2); 107.68 (C-5′); 138.44 (C-6′); 151.80 (C-2′); 163.88 (C-4′). FAB MS, *m/z* (rel.%): 251 (100) [M + H], 127 (30). For $C_{13}H_{18}N_2O_4$ (250.3) calculated: 62.38% C, 7.25% H, 11.19% N; found: 62.11% C, 7.31% H, 10.51% N.

1-[(1R,2R*,3S*,4S*,5S*,6R*)-5,6-Dihydroxy-3-(hydroxymethyl)bicyclo[2.2.1]hept-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**7a**): Chromatography in ethyl acetate–acetone–ethanol–water (36:6:5:3) yielded 110 mg (39%) of **7a** as a viscous oil, slowly crystallized from 2-propanol. M.p. 225–227 °C. ^{1}H NMR: 1.55 brdpent, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ *J*(7a,5) ~ *J*(7a,6) ~ 1.6, J_{gem} = 10.9 (H-7a); 1.76 dq, 1 H, *J*(7b,1) ~ *J*(7b,2) ~ *J*(7b,4) ~ 1.2 (H-7b); 1.79 d, 3 H, *J*(CH_3,6′) = 1.0 (CH_3); 1.99 brdq, 1 H, *J*(1,4) ~ 1.5, *J*(1,6) < 1.0 (H-1); 2.07 dtd, 1 H, *J*(3,4) = 4.0, *J*(3,2) = 6.2, *J*(3,CHa) = 6.2, *J*(3,CHb) = 8.7 (H-3); 2.17 brdq, 1 H, *J*(4,1) = 1.8 (H-4); 3.38 ddd, 1 H, *J*(CHa,OH) = 5.3, J_{gem} = 10.5 (CHa); 3.50 ddd, 1 H, *J*(CHb,OH) = 4.8 (CHb); 3.60 brtd, 1 H, *J*(6,5) ~ *J*(6,OH) ~ 5.0 (H-6); 3.77 dd, 1 H (H-2); 3.87 brtd, 1 H, *J*(5,OH) = 5.2, *J*(5,4) ~ 1.0 (H-5); 4.56 dd, 1 H (CH_2OH); 4.68 d, 1 H (OH-5); 4.70 d, 1 H (OH-6); 7.56 brq, 1 H (H-6′); 11.22 s, 1 H (NH). ^{13}C NMR: 12.27 (CH_3); 31.15 (C-7); 44.92 (C-3); 44.48 (C-4); 49.64 (C-1); 57.29 (C-2); 60.00 (OCH_2); 67.62 (C-6); 72.39 (C-5); 108.99 (C-5′); 137.67 (C-6′); 151.58 (C-2′); 163.79 (C-4′). FAB MS, *m/z* (rel.%): 283 (60) [M + H], 265 (10) [M + H – H_2O], 181 (6), 127 (100), 91 (31). For $C_{13}H_{18}N_2O_5$ (282.3) calculated: 55.31% C, 6.43% H, 9.92% N; found: 55.09% C, 6.53% H, 9.50% N.

1-[(1R,2S*,3R*,4S*,5S*,6R*)-5,6-Dihydroxy-3-(hydroxymethyl)bicyclo[2.2.1]hept-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**7b**): Chromatography in ethyl acetate–acetone–ethanol–water (36:6:5:3) yielded 164 mg (58%) of **7b** as a viscous oil, slowly crystallized from 2-propanol–water (10:1). M.p. 232–234 °C. ^{1}H NMR: 1.35 brdpent, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ *J*(7a,5) ~ *J*(7a,6) ~ 1.5, J_{gem} = 10.6 (H-7a); 1.69 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) ~ 1.7 (H-7b); 1.80 d, 3 H, *J*(CH_3,6′) = 1.1 (CH_3); 1.94 brqd, 1 H, *J*(3,2) ~ *J*(3,CH_2) ~ 6.6 (H-3); 2.00 brq, 1 H, *J*(4,1) = 1.3, *J*(4,5) = 1.0 (H-4); 2.19 brdq, 1 H, *J*(1,2) ~ 4.0 (H-1); 3.25 ddd, 1 H, *J*(CHa,OH) = 5.4, *J*(CHa,3) = 6.6, J_{gem} = 10.5 (CHa); 3.36 ddd, 1 H, *J*(CHb,OH) = 4.8, *J*(CHb,3) = 7.4 (CHb); 3.60 brdt, 1 H, *J*(6,5) ~ *J*(6,OH) ~ 5.2 (H-6); 3.94 brtt, 1 H, *J*(5,OH) ~ 5.2 (H-5); 4.08 dd, 1 H (H-2); 4.59 d, 1 H (OH-5); 4.70 d, 1 H (OH-6); 4.75 t, 1 H (CH_2OH); 7.47 brq, 1 H (H-6′); 11.29 s, 1 H (NH). ^{13}C NMR: 12.17 (CH_3); 29.36 (C-7); 40.47 (C-3); 45.79 (C-4); 47.65 (C-1); 59.10 (C-2); 63.33 (OCH_2); 67.60 (C-6); 72.49 (C-5); 107.96 (C-5′); 138.48 (C-6′); 151.77 (C-2′); 163.83 (C-4′). FAB MS, *m/z* (rel.%): 283 (27) [M + H], 265 (8) [M + H – H_2O], 215 (10), 127 (15), 91 (100). For $C_{13}H_{18}N_2O_5$ (282.3) calculated: 55.31% C, 6.43% H, 9.92% N; found: 55.32% C, 6.68% H, 9.75% N.

(1*R**,2*R**,3*R**,6*S**,7*S**,9*R**)-2-Iodo-5-oxo-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-carboxylic Acid (**9a**) and Ethyl (1*R**,2*R**,3*R**,6*S**,7*S**,9*R**)-2-Iodo-5-oxo-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-carboxylate (**9b**)

Mixture of the fumaric acid monoethyl ester (7.5 g, 52 mmol), cyclopentadiene **8** (5.2 ml, 62 mmol, freshly distilled) and dioxane (25 ml) was heated at 60 °C for 1 h. Reaction mixture was evaporated and dissolved in saturated Na_2CO_3 aqueous solution (200 ml) and water phase was washed with hexane (75 ml). Water phase was diluted with water (100 ml) and chloroform (100 ml). Iodine (13.2 g, 52 mmol), potassium iodide (5 g) and sodium bicarbonate (26 g) were added and reaction mixture was vigorously stirred overnight. Solid

