SYNTHESIS OF NOVEL CARBOCYCLIC NUCLEOSIDE ANALOGUES CONTAINING BICYCLO[2.2.1]HEPT-2-ENE-2-METHANOL

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

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

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Starting ethyl (1*R**,2*R**,3*R**,4*S**)-3-bromobicyclo[2.2.1]hept-5-ene-2-carboxylate (**9**) was reduced with $LiAlH_4$ and benzoylated giving [(1*R**,2*R**,3*R**,4*S**)-3-bromobicyclo[2.2.1]hept-5-en-2-yl]methyl benzoate (**11**). Treatment of **11** with NaN_3 and CrO_3 in acetic acid afforded [(1*R**,2*S**,3*R**,4*R**,5*S**,6*R**)-6-azido-3-bromo-5-hydroxybicyclo[2.2.1]hept-2-yl]methyl benzoate (**12a**) and [(1*R**,2*S**,3*S**,4*R**,5*S**,6*R**)-5-azido-3-bromo-6-hydroxybicyclo[2.2.1]heptan-2-yl]-methyl benzoate (**12b**). These key intermediates were separated and converted in five reaction steps to (1*R**,2*R**,3*S**,4*S**)-3-[(5-amino-6-chloropyrimidin-4-yl)amino]-5-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**17a**) and (1*R**,2*R**,3*S**,4*S**)-3-[(5-amino-6-chloropyrimidin-4-yl)-amino]-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (**17b**). Ring closure with triethyl orthoformate led to (1*R**,2*R**,3*S**,4*S**)-5-(chloromethyl)-3-(6-chloro-9*H*-purin-9-yl)bicyclo-[2.2.1]hept-5-en-2-ol (**18a**) and (1*R**,2*R**,3*S**,4*S**)-6-(chloromethyl)-3-(6-chloro-9*H*-purin-9-yl)-bicyclo[2.2.1]hept-5-en-2-ol (**18b**) using hydrochloric acid as a catalyst or (1*R**,2*R**,3*S**,4*S**)-3-(6-chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (**19a**) and (1*R**,2*R**,3*S**,4*S**)-3-(6-chloro-9*H*-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (**19b**) using trifluoroacetic acid as a catalyst. From **19a** and **19b**, 6-amino- and 6-(cyclopropylamino)purine derivatives **20** and **21** were prepared.

Keywords: Nucleosides; Carbocyclic nucleosides; Norbornanes; Norbornenes; Purines; 6-Chloropurine; Adenine; 6-(Cyclopropylamino)purine; Antivirals.

The search for new carbocyclic nucleosides, in which the furan ring of natural nucleosides is replaced by a carbocyclic system, is a promising field of research. These analogues exhibit increased resistance to hydrolases and phosphorylases, but in certain cases do not show reduced reactivity with other enzymes involved in the nucleotide metabolism[1]. A number of synthetic carbocyclic nucleosides with important therapeutic properties were discovered. U.S. Food and Drug Administration approved abacavir (Ziagen™; **1**)[2] for the treatment of HIV-1 infections and entecavir (Baraclude; **2**)[3] for the treatment of chronic hepatitis B virus (HBV) infections (Chart 1). Jacobson

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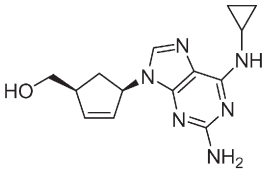
and co-workers[4] described bisphosphate of the 2-iodo-(6-methylamino)-purine analogue containing the oxabicyclo[2.2.1]heptane moiety which displayed potent binding affinity to the human $P2Y_1$ receptor.



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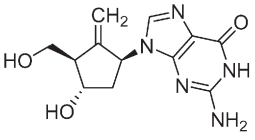

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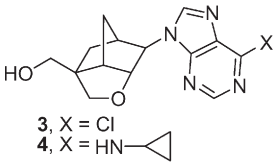
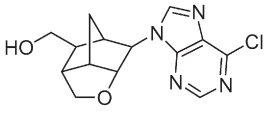
CHART 1

We reported the synthesis of novel racemic conformationally-locked carbocyclic purine nucleoside analogues derived from 4-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-6-methanol[5], 4-oxatricyclo[4.2.1.$0^{3,7}$]nonane-9-methanol and their Pro-Tides[6], 5,5- and 6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ols[7], 3-(hydroxymethyl)bicyclo[2.2.1]heptane-2,5-diol[8], 2- and 3-(hydroxymethyl)bicyclo[2.2.1]heptanes[9], and analogues[10] with a bicyclo[2.2.1]-heptene or -heptane ring system substituted with nucleobase at position 7. Nucleoside analogues **3**, **4** (ref.[5]), **5**, **6**, **7**, and **8** (ref.[6]) in Chart 2 exhibit a weak activity in tests for anti-HIV-1 and anti-HIV-2 in human T-lymphocyte (CEM) cells.



3, X = Cl
4, X = HN



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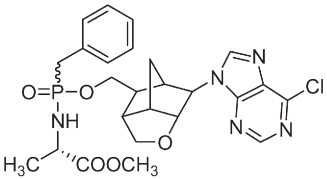

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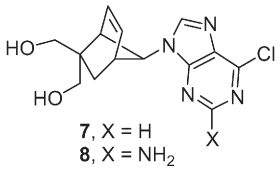


7, X = H
8, X = NH_2

CHART 2

Recently, we discovered, that some 6-chloro- and 2,6-dichloropurines bearing in the position 9 substituted bicyclic hydrocarbons show activity against the *Coxsackie* virus (CVB3)[9,11]. The virus is a cytolytic virus of the *Picornaviridae* family[12], a genus enterovirus. The enteroviruses (polioviruses,

coxsackieviruses, echoviruses) are associated with several human and mammalian diseases. Enteroviruses are the second most common viral infectious agents in humans (after rhinoviruses). In most cases infection is asymptomatic or causes only mild symptoms, but also acute haemorrhagic conjunctivitis, herpangina, aseptic meningitis, infectious myocarditis, infectious pericarditis, and pleurodynia.

This study concerns a synthesis of novel racemic carbocyclic purine nucleosides derived from 5- or 6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol and 5- or 6-(chloromethyl)bicyclo[2.2.1]hept-5-en-2-ol. Chart 3 describes the target compounds.

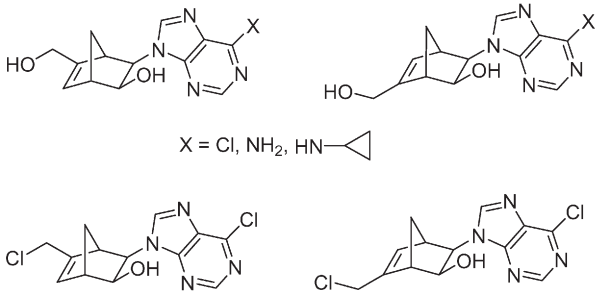
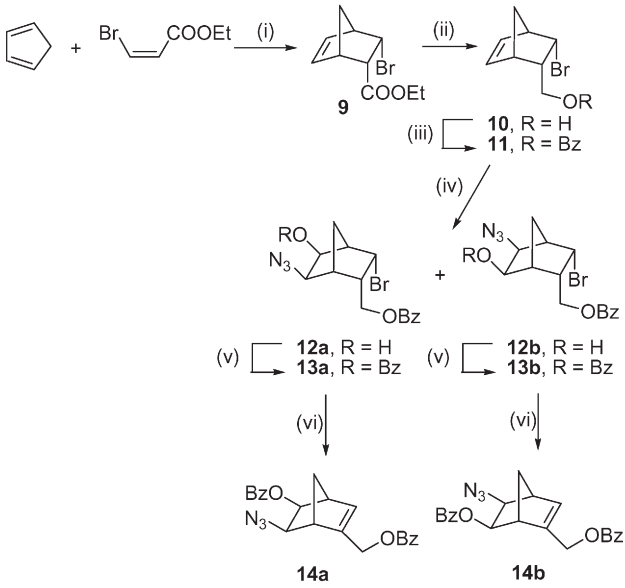