$Na_2S_2O_3$ was added until the brown color disappeared and the organic phase was separated. Water phase was washed with $CHCl_3$ (2 × 100 ml). Organic phases were dried over anhydrous sodium sulfate and evaporated. Recrystallization of the crude product from ethyl acetate gave 7.1 g (41%) of **9b**. NMR spectrum was in agreement with previously published data[17]. pH of the water phase was adjusted to 4 and water phase was extracted with $CHCl_3$ (4 × 100 ml). Organic phases were dried over anhydrous sodium sulfate and evaporated. Crude product was purified by chomatography on silica gel (250 g) in toluene–ethyl acetate (4:1) to afford 6.1 g of **9a** (31%). NMR spectrum was in agreement with previously published data[20].

tert-Butyl [(1*R**,2*R**,3*R**,6*S**,7*S**,9*R**)-2-Iodo-5-oxo-4-oxatricyclo[4.2.1.$0^{3,7}$]non-9-yl]carbamate (**10a**)

To a solution of the carboxylic acid **9a** (3.42 g, 11.1 mmol) and triethylamine (1.9 ml, 13.5 mmol) in acetone (45 ml) at 0 °C, ethyl chloroformate (1.1 ml, 11.5 mmol) was added dropwise over several minutes. After the addition was complete the solution was stirred at 0 °C for 1 h. A solution of sodium azide (2.17 g, 33.4 mmol) in water (35 ml) was then added and the reaction mixture was stirred at 0 °C for an additional 1 h. The solution was then poured in ice water (100 ml) and the resulting mixture was extracted with ethyl acetate (4 × 100 ml). The combined organic phases were washed with saturated solution of sodium bicarbonate (2 × 100 ml), dried over anhydrous sodium sulfate and evaporated. Residue was redissolved in dry toluene (50 ml), heated under reflux for 1.5 h and evaporated. *tert*-Butyl alcohol (45 ml) was then added to the residue and the solution was refluxed for 2.5 h. Reaction mixture was evaporated and chromatographed on a column of silica gel (250 g) in toluene–ethyl acetate (7:1) to afford 2.14 g (50.9%) of carbamate **10a** as a white solid. M.p. 169–170 °C. ^{1}H NMR: 1.39 s, 9 H (CH_3); 2.01 bd, 1 H, J_{gem} = 11.9 (H-8a); 2.07 bd, 1 H, J_{gem} = 11.9 (H-8b); 2.38 bd, 1 H, *J*(6,7) = 4.7 (H-6); 2.49 m, 1 H (H-1); 3.16 tq, 1 H, *J*(7,3) = *J*(7,6) = 4.9, *J*(7,8) = *J*(7,1) = 1.5 (H-7); 3.72 bd, 1 H, *J*(9,NH) = 6.8 (H-9); 4.05 bd, 1 H, *J*(2,8b) = 2.3 (H-2); 5.06 dm, 1 H, *J*(3,7) = 5.1 (H-3); 7.44 bd, 1 H, *J*(NH,9) = 6.8 (NH). ^{13}C NMR: 27.54 (C-2); 28.39 (CH_3); 34.03 (C-8); 45.61 (C-7); 46.12 (C-6); 53.30 (C-1); 55.64 (C-9); 78.80 (**C**(CH_3)$_3$); 87.83 (C-3); 154.68 (CON); 177.03 (COO). FAB MS, *m/z* (rel.%): 380 (1) [M + H], 324 (48), 57 (100). For $C_{13}H_{18}INO_4$ (379.2) calculated: 41.18% C, 4.78% H, 33.47% I, 3.69% N; found: 41.20% C, 4.84% H, 33.56% I, 3.58% N.

(1*R**,2*S**,3*S**,4*S**)-3-(Ethoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (**10b**)

A mixture of iodoester **9b** (3.36 g, 10 mmol) and zinc dust (2.62 g, 40 mmol) in ethanol–water (60 ml, 5:1) was refluxed for 1 h. The reaction mixture was cooled and filtered through celite pad. The filtrate was evaporated, dissolved in ethyl acetate (250 ml) and organic phase was washed with brine (50 ml). Water phase was then extracted with ethyl acetate (100 ml). Combined organic phases were dried over anhydrous sodium sulfate and evaporated. Crude product (2.1 g, 100%) was used in the next step without purification. Analytical sample was chromatographed on silica gel column in toluene–ethyl acetate (7:1). ^{1}H NMR: 1.20 t, 3 H, *J*(CH_3,CH_2) = 7.1 (CH_3); 1.34 dm, 1 H, J_{gem} = 8.6 (H-7a); 1.51 dm, 1 H, J_{gem} = 8.7 (H-7b); 2.47 m, 1 H (H-3); 3.02 m, 1 H (H-4); 3.16–3.18 m, 2 H (H-1, H-2); 4.06–4.12 m, 2 H (C**H**$_2$$CH_3$); 6.07 bdd, 1 H, *J*(6,5) = 5.8, *J*(6,1) = 2.2 (H-6); 6.29 dd, 1 H, *J*(5,6) = 5.7, *J*(5,4) = 3.1 (H-5). ^{13}C NMR: 14.34 (CH_3); 45.22 (C-1); 46.80 (C-3); 47.27 (C-4); 47.28 (C-7); 47.77 (C-2); 60.67 (**C**$H_2$$CH_3$); 135.34 (C-6); 137.62 (C-5); 174.12, 174.17 (COO).

ESI MS, *m/z* (rel.%): 233 (100) [M + Na], 211 (20) [M + H]. For $C_{11}H_{14}O_4$ (210.2) calculated: 62.85% C, 6.71% H; found: 62.66% C, 6.68% H.

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

A mixture of iodolactone **10a** (2.14 g, 5.64 mmol) and zinc dust (1.5 g, 23.1 mmol) in ethanol (140 ml) was refluxed for 2 h. The reaction mixture was cooled and filtered through celite pad. The filtrate was evaporated, dissolved in ethyl acetate (250 ml) and organic phase was washed with brine (50 ml). Water phase was then extracted with ethyl acetate (100 ml). Combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in methanol (120 ml), aqueous HCl was added (3 ml, 1:1), reaction mixture was stirred for 4 days and evaporated. The residue was redissolved in water (150 ml). Water phase was extracted with ether (100 ml) and evaporated. The residue (from water phase) was then dried in vacuum oven at 60 °C for 1 day and suspended in dry THF (50 ml). $LiAlH_4$ (powder, 1 g, 26.3 mmol) was carefully added to the suspension. The reaction mixture was refluxed under argon for 12 h. After slowly adding ethyl acetate (15 ml), ethanol (15 ml), water (25 ml) and aqueous KOH (20 ml, 10%), the reaction mixture was filtered through diatomaceous earth and residual solids were washed with methanol. Filtrate was evaporated and dissolved in water–methanol (30 ml, 2:1) and pH was adjusted to neutral with aqueous HCl (10%). Solution was applied onto a Dowex 50 (H^+ form, 200 ml). Column was eluted with water (400 ml), methanol (300 ml) and then with 3.5 M methanolic ammonia. Fractions containing product were evaporated to yield 480 mg (61%) of the crude desired amine **11a**. ESI MS, *m/z* (rel.%): 140 (100) [M + H].