CHART 3

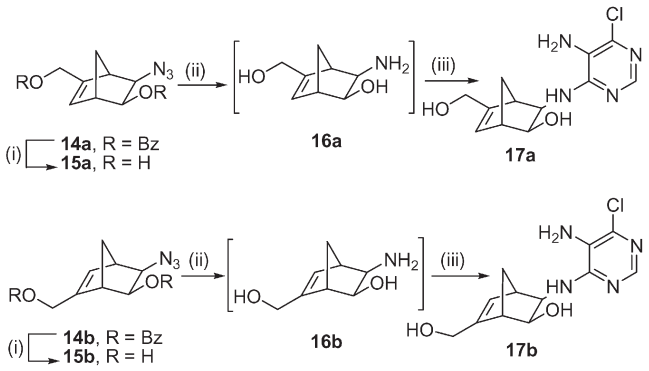
The starting racemic *endo*-bromo-*endo*-(ethoxycarbonyl) derivative **9** was prepared by boron tribromide catalyzed Diels–Alder reaction of cyclopentadiene with ethyl (2*Z*)-3-bromoacrylate[13] performed at –78 °C. Leahy and Boyer[14] synthesized this compound as optically pure product using Hawkin's catalyst. Reduction of the Diels–Alder product **9** with lithium aluminium hydride afforded hydroxymethyl derivative **10** (85%) and subsequent benzoylation with benzoyl chloride in pyridine gave benzoate **11** (90%). The reaction of alkene **11** with sodium azide and chromium trioxide in acetic acid afforded azides **12a** (23.5%) and **12b** (30%) as main products besides a non-separable mixture of minor by-products. An analogous reaction of (bicyclo[2.2.1]hept-5-ene-2,2-diyl)dimethyl dibenzoate led to [(1*R**,4*S**,5*S**,6*R**)-5-azido-6-hydroxybicyclo[2.2.1]heptane-2,2-diyl]dimethyl dibenzoate and [(1*R**,4*S**,5*R**,6*R**)-6-azido-5-hydroxybicyclo[2.2.1]heptane-2,2-diyl]dimethyl dibenzoate as main products[7]. Benzoylation of **12a** and **12b** with benzoyl chloride in pyridine gave crystalline benzoates **13a** (93%) and **13b** (84%). Treatment of **13a** or **13b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in hexamethylphosphoramide (HMPA) at 80 °C for 4.5 h afforded **14a** (70%) or **14b** (68%) (Scheme 1).



(i) BBr_3/CH_2Cl_2, -78 °C, 81%;
(ii) $LiAlH_4$/THF, 0 °C, 85%;
(iii) BzCl/pyridine, 90%;
(iv) NaN_3/AcOH/CrO_3, 23.5% of **12a**, 30% of **12b**;
(v) BzCl/pyridine, 93% of **13a**, 84% of **13b**;
(vi) DBU/HMPA, 80 °C, 70% of **14a**, 68% of **14b**

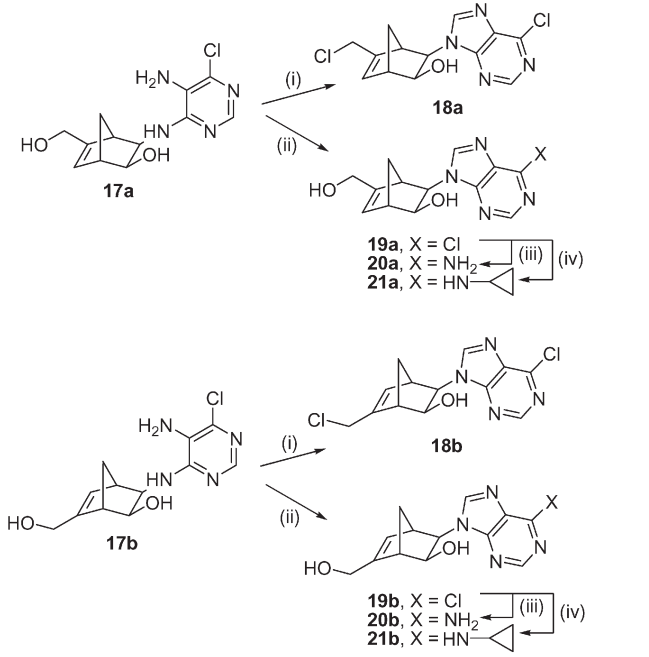
SCHEME 1

The benzoates **14a** and **14b** were deprotected with 0.1 M methanolic sodium methoxide. The obtained deprotected azides **15a** (83%) and **15b** (77%) are unstable. Therefore, they were immediately reduced with lithium aluminium hydride in tetrahydrofuran at 0 °C giving amines **16a** and **16b**. The amines were used without purification in the next reaction step; **16a** and **16b** were converted to the 6-chloropurine derivatives using described procedures[5,7–9,15,16]. Coupling of amine **16a** or **16b** with 4,6-dichloropyrimidin-5-amine in ethanol and triethylamine gave pyrimidinylamino derivative **17a** (19% based on **15a**) or **17b** (22% based on **15b**) (Scheme 2). Ring closure of **17a** or **17b** with triethyl orthoformate in the presence of concentrated hydrochloric acid and subsequent hydrolysis with a mixture of tetrahydrofuran and dilute hydrochloric acid afforded chloromethyl derivative **18a** (44%) or **18b** (50%) (Scheme 3). The desired hydroxymethyl derivatives **19a** and **19b** were prepared by the same procedure, but hydrochloric acid in the ring closure reaction was replaced by trifluoroacetic acid



(i) 0.1M MeONa in MeOH, 83% of **15a**, 77% of **15b**; (ii) $LiAlH_4$/THF, 0 °C; (iii) 4,6-dichloropyrimidin-5-amine/TEA/EtOH, 100 °C, 19% of **17a**, 22% of **17b** both calculated on **15a** or **15b**

SCHEME 2



(i) 1. $CH(OEt)_3$/HCl, 2. THF/H_2O/HCl, 44% of **18a**, 50% of **18b**; (ii) 1. $CH(OEt)_3$/TFA, 2. THF/H_2O/HCl, 51% of **19a**, 57% of **19b**; (iii) NH_3 (l), 70 °C, 51% of **20a**, 56% of **20b**; (iv) cyclopropylamine, 76.5% of **21a**, 80% of **21b**

SCHEME 3

(TFA). Compounds **19a** and **19b** were obtained in 51 and 57% yields, respectively. The chloropurine derivatives **19a** and **19b** were ammonolysed with liquid ammonia at 70 °C to give adenine derivatives **20a** (51%) and **20b** (56%). Aminolysis of **19a** or **19b** with cyclopropylamine led to cyclopropylamino derivative **21a** (76.5%) or **21b** (80%).

The structures of the prepared compounds were confirmed by NMR spectroscopy. Complete assignment of all ^{1}H and ^{13}C NMR resonances is based on combination of ^{1}H, ^{13}C APT, H,H-COSY, H,C-HSQC, and H,C-HMBC experiments. The compound **20a** is poorly soluble in dimethyl sulfoxide; therefore, only the ^{1}H NMR spectrum could be taken. Nevertheless, the structure of **20a** was uniquely determined on the basis of comparison of ^{1}H NMR spectra of compounds **20a**, **20b**, and **21a**.

In conclusion, novel racemic carbocyclic nucleoside analogues of 6-chloropurine, adenine, and 6-(cyclopropylamino)purine derived from 5- or 6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol and analogues of 6-chloropurine derived from 5- or 6-(chloromethyl)bicyclo[2.2.1]hept-5-en-2-ol were synthesized. The target compounds were tested for the activity against *Coxsackie* virus (CVB3) in Vero cells. Preliminary data showed that only compound **19b** exhibits a weak activity (EC_{50} 46.3 μM, TC_{50} > 342 μM). The corresponding chloromethyl derivative **18b** is cytotoxic to Vero cells (EC_{50} > 342 μM, TC_{50} 45.6 μM)[17].