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

To a solution of the acid **10b** (2.10 g, 10 mmol) and triethylamine (1.7 ml, 12 mmol) in acetone (30 ml) at 0 °C, ethyl chloroformate (1.1 ml, 11.5 mmol) was added dropwise over several minutes. After the addition was complete the solution was stirred at 0 °C for 1 h. A solution of sodium azide (2.17 g, 33.4 mmol) in water (35 ml) was then added and the reaction mixture was stirred at 0 °C for an additional 1 h. The solution was then poured in ice water (100 ml) and the resulting mixture was extracted with ethyl acetate (3 × 100 ml). The combined organic phases were washed with saturated solution of sodium bicarbonate (2 × 100 ml), dried over anhydrous sodium sulfate and evaporated. The residue was redissolved in mixture of THF (20 ml) and 2 M aqueous HCl (20 ml), and heated under reflux for 13 h. The reaction mixture was extracted with ether (50 ml) and water phase was evaporated. Residue (from water phase) was then dried in vacuum oven at 60 °C for one day and suspended in dry THF (50 ml). $LiAlH_4$ (powder, 1.5 g, 39.5 mmol) was slowly added to the suspension. The reaction mixture was refluxed under argon for 12 h. After slowly adding ethyl acetate (25 ml), ethanol (25 ml), water (25 ml) and aqueous KOH (20 ml, 10%), reaction mixture was filtered through diatomaceous earth and residual solids were washed with methanol. Filtrate was evaporated and the residue was dissolved in water–methanol (30 ml, 2:1). The solution was applied onto a Dowex 50 (H^+ form, 200 ml). Column was eluted with water (400 ml), methanol (300 ml) and then with 3.5 M methanolic ammonia. Fractions containing product were evaporated to yield 940 mg (67%) of the crude desired amine **11b**. ESI MS, *m/z* (rel.%): 140 (100) [M + H].

[(1*R**,2*S**,3*S**,4*S**)-3-(Acetylamino)bicyclo[2.2.1]hept-5-en-2-yl]methyl Acetate (**12a**) and [(1*R**,2*R**,3*R**,4*S**)-3-(Acetylamino)bicyclo[2.2.1]hept-5-en-2-yl]methyl Acetate (**12b**)

Acetic anhydride (0.5 ml) was added to a stirred ice-cooled solution of amine **11** (140 mg, 1 mmol) in pyridine (4 ml) and the mixture was left overnight. Methanol (2 ml) was added and, after 10 min, the mixture was evaporated. The residue was codistilled with toluene and chromatographed on a silica gel column (35 g) in ethyl acetate → ethyl acetate–toluene–acetone–ethanol (17:4:3:1).

[(1R,2S*,3S*,4S*)-3-(Acetylamino)bicyclo[2.2.1]hept-5-en-2-yl]methyl acetate* (**12a**): Yield 178 mg (80%) as an oil. ^{1}H NMR: 1.48 dq, 1 H, J_{gem} = 8.6, J(7a,1) = J(7a,4) = J(7a,3) = 1.8 (H-7a); 1.62 dm, 1 H, J_{gem} = 8.6 (H-7b); 1.80 s, 3 H (CH_3CON); 1.98 s, 3 H (CH_3COO); 2.03 m, 1 H (H-2); 2.57 m, 1 H (H-4); 2.76 m, 1 H (H-1); 3.06 bddd, 1 H, J(3,NH) = 7.3, J(3,2) = 4.0, J(3,7a) = 1.8 (H-3); 3.64 dd, 1 H, J_{gem} = 10.9, J(CH_2,2) = 9.9 (CH_2Oa); 3.96 dd, 1 H, J_{gem} = 10.9, J(CH_2,2) = 6.3 (CH_2Ob); 6.09 dd, 1 H, J(6,5) = 5.7, J(6,1) = 2.8 (H-6); 6.20 dd, 1 H, J(5,6) = 5.7, J(5,4) = 3.2 (H-5); 8.05 bd, 1 H, J(NH,3) = 7.3 (NH). ^{13}C NMR: 20.97 (CH_3COO); 22.92 (CH_3CON); 42.87 (C-1); 46.25 (C-2); 46.67 (C-7); 48.37 (C-4); 52.82 (C-3); 66.47 (CH_2O); 135.69 (C-6); 136.39 (C-5); 169.16 (CON); 170.54 (COO). ESI MS, *m/z* (rel.%): 246 (100) [M + Na], 224 (5) [M + H].

[(1R,2R*,3R*,4S*)-3-(Acetylamino)bicyclo[2.2.1]hept-5-en-2-yl]methyl acetate* (**12b**): Yield 206 mg (92%) as an oil. ^{1}H NMR: 1.31 dq, 1 H, J_{gem} = 9.0, J(7a,1) = J(7a,4) = J(7a,2) = 2.0 (H-7a); 1.38 m, 1 H (H-2); 1.53 dm, 1 H, J_{gem} = 9.0 (H-7b); 1.74 s, 3 H (CH_3CON); 2.00 s, 3 H (CH_3COO); 2.62 m, 1 H (H-1); 2.86 m, 1 H (H-4); 3.77 dt, 1 H, J(3,NH) = 7.1, J(3,2) = J(3,4) = 3.9 (H-3); 3.97 dd, 1 H, J_{gem} = 11.0, J(CH_2,2) = 9.5 (CH_2Oa); 4.27 dd, 1 H, J_{gem} = 11.0, J(CH_2,2) = 5.7 (CH_2Ob); 6.07 dd, 1 H, J(5,6) = 5.7, J(5,4) = 2.8 (H-5); 6.36 dd, 1 H, J(6,5) = 5.7, J(6,1) = 3.2 (H-6); 7.47 bd, 1 H, J(NH,3) = 7.2 (NH). ^{13}C NMR: 21.01 (CH_3COO); 22.69 (CH_3CON); 44.09 (C-1); 44.90 (C-7); 45.78 (C-4); 46.76 (C-2); 53.00 (C-3); 66.49 (CH_2O); 133.96 (C-5); 138.88 (C-6); 169.62 (CON); 170.65 (COO). ESI MS, *m/z* (rel.%): 246 (100) [M + Na], 224 (8) [M + H]. For $C_{12}H_{17}NO_3$ (223.3) calculated: 64.55% C, 7.67% H, 6.27% N; found: 64.20% C, 8.03% H, 6.14% N.