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 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 (ionization with Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3:1 or bis-(2-hydroxyethyl) disulfide matrix). 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 13 Pa and 50 °C.

Ethyl (1*R**,2*R**,3*R**,4*S**)-3-Bromobicyclo[2.2.1]hept-5-ene-2-carboxylate (**9**)

A 1 M solution of boron tribromide in THF (8 ml) was added to a stirred solution of ethyl (2*Z*)-3-bromoacrylate[13] (17.9 g, 100 mmol) in dichloromethane (35 ml) at –78 °C under argon atmosphere and then cyclopentadiene (40 ml) was slowly added to the solution. The mixture was stirred at –78 °C for 4 h, saturated aqueous $KHCO_3$ (20 ml) was added and temperature was allowed to rise to room temperature. The mixture was diluted with chloroform (150 ml), the organic layer was separated, washed with 10% aqueous $KHCO_3$ (2 × 100 ml),

dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on a silica gel column (1 kg) in toluene afforded 19.9 g (81%) of compound **9** as colorless oil. For $C_{10}H_{13}BrO_2$ (245.1) calculated: 49.00% C, 5.35% H, 32.60% Br; found: 48.84% C, 5.39% H, 32.69% Br. FAB MS, *m/z* (rel.%): 247/245 (96/100) [M + H], 219/217 (86/88). ^{1}H NMR: 1.18 t, 3 H (CH_3); 1.42 dm, 1 H, J_{gem} = 9.0 (H-7a); 1.47 dt, 1 H, *J*(7b,1) ~ *J*(7b,4) = 2.0 (H-7b); 3.02 m, 1 H (H-1); 3.18 m, 1 H (H-4); 3.31 dd, 1 H, *J*(2,1) = 3.0, *J*(2,3) = 9.1 (H-2); 4.02 q, 2 H, *J*(CH_2,CH_3) = 7.1 (CH_2); 4.80 dd, 1 H, *J*(3,4) = 3.6 (H-3); 6.02 dd, 1 H, *J*(5,4) = 3.0, *J*(5,6) = 5.7 (H-5); 6.41 dd, 1 H, *J*(6,1) = 3.0 (H-6). ^{13}C NMR: 14.28 (CH_3); 44.33 (C-1); 46.87 (C-7); 49.08 (C-2); 49.46 (C-4); 52.66 (C-3); 59.99 (CH_2); 134.13 (C-5); 136.94 (C-6); 170.55 (C=O).

(1*R**,2*R**,3*R**,4*S**)-3-Bromobicyclo[2.2.1]hept-5-ene-2-methanol (**10**)

A solution of ester **9** (18.87 g, 77 mmol) in tetrahydrofuran (70 ml) was added dropwise to a stirred 1.0 M solution of lithium aluminium hydride in tetrahydrofuran (60 ml) at 0 °C under argon atmosphere. The mixture was stirred at 0 °C for 4 h, the excess of the hydride was decomposed by slow addition of water. Then solid CO_2 was added to adjust pH of the mixture to ~8. The thick suspension was filtered with a Celite pad, the filter was washed with ethyl acetate (5 × 100 ml) and the collected filtrates were evaporated. Chromatography of the residue on a silica gel column (1 kg) in toluene–ethyl acetate (4:1) gave 13.29 g (85%) of **10** in the form of a syrup. For $C_8H_{11}BrO$ (203.1) calculated: 47.31% C, 5.46% H, 39.35% Br; found: 47.23% C, 5.59% H, 39.18% Br. FAB MS, *m/z* (%): 205/203 (69/75) [M + H], 123 (100). ^{1}H NMR: 1.37 dm, 1 H, J_{gem} = 8.8 (H-7a); 1.51 dt, 1 H, J_{gem} = 8.8, *J*(7b,1) = *J*(7b,4) = 2.1 (H-7b); 2.18 m, 1 H (H-2); 2.90 m, 1 H and 3.32 m, 1 H (CH_2O); 2.94 m, 1 H (H-1); 3.15 m, 1 H (H-4); 4.51 t, 1 H, *J*(OH,CH_2) = 5.1 (OH); 4.63 dd, 1 H, *J*(3,2) = 8.6, *J*(3,4) = 3.6 (H-3); 6.06 dd, 1 H, *J*(5,6) = 5.7, *J*(5,4) = 2.9 (H-5); 6.25 dd, 1 H, *J*(6,5) = 5.8, *J*(6,1) = 3.1 (H-6). ^{13}C NMR: 42.73 (C-2); 43.70 (C-1); 47.02 (C-7); 50.14 (C-4); 54.78 (C-3); 64.15 (CH_2O); 135.62 (C-6); 135.72 (C-5).

[(1*R**,2*R**,3*R**,4*S**)-3-Bromobicyclo[2.2.1]hept-5-en-2-yl]methyl Benzoate (**11**)

Benzoyl chloride (8.4 ml, 72 mmol) was added at 0 °C to a stirred solution of hydroxy derivative **10** (12.18 g, 60 mmol) in pyridine (120 ml) and the mixture was allowed to stand at room temperature overnight. Pyridine was then evaporated and the residue was partitioned between ethyl acetate (450 ml) and water (150 ml). The organic phase was washed with water (150 ml), 5% hydrochloric acid (to acid reaction of the aqueous phase), 10% sodium hydrogencarbonate solution (3 × 150 ml), dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethanol afforded 16.61 g (90%) of benzoate **11**, m.p. 57–58 °C. For $C_{15}H_{15}BrO_2$ (307.2) calculated: 58.65% C, 4.92% H, 26.01% Br; found: 58.63% C, 4.81% H, 25.97% Br. ^{1}H NMR: 1.49 dm, 1 H, J_{gem} = 9.0 (H-7a); 1.56 dt, 1 H, J_{gem} = 9.0, *J*(7b,1) = *J*(7b,4) = 2.0 (H-7b); 2.61 tdd, 1 H, *J*(2,3) = *J*(2,CH^aO) = 8.6, *J*(2,CH^bO) = 6.9, *J*(2,1) = 3.2 (H-2); 3.01 m, 1 H (H-1); 3.23 m, 1 H (H-4); 3.91 dd, 1 H, *J*(CH^aH,2) = 8.7 and 4.13 dd, 1 H, *J*(CH^bH,2) = 6.9, J_{gem} = 10.9 (CH_2O); 4.77 dd, 1 H, *J*(3,2) = 8.5, *J*(3,4) = 3.6 (H-3); 6.16 dd, 1 H, *J*(5,6) = 5.7, *J*(5,4) = 2.9 (H-5); 6.31 dd, 1 H, *J*(6,5) = 5.7, *J*(6,1) = 3.0 (H-6); 7.54 m, 2 H, 7.66 m, 1 H and 7.99 m, 2 H (arom.). ^{13}C NMR: 39.65 (C-2); 44.33 (C-1); 47.30 (C-7); 50.12 (C-4); 54.01 (C-3); 67.40 (CH_2O); 128.96, 129.39, 129.94 and 133.55 (arom.); 135.15 (C-6); 136.54 (C-5); 165.73 (C=O).

[(1*R**,2*S**,3*R**,4*R**,5*S**,6*R**)-6-Azido-3-bromo-5-hydroxybicyclo[2.2.1]heptan-2-yl]-methyl Benzoate (**12a**) and
[(1*R**,2*S**,3*S**,4*R**,5*S**,6*R**)-5-Azido-3-bromo-6-hydroxybicyclo[2.2.1]heptan-2-yl]-methyl Benzoate (**12b**)

Chromium(VI) oxide (1.52 g, 15.2 mmol) was added to a stirred ice-cool mixture of acetic acid (130 ml), alkene **11** (4.61 g, 15 mmol) and sodium azide (21 g). After 15 min, the mixture was warmed to room temperature, stirred for another 45 min, filtered and evaporated. The residue was extracted with toluene (300 ml), the insoluble portion was filtered off with a Celite pad, washed with toluene and the combined filtrates were evaporated. The residue was chromatographed on silica gel (800 g) in ethyl acetate–toluene (1:15).