[(1*R**,2*S**,3*S**,4*S**)-3-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol (**13a**) and [(1*R**,2*R**,3*R**,4*S**)-3-(6-Chloro-9*H*-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol (**13b**)

A mixture of amine **11** (840 mg, 6 mmol), 4,6-dichloropyrimidin-5-amine (1.48 g, 9 mmol) and triethylamine (3.6 ml) in ethanol (18 ml) was heated in a pressure vessel at 105 °C for 6 days, and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g) in ethyl acetate–toluene–ethanol–water (17:4:3:1). To a suspension of pyrimidine in triethyl orthoformate (130 ml), concentrated hydrochloric acid (2.3 ml) was added and the reaction mixture was vigorously stirred at room temperature for 3 days (suspension dissolved). Solution was evaporated, residue was redissolved in a mixture of tetrahydrofuran (17 ml) and 0.5 M hydrochloric acid (17 ml) and stirred at room temperature for 4 h. After neutralization with solid sodium hydrogencarbonate, the mixture was evaporated to a one fourth of original volume and adsorbed on silica gel. The silica gel was placed on the top of a silica gel column (200 g) and nucleosides were isolated by chromatography.

[(1R,2S*,3S*,4S*)-3-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol* (**13a**): Chromatography in ethyl acetate–toluene–acetone–ethanol (17:4:3:1) afforded 995 mg (60%) of the chloropurine nucleoside **13a**. Sample was crystallized from water. M.p. 158–159 °C.

^{1}H NMR: 1.63 dq, 1 H, *J*(7b,1) ~ *J*(7b,3) ~ *J*(7b,4) ~ 1.7, J_{gem} = 9.2 (H-7b); 2.03 brdt, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ 1.5 (H-7a); 2.79 dddd, 1 H, *J*(2,1) = 3.2, *J*(2,3) = 4.5, *J*(2,CHa) = 7.2, *J*(2,CHa) = 8.2 (H-2); 3.03 m, 1 H (H-1); 3.10 brdq, 1 H, *J*(4,1) ~ 1.7, *J*(4,5) = 3.2 (H-4); 3.33 ddd, 1 H, *J*(CHa,OH) = 4.9, J_{gem} = 10.5 (CHa); 3.44 ddd, 1 H, *J*(CHb,OH) = 5.5 (CHb); 4.01 dd, 1 H (H-3); 4.65 t, 1 H (OH); 6.30 dd, 1 H, *J*(6,1) = 2.7, *J*(6,5) = 5.7 (H-6); 6.34 dd, 1 H (H-5); 8.78 s, 1 H and 8.96 s, 1 H (H-2′, H-8′). ^{13}C NMR: 43.35 (C-1); 47.09 (C-7); 48.33 (C-2); 48.53 (C-4); 59.35 (C-3); 63.94 (OCH_2); 131.47 (C-5′); 135.20 (C-6); 137.38 (C-5); 146.27 (C-8′); 149.16 (C-6′); 151.42 (C-2′); 152.46 (C-4′). FAB MS, *m/z* (rel.%): 277/279 (10/5) [M + H], 155 (15) 57 (100). For $C_{13}H_{13}ClN_4O$ (276.7) calculated: 56.42% C, 4.74% H, 12.81% Cl, 20.25% N; found: 56.25% C, 4.76% H, 12.74% Cl, 19.96% N.

[(1R,2R*,3R*,4S*)-3-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol* (**13b**): Chromatography in ethyl acetate–toluene–acetone–ethanol (17:5:3:1) afforded 913 mg (55%) of the chloropurine nucleoside **13b**. Sample was crystallized from ether–methanol (10:1). M.p. 156–157 °C. ^{1}H NMR: 1.49 dq, 1 H, *J*(7b,1) ~ *J*(7b,2) ~ *J*(7b,4) ~ 2.0, J_{gem} = 9.2 (H-7b); 1.84 brdt, 1 H, *J*(7a,1) ~ *J*(7a,4) ~ 1.5 (H-7a); 2.23 tdd, 1 H, *J*(2,3) = 4.4, *J*(2,CHa) = 7.2, *J*(2,CHa) = 7.2 (H-2); 2.87 m, 1 H (H-1); 3.30 m, 1 H (H-4); 3.64 ddd, 1 H, *J*(CHa,OH) = 4.8, J_{gem} = 10.7 (CHa); 3.70 ddd, 1 H, *J*(CHb,OH) = 5.5 (CHb); 4.84 brt, 1 H, *J*(3,4) = 4.0 (H-3); 4.84 t, 1 H (OH); 5.88 dd, 1 H, *J*(5,4) = 2.8, *J*(5,6) = 5.6 (H-5); 6.59 dd, 1 H, *J*(6,1) = 3.2 (H-6); 8.52 s, 1 H and 8.80 s, 1 H (H-2′, H-8′). ^{13}C NMR: 44.41 (C-1); 45.31 (C-7); 46.79 (C-4); 48.24 (C-2); 58.84 (C-3); 63.77 (OCH_2); 131.19 (C-5′); 132.79 (C-5); 140.82 (C-6); 145.72 (C-8′); 149.08 (C-6′); 151.48 (C-2′); 152.57 (C-4′). FAB MS, *m/z* (rel.%): 277/279 (15/7) [M + H], 121 (100). For $C_{13}H_{13}ClN_4O \cdot 1/4H_2O$ (281.2) calculated: 55.52% C, 4.84% H, 12.61% Cl, 19.92% N; found: 55.50% C, 4.69% H, 12.42% Cl, 19.73% N.

[(1*R**,2*S**,3*S**,4*S**)-3-(6-Amino-9*H*-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol (**14a**) and [(1*R**,2*R**,3*R**,4*S**)-3-(6-Amino-9*H*-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol (**14b**)

Chloropurine derivative **13** (560 mg, 2 mmol) was heated with liquid ammonia (35 ml) and methanol (6 ml) in an autoclave at 75 °C for 48 h. Ammonia was then evaporated, the product was purified by chromatography on silica gel (150 g) in ethyl acetate–acetone–ethanol–water (95:15:9:6) and crystallized from ethanol.

[(1R,2S*,3S*,4S*)-3-(6-Amino-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol* (**14a**): Yield 428 mg (83%). M.p. 198.5–200 °C. ^{1}H NMR: 1.61 dq, 1 H, J_{gem} = 9.0, *J*(7a,1) = *J*(7a,4) = *J*(7a,3) = 1.7 (H-7a); 1.99 dm, 1 H, J_{gem} = 9.0 (H-7b); 2.66 m, 1 H (H-2); 2.98–3.02 m, 2 H (H-1, H-4); 3.28 ddd, 1 H, J_{gem} = 10.5, *J*(CH_2,2) = 8.2, *J*(CH_2,OH) = 5.1 (CH_2Oa); 3.43 ddd, 1 H, J_{gem} = 10.4, *J*(CH_2,2) = 7.1, *J*(CH_2,OH) = 5.1 (CH_2Ob); 3.84 dd, 1 H, *J*(3,2) = 4.4, *J*(3,7b) = 1.7 (H-3); 4.79 t, 1 H, *J*(OH,CH_2) = 5.2 (OH); 6.27 dd, 1 H, *J*(6,5) = 5.7, *J*(6,1) = 2.8 (H-6); 6.32 dd, 1 H, *J*(5,6) = 5.7, *J*(5,4) = 3.2 (H-5); 7.24 bs, 2 H (NH_2); 8.13 s, 1 H (H-2′); 8.37 s, 1 H (H-8′). ^{13}C NMR: 43.47 (C-1); 47.14 (C-7); 48.65, 48.70 (C-2, C-4); 58.28 (C-3); 64.17 (CH_2O); 119.37 (C-5′); 135.49 (C-6); 137.17 (C-5); 139.42 (C-8′); 150.08 (C-4′); 152.42 (C-2′); 156.25 (C-6′). FAB MS, *m/z* (rel.%): 258 (100) [M + H]. For $C_{13}H_{15}N_5O$ (257.3) calculated: 60.69% C, 5.88% H, 27.22% N; found: 60.36% C, 5.78% H, 26.96% N.

[(1R,2R*,3R*,4S*)-3-(6-Amino-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol* (**14b**): Yield 423 mg (82%). M.p. 251.5–253 °C (decomp.). ^{1}H NMR: 1.45 dq, 1 H, J_{gem} = 9.2, *J*(7a,1) = *J*(7a,4) = *J*(7a,2) = 2.0 (H-7a); 1.75 dm, 1 H, J_{gem} = 9.2 (H-7b); 2.07 tdd, 1 H, *J*(2,CH_2) = 7.3, *J*(2,3) = 4.5, *J*(2,7a) = 2.2 (H-2); 2.82 m, 1 H (H-1); 3.20 m, 1 H (H-4); 3.59 ddd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 7.4, *J*(CH_2,OH) = 4.9 (CH_2Oa); 3.65 ddd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 7.0,

J(CH$_2$,OH) = 5.4 (CH$_2$Ob); 4.65 bt, 1 H, J(3,2) ~ J(3,4) ~ 3.9 (H-3); 5.10 t, 1 H, J(OH,CH$_2$) = 5.2 (OH); 5.85 dd, 1 H, J(5,6) = 5.7, J(5,4) = 2.8 (H-5); 6.55 dd, 1 H, J(6,5) = 5.7, J(6,1) = 3.2 (H-6); 7.18 bs, 2 H (NH$_2$); 7.93 s, 1 H (H-8′); 8.14 s, 1 H (H-2′). ^{13}C NMR: 44.79 (C-1); 45.80 (C-7); 47.25 (C-4); 48.84 (C-2); 58.27 (C-3); 64.43 (CH$_2$O); 119.20 (C-5′); 133.38 (C-5); 139.60 (C-8′); 140.92 (C-6); 150.44 (C-4′); 152.86 (C-2′); 156.35 (C-6′). ESI MS, *m/z* (rel.%): 280 (100) [M + Na], 258 (20) [M + H]. For $C_{13}H_{15}N_5O \cdot 1/6\ H_2O$ (260.9) calculated: 59.85% C, 5.95% H, 26.84% N; found: 59.94% C, 5.93% H, 26.82% N.

{(1*R**,2*S**,3*S**,4*S**)-3-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-bicyclo[2.2.1]hept-5-en-2-yl}methanol (**15a**) and {(1*R**,2*R**,3*R**,4*S**)-3-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-bicyclo[2.2.1]hept-5-en-2-yl}methanol (**15b**)

Mixture of chloropurine derivative **13a** or **13b** (330 mg, 1.2 mmol), cyclopropylamine (2 ml) and methanol (2 ml) was set aside overnight and evaporated. Product was purified by chromatography on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4).

{(1R,2S*,3S*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-5-en-2-yl}methanol* (**15a**): Yield 292 mg (89%). M.p. 145.5–146.5 °C (acetone). ^{1}H NMR: 0.61 m, 2 H, 0.72 m, 2 H and 3.05 m, 1 H (cyclopropyl); 1.61 dq, 1 H, J(7b,1) ~ J(7b,3) ~ J(7b,4) ~ 1.7, J_{gem} = 9.0 (H-7b); 1.99 brdt, 1 H, J(7a,1) ~ J(7a,4) ~ 1.5 (H-7a); 2.66 dddd, 1 H, J(2,1) = 3.2, J(2,3) = 4.5, J(2,CHa) = 7.2, J(2,CHa) = 8.2 (H-2); 3.00 m, 1 H (H-1); 3.02 m, 1 H (H-4); 3.28 ddd, 1 H, J(CHa,OH) = 5.4, J_{gem} = 10.6 (CHa); 3.44 ddd, 1 H, J(CHb,OH) = 5.0 (CHb); 4.75 t, 1 H (OH); 5.79 brdd, 1 H, J(3,4) = 1.0 (H-3); 6.27 dd, 1 H, J(6,1) = 2.8, J(6,5) = 5.7 (H-6); 6.32 dd, 1 H, J(5,4) = 3.2 (H-5); 7.88 brs, 1 H (NH); 8.23 s, 1 H and 8.37 s, 1 H (H-2′, H-8′). ^{13}C NMR: 6.56, 2 C (2 × CH$_2$); 24.00 (NCH); 43.41 (C-1); 47.07 (C-7); 48.62 (C-4); 48.62 (C-2); 58.21 (C-3); 64.10 (OCH$_2$); 119.70 (C-5′); 135.40 (C-6); 137.10 (C-5); 139.15 (C-8′); 149.00 (C-4′); 151.21 (C-2′); 155.73 (C-6′). FAB MS, *m/z* (rel.%): 298 (10) [M + H], 176 (20), 133 (50), 56 (100). For $C_{16}H_{19}ClN_5O$ (297.4) calculated: 64.63% C, 6.44% H, 23.55% N; found: 64.46% C, 6.52% H, 23.38% N.