[(1R,2S*,3R*,4R*,5S*,6R*)-6-Azido-3-bromo-5-hydroxybicyclo[2.2.1]heptan-2-yl]methyl benzoate* (**12a**): Yield 1.29 g (23.5%) of a syrup. For $C_{15}H_{16}BrN_3O_3$ (366.2) calculated: 49.20% C, 4.40% H, 21.82% Br, 11.47% N; found: 49.38% C, 4.45% H, 21.89% Br, 11.27% N. ^{1}H NMR: 1.40 dp, 1 H, J_{gem} = 10.6, J(7a,1) = J(7a,4) = J(7a,5) = J(7a,6) = 1.6 (H-7a); 1.94 dt, 1 H, J_{gem} = 10.6, J(7b,1) = J(7b,4) = 1.9 (H-7b); 2.21 m, 1 H (H-1); 2.35 m, 1 H (H-4); 2.55 dddd, 1 H, J(2,3) = 10.5, J(2,CH_2Oa) = 8.6, J(2,CH_2Ob) = 7.5, J(2,1) = 4.1 (H-2); 3.98 dd, 1 H, J(6,5) = 6.2, J(6,7a) = 1.8 (H-6); 4.20 dd, 1 H, J(CH^{a}H,2) = 8.6 and 4.33 dd, 1 H, J(CH^{b}H,2) = 7.5, J_{gem} = 11.3 (CH_2O); 4.40 td, 1 H, J(5,OH) = J(5,6) = 6.2, J(5,7a) = 1.8 (H-5); 4.71 dd, 1 H, J(3,2) = 10.5, J(3,4) = 4.5 (H-5); 5.44 d, 1 H, J(OH,5) = 6.0 (OH); 7.54 m, 2 H, 7.67 m, 1 H and 7.97 m, 2 H (arom.). ^{13}C NMR: 32.88 (C-7); 38.51 (C-2); 43.63 (C-1); 51.64 (C-4); 53.41 (C-3); 60.78 (C-6); 64.53 (CH_2O); 72.65 (C-5); 128.99, 129.37, 129.83 and 133.62 (arom.); 165.63 (C=O).

[(1R,2S*,3S*,4R*,5S*,6R*)-5-Azido-3-bromo-6-hydroxybicyclo[2.2.1]heptan-2-yl]methyl benzoate* (**12b**): Yield 1.65 g (30%) of a syrup. For $C_{15}H_{16}BrN_3O_3$ (366.2) calculated: 49.20% C, 4.40% H, 21.82% Br, 11.47% N; found: 49.49% C, 4.52% H, 21.68% Br, 11.19% N. ^{1}H NMR: 1.43 dm, 1 H, J_{gem} = 10.7 (H-7a); 1.98 dt, 1 H, J_{gem} = 10.7, J(7b,1) = J(7b,4) = 1.9 (H-7b); 2.23 m, 1 H (H-1); 2.40 m, 1 H (H-4); 2.57 dtd, 1 H, J(2,3) = 10.6, J(2,CH_2O) = 8.1, J(2,1) = 4.1 (H-2); 4.00 dd, 1 H, J(5,6) = 6.2, J(5,7a) = 1.9 (H-5); 4.19 m, 2 H (CH^{a}H-O, H-6); 4.30 dd, 1 H, J_{gem} = 11.2, J(CH^{b}H,2) = 7.8 (CH^{b}H-O); 4.69 dd, 1 H, J(3,2) = 10.6, J(3,4) = 4.4 (H-3); 5.38 d, 1 H, J(OH,6) = 5.5 (OH); 7.54 m, 2 H, 7.67 m, 1 H and 7.98 m, 2 H (arom.). ^{13}C NMR: 32.75 (C-7); 37.82 (C-2); 45.98 (C-1); 49.70 (C-4); 53.52 (C-3); 63.41 (C-5); 64.47 (CH_2O); 69.88 (C-6); 128.99, 129.40, 129.82 and 133.63 (arom.); 165.67 (C=O).