{(1R,2R*,3R*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-5-en-2-yl}methanol* (**15b**): Yield 310 mg (94%) as a foam. ^{1}H NMR: 0.59 m, 2 H and 0.71 m, 2 H (CH$_2$ of cyclopropyl); 1.46 dq, 1 H, J_{gem} = 9.1, J(7a,1) = J(7a,4) = J(7a,2) = 1.9 (H-7a); 1.79 dm, 1 H, J_{gem} = 9.1 (H-7b); 2.10 m, 1 H (H-2); 2.84 m, 1 H (H-1); 2.99 bs, 1 H (CH of cyclopropyl); 3.23 m, 1 H (H-4); 3.60 m, 1 H and 3.67 m, 1 H (CH$_2$O); 4.68 bt, 1 H, J(3,2) ~ J(3,4) ~ 3.9 (H-3); 4.93 m, 1 H (OH); 5.88 bdd, 1 H, J(5,6) = 5.7, J(5,4) = 2.8 (H-5); 6.56 bdd, 1 H, J(6,5) = 5.7, J(6,1) = 3.1 (H-6); 7.86 bs, 1 H (NH); 7.93 s, 1 H (H-8′); 8.24 s, 1 H (H-2′). ^{13}C NMR: 6.63 (CH$_2$ of cyclopropyl); 44.48 (C-1); 45.42 (C-7); 46.86 (C-4); 48.46 (C-2); 57.76 (C-3); 64.03 (CH$_2$O); 119.46 (C-5′); 133.16 (C-5); 138.86 (C-8′); 140.43 (C-6); 149.41 (C-4′); 152.36 (C-2′); 155.74 (C-6′). FAB MS, *m/z* (rel.%): 298 (100) [M + H]. For $C_{16}H_{19}ClN_5O \cdot 1/4H_2O$ (301.9) calculated: 63.66% C, 6.51% H, 23.20% N; found: 63.91% C, 6.74% H, 22.96% N.

Preparation of the Saturated Nucleosides **16a**, **16b**, **17a** and **17b**. General Procedure

A mixture of unsaturated compound **14** or **15** (0.6 mmol) and palladium on charcoal (20 mg) in methanol (10 ml) was stirred in atmosphere of hydrogen overnight. The catalyst was filtered off, washed with methanol and filtrate was evaporated. The residue was chromatographed on silica gel column (10 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4).

[(1R,2R*,3R*,4S*)-3-(6-Amino-9H-purin-9-yl)bicyclo[2.2.1]hept-2-yl]methanol* (**16a**): Yield 133 mg (86%) after crystallization from ethanol. M.p. 200.5–202 °C. ^{1}H NMR: 1.27–1.40 m, 3 H (H-5endo, H-6exo, H-7a); 1.53 m, 1 H (H-6endo); 1.61 tt, 1 H, J_{gem} = *J*(5ex,6ex) = 11.9, *J*(5ex,6en) = *J*(5ex,4) = 4.5 (H-5exo); 1.91 dm, 1 H, J_{gem} = 10.2 (H-7b); 2.38 bd, 1 H, *J*(4,5ex) = 4.8 (H-4); 2.41–2.48 m, 2 H (H-1, H-2); 3.48 ddd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 8.0, *J*(CH_2,OH) = 5.2 (CH_2Oa); 3.63 ddd, 1 H, J_{gem} = 10.6, *J*(CH_2,2) = 6.5, *J*(CH_2,OH) = 4.8 (CH_2Ob); 3.90 dd, 1 H, *J*(3,2) = 4.9, *J*(3,7a) = 1.2 (H-3); 4.71 t, 1 H, *J*(OH,CH_2) = 5.0 (OH); 7.22 bs, 2 H (NH_2); 8.13 s, 1 H (H-2′); 8.30 s, 1 H (H-8′). ^{13}C NMR: 21.69 (C-6); 27.63 (C-5); 37.24 (C-7); 38.13 (C-1); 43.32 (C-4); 51.00 (C-2); 60.98 (C-3); 61.44 (CH_2O); 119.27 (C-5′); 139.08 (C-8′); 149.69 (C-4′); 152.37 (C-2′); 156.22 (C-6′). FAB MS, *m/z* (rel.%): 260 (100) [M + H], 136 (60). For $C_{13}H_{17}N_5O \cdot 1/6H_2O$ (262.3) calculated: 59.52% C, 6.66% H, 26.70% N; found: 59.49% C, 6.61% H, 26.41% N.

[(1R,2S*,3S*,4S*)-3-(6-Amino-9H-purin-9-yl)bicyclo[2.2.1]hept-2-yl]methanol* (**16b**): Yield 121 mg (78%) after crystallization from ethanol. M.p. 244–245 °C. ^{1}H NMR: 1.01 m, 1 H (H-5endo); 1.28–1.35 m, 2 H (H-5exo, H-7a); 1.52–1.62 m, 2 H (H-6); 1.71 dm, 1 H, J_{gem} = 10.2 (H-7b); 2.22 m, 1 H (H-1); 2.30 m, 1 H (H-2); 2.66 m, 1 H (H-4); 3.31 ddd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 7.2, *J*(CH_2,OH) = 5.4 (CH_2Oa); 3.45 ddd, 1 H, J_{gem} = 10.5, *J*(CH_2,2) = 7.4, *J*(CH_2,OH) = 4.7 (CH_2Ob); 4.37 ddd, 1 H, *J*(3,2) = 5.4, *J*(3,4) = 4.0, *J*(3,5ex) = 1.8 (H-3); 4.73 t, 1 H, *J*(OH,CH_2) = 5.1 (OH); 7.19 bs, 2 H (NH_2); 8.12 s, 1 H (H-2′); 8.27 s, 1 H (H-8′). ^{13}C NMR: 21.52 (C-5); 28.97 (C-6); 35.25 (C-7); 38.64 (C-1); 41.28 (C-4); 47.01 (C-2); 60.05 (C-3); 63.80 (CH_2O); 119.45 (C-5′); 139.87 (C-8′); 150.43 (C-4′); 152.35 (C-2′); 156.13 (C-6′). ESI MS, *m/z* (rel.%): 282 (100) [M + Na], 260 (48) [M + H]. For $C_{13}H_{17}N_5O \cdot 1/6H_2O$ (262.3) calculated: 59.52% C, 6.66% H, 26.70% N; found: 59.59% C, 6.58% H, 26.64% N.

{(1R,2R*,3R*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-2-yl}methanol* (**17a**): Yield 135 mg (75%) after crystallization from acetone. M.p. 165–166 °C. ^{1}H NMR: 0.59 m, 2 H and 0.71 m, 2 H (CH_2 of cyclopropyl); 1.27–1.40 m, 3 H (H-5endo, H-6exo, H-7a); 1.53 m, 1 H (H-6endo); 1.61 tt, 1 H, J_{gem} = *J*(5ex,6ex) = 11.7, *J*(5ex,6en) = *J*(5ex,4) = 4.5 (H-5exo); 1.90 dm, 1 H, J_{gem} = 10.1 (H-7b); 2.37 bd, 1 H, *J*(4,5ex) = 4.6 (H-4); 2.41–2.48 m, 2 H (H-1, H-2); 3.00 bs, 1 H (CH of cyclopropyl); 3.48 ddd, 1 H, J_{gem} = 10.6, *J*(CH_2,2) = 7.8, *J*(CH_2,OH) = 5.1 (CH_2Oa); 3.63 ddd, 1 H, J_{gem} = 10.5, *J*(CH_2,2) = 6.4, *J*(CH_2,OH) = 4.9 (CH_2Ob); 3.92 dd, 1 H, *J*(3,2) = 4.9, *J*(3,7a) = 1.2 (H-3); 4.70 t, 1 H, *J*(OH,CH_2) = 5.0 (OH); 7.88 bs, 1 H (NH); 8.23 s, 1 H (H-2′); 8.30 s, 1 H (H-8′). ^{13}C NMR: 6.67 (CH_2 of cyclopropyl); 21.69 (C-6); 27.64 (C-5); 37.23 (C-7); 38.13 (C-1); 43.33 (C-4); 51.01 (C-2); 60.96 (C-3); 61.44 (CH_2O); 119.66 (C-5′); 138.92 (C-8′); 149.10 (C-4′); 152.26 (C-2′); 155.77 (C-6′). FAB MS, *m/z* (rel.%): 300 (100) [M + H], 176 (30). For $C_{16}H_{21}N_5O$ (299.4) calculated: 64.19% C, 7.07% H, 23.39% N; found: 63.91% C, 7.12% H, 23.12% N.

{(1R,2S*,3S*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]bicyclo[2.2.1]hept-2-yl}methanol* (**17b**): Yield 140 mg (78%) as a foam. ^{1}H NMR: 0.60 m, 2 H and 0.71 m, 2 H (CH_2 of cyclopropyl); 0.99 m, 1 H (H-5endo); 1.27–1.35 m, 2 H (H-5exo, H-7a); 1.53–1.59 m, 2 H (H-6); 1.71 dm, 1 H, J_{gem} = 10.2 (H-7b); 2.21 m, 1 H (H-1); 2.30 m, 1 H (H-2); 2.66 m, 1 H (H-4); 2.99 bs, 1 H (CH of cyclopropyl); 3.31 ddd, 1 H, J_{gem} = 10.7, *J*(CH_2,2) = 7.0, *J*(CH_2,OH) = 5.4 (CH_2Oa); 3.46 ddd, 1 H, J_{gem} = 10.8, *J*(CH_2,2) = 7.4, *J*(CH_2,OH) = 4.4 (CH_2Ob); 4.38 m, 1 H (H-3); 4.75 t, 1 H, *J*(OH,CH_2) = 5.1 (OH); 7.88 bs, 1 H (NH); 8.22 s, 1 H (H-2′); 8.28 s, 1 H (H-8′). ^{13}C NMR: 6.65 (CH_2 of cyclopropyl); 21.58 (C-5); 29.01 (C-6); 35.33 (C-7); 38.67 (C-1); 41.34 (C-4); 47.06 (C-2); 60.08 (C-3); 63.85 (CH_2O); 119.90 (C-5′); 139.78 (C-8′); 149.77 (C-4′); 152.34 (C-2′); 155.78 (C-6′). FAB MS, *m/z* (rel.%): 300 (100)

[M + H], 176 (20). For $C_{16}H_{21}N_5O$ (299.4) calculated: 64.19% C, 7.07% H, 23.39% N; found: 64.19% C, 7.26% H, 23.11% N.

Preparation of the *cis*-Hydroxylated Compounds **18a**, **18b**, **19a** and **19b**. General Procedure

Unsaturated nucleoside **14** or **15** (0.6 mmol) was dissolved in a mixture of acetone–water (27.5 ml, 10:1). Solution of NMMO (50% in water, 0.9 ml) and water solution of osmium tetroxide (30 µl, 100 mg/5 ml) was added, the reaction mixture was stirred at r.t. for 2 days and evaporated. The product was isolated by column chromatography on silica gel.

(1R,2R*,3S*,4S*,5S*,6R*)-5-(6-Amino-9H-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]heptane-2,3-diol* (**18a**): Chromatography on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (17:3:3:2). Yield 109 mg (62%) after crystallization from ethanol. M.p. 258.5–260.5 °C (decomp.). ^{1}H NMR: 1.71 dm, 1 H, J_{gem} = 10.7 (H-7a); 1.84 dm, 1 H, J_{gem} = 10.6 (H-7b); 2.21 m, 1 H (H-4); 2.25 m, 1 H (H-1); 2.43 m, 1 H (H-6); 3.48 ddd, 1 H, J_{gem} = 10.9, J(CH$_2$,6) = 7.9, J(CH$_2$,OH) = 5.2 (CH$_2$Oa); 3.58 ddd, 1 H, J_{gem} = 11.0, J(CH$_2$,6) = 7.0, J(CH$_2$,OH) = 4.5 (CH$_2$Ob); 3.75 m, 1 H (H-3); 3.92–3.96 m, 2 H (H-2, H-5); 4.74–4.79 m, 3 H (OH); 7.23 bs, 2 H (NH$_2$); 8.13 s, 1 H (H-2′); 8.28 s, 1 H (H-8′).^{13}C NMR: 31.24 (C-7); 45.37 (C-1); 48.61 (C-6); 50.77 (C-4); 57.22 (C-5); 60.24 (CH$_2$O); 67.73 (C-2); 71.90 (C-3); 119.29 (C-5′); 139.25 (C-8′); 149.72 (C-4′); 152.41 (C-2′); 156.24 (C-6′). FAB MS, *m/z* (rel.%): 292 (100) [M + H]. For $C_{13}H_{17}N_5O\cdot 1/2H_2O$ (301.3) calculated: 51.99% C, 6.04% H, 23.32% N; found: 52.12% C, 5.98% H, 23.07% N.

(1R,2R*,3S*,4S*,5R*,6S*)-5-(6-Amino-9H-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]heptane-2,3-diol* (**18b**): Chromatography on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (17:3:3:2). Yield 168 mg (95%) after crystallization from ethanol. M.p. 258.5–260 °C (decomp.). ^{1}H NMR: 1.46 dm, 1 H, J_{gem} = 10.7 (H-7a); 1.76 dm, 1 H, J_{gem} = 10.7 (H-7b); 2.04 m, 1 H (H-1); 2.31 m, 1 H (H-6); 2.48 m, 1 H (H-4); 3.33–3.49 m, 3 H (CH$_2$O, H-3); 3.94 bt, 1 H, J(2,3) = J(2,OH) = 5.1 (H-2); 4.28 dd, 1 H, J(5,6) = 5.9, J(5,4) = 4.1 (H-5); 4.65–4.67 m, 2 H (2-OH, 3-OH); 4.81 t, 1 H, J(OH,CH$_2$) = 5.2 (CH$_2$O**H**); 7.24 bs, 2 H (NH$_2$); 8.14 bs, 1 H (H-2′); 8.24 s, 1 H (H-8′). ^{13}C NMR: 29.36 (C-7); 42.40 (C-6); 45.92 (C-1); 48.35 (C-4); 57.65 (C-5); 63.32 (CH$_2$O); 68.13 (C-3); 72.87 (C-2); 119.55 (C-5′); 140.17 (C-8′); 150.44 (C-4′); 152.52 (C-2′); 156.23 (C-6′). ESI MS, *m/z* (rel.%): 314 (100) [M + Na], 292 (86) [M + H]. For $C_{13}H_{17}N_5O$ (291.3) calculated: 53.60% C, 5.88% H, 24.04% N; found: 53.27% C, 5.87% H, 23.62% N.

(1R,2R*,3S*,4S*,5S*,6R*)-5-[6-(Cyclopropylamino)-9H-purin-9-yl]-6-(hydroxymethyl)bicyclo-[2.2.1]heptane-2,3-diol* (**19a**): Chromatography on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (72:12:10:6). Yield 169 mg (85%) after crystallization from acetone–methanol (10:1). M.p. 202–203.5 °C (decomp.). ^{1}H NMR: 0.59 m, 2 H and 0.71 m, 2 H (CH$_2$ of cyclopropyl); 1.71 dm, 1 H, J_{gem} = 10.7 (H-7a); 1.84 dm, 1 H, J_{gem} = 10.6 (H-7b); 2.21 m, 1 H (H-4); 2.25 m, 1 H (H-1); 2.43 m, 1 H (H-6); 2.99 bs, 1 H (CH of cyclopropyl); 3.49 ddd, 1 H, J_{gem} = 10.9, J(CH$_2$,6) = 7.9, J(CH$_2$,OH) = 5.1 (CH$_2$Oa); 3.59 ddd, 1 H, J_{gem} = 10.9, J(CH$_2$,6) = 7.0, J(CH$_2$,OH) = 4.6 (CH$_2$Ob); 3.75 td, 1 H, J(3,2) = J(3,OH) = 5.7, J(3,7a) = 1.6 (H-3); 3.94 bt, 1 H, J(2,3) = J(2,OH) = 5.6 (H-2); 3.97 dd, 1 H, J(5,6) = 5.3, J(5,7b) = 1.0 (H-5); 4.75 d, 1 H, J(OH,2) = 5.1 (2-OH); 4.76 d, 1 H, J(OH,3) = 5.2; 4.77 t, 1 H, J(OH,CH$_2$) = 5.1 (CH$_2$O**H**); 7.89 bs, 1 H (NH); 8.23 bs, 1 H (H-2′); 8.29 s, 1 H (H-8′). ^{13}C NMR: 6.63 (CH$_2$ of cyclopropyl); 31.23 (C-7); 45.36 (C-1); 48.62 (C-6); 50.77 (C-4); 57.18 (C-5); 60.23 (CH$_2$O); 67.72 (C-2); 71.89 (C-3); 119.67 (C-5′); 139.06 (C-8′); 149.02 (C-4′); 152.30 (C-2′); 155.82

(C-6′). FAB MS, *m/z* (rel.%): 332 (100) [M + H], 176 (80). For $C_{16}H_{21}N_5O_3$ (331.4) calculated: 57.99% C, 6.39% H, 21.13% N; found: 57.97% C, 6.40% H, 21.00% N.

(1R,2R*,3S*,4S*,5R*,6S*)-5-[6-(Cyclopropylamino)-9H-purin-9-yl]-6-(hydroxymethyl)bicyclo-[2.2.1]heptane-2,3-diol* (**19b**): Chromatography on silica gel (50 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4). Yield 155 mg (78%) as a foam. ^{1}H NMR: 0.60 m, 2 H and 0.72 m, 2 H (CH_2 of cyclopropyl); 1.46 dm, 1 H, J_{gem} = 10.7 (H-7a); 1.76 dm, 1 H, J_{gem} = 10.6 (H-7b); 2.04 m, 1 H (H-1); 2.31 m, 1 H (H-6); 2.49 m, 1 H (H-4); 3.00 bs, 1 H (CH of cyclopropyl); 3.31–3.50 m, 3 H (CH_2O, H-3); 3.94 bt, 1 H, *J*(2,3) = *J*(2,OH) = 5.2 (H-2); 4.29 dd, 1 H, *J*(5,6) = 5.8, *J*(5,4) = 4.1 (H-5); 4.65 d, 1 H, *J*(OH,2) = 4.8 (2-OH); 4.66 d, 1 H, *J*(OH,3) = 5.5 (3-OH); 4.80 t, 1 H, *J*(OH,CH_2) = 5.1 (CH_2O**H**); 7.91 bs, 1 H (NH); 8.24 bs, 1 H (H-2′); 8.25 s, 1 H (H-8′). ^{13}C NMR: 6.64 (CH_2 of cyclopropyl); 29.36 (C-7); 42.41 (C-6); 45.91 (C-1); 48.34 (C-4); 57.65 (C-5); 63.31 (CH_2O); 68.12 (C-3); 72.86 (C-2); 119.95 (C-5′); 140.00 (C-8′); 149.72 (C-4′); 152.41 (C-2′); 155.79 (C-6′). FAB MS, *m/z* (rel.%): 332 (100) [M + H], 176 (40). For $C_{16}H_{21}N_5O_3 \cdot 1/3H_2O$ (337.4) calculated: 56.96% C, 6.47% H, 20.76% N; found: 56.88% C, 6.59% H, 20.55% N.

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