[(1*R**,2*S**,3*R**,4*R**,5*S**,6*R**)-6-Azido-5-(benzoyloxy)-3-bromobicyclo[2.2.1]heptan-2-yl]-methyl Benzoate (**13a**) and
[(1*R**,2*S**,3*S**,4*R**,5*S**,6*R**)-5-Azido-6-(benzoyloxy)-3-bromobicyclo[2.2.1]heptan-2-yl]-methyl Benzoate (**13b**)

Benzoyl chloride (2.1 ml, 18 mmol) was added to a stirred and cooled solution of hydroxy derivative **12a** or **12b** (5.49 g, 15 mmol) in pyridine (40 ml) and the mixture was left standing at room temperature overnight. Water (30 ml) was then slowly added and, after 1 h, the deposited crystals were filtered off and washed with ethanol.

[(1R,2S*,3R*,4R*,5S*,6R*)-6-Azido-5-(benzoyloxy)-3-bromobicyclo[2.2.1]heptan-2-yl]methyl benzoate* (**13a**): Yield 6.57 g (93%). M.p. 143–144 °C. For $C_{22}H_{20}BrN_3O_4$ (470.3) calculated: 56.18% C, 4.29% H, 16.99% Br, 8.93% N; found: 55.97% C, 4.20% H, 17.11% Br, 8.81% N. ^{1}H NMR: 1.65 dm, 1 H, J_{gem} = 11.0 (H-7a); 2.02 dt, 1 H, J_{gem} = 11.0, J(7b,4) = J(7b,1) = 1.9 (H-7b); 2.45 m, 1 H (H-1); 2.70 m, 1 H (H-2); 2.75 m, 1 H (H-4); 4.36 dd, 1 H, J(CH^{a}H,2) = 8.4 and 4.42 dd, 1 H, J_{gem} = 11.4, J(CH^{b}H,2) = 7.6 (CH_2O); 4.47 dd, 1 H, J(6,5) = 6.3,

J(6,7a) = 1.8 (H-6); 4.83 dd, 1 H, *J*(3,2) = 10.6, *J*(3,4) = 4.6 (H-3); 5.59 dd, 1 H, *J*(5,6) = 6.3, *J*(5,7a) = 1.8 (H-5); 7.56 m, 4 H, 7.68 m, 2 H and 8.01 m, 4 H (arom.). ^{13}C NMR: 33.59 (C-7); 38.53 (C-2); 43.98 (C-1); 49.11 (C-4); 51.86 (C-3); 60.53 (C-6); 64.42 (2-CH_2); 75.17 (C-5); 128.97, 129.06, 129.32, 129.40, 129.50, 129.81, 133.62 and 133.87 (arom.); 165.23 (5-O-CO); 165.64 (2-CH_2-O-CO).

[(1R,2S*,3S*,4R*,5S*,6R*)-5-Azido-6-(benzoyloxy)-3-bromobicyclo[2.2.1]heptan-2-yl]methyl benzoate* (**13b**): Yield 5.92 g (84%). M.p. 117–118 °C. For $C_{22}H_{20}BrN_3O_4$ (470.3) calculated: 56.18% C, 4.29% H, 16.99% Br, 8.93% N; found: 56.02% C, 4.27% H, 17.16% Br, 8.75% N. ^{1}H NMR: 1.66 dm, 1 H, J_{gem} = 11.1 (H-7a); 2.03 dt, 1 H, J_{gem} = 11.1, *J*(7b,4) = *J*(7b,1) = 1.9 (H-7b); 2.58 m, 1 H (H-1); 2.64 m, 1 H (H-4); 2.74 m, 1 H (H-2); 4.34 dd, 1 H, *J*(CH^{a}H,2) = 8.0 and 4.42 dd, 1 H, J_{gem} = 11.3, *J*(CH^{b}H,2) = 7.9 (CH_2O); 4.47 dd, 1 H, *J*(5,6) = 6.3, *J*(5,7a) = 1.9 (H-5); 4.82 dd, 1 H, *J*(3,2) = 10.7, *J*(3,4) = 4.4 (H-3); 5.39 dd, 1 H, *J*(6,5) = 6.3, *J*(6,7a) = 1.6 (H-6); 7.55 m, 4 H, 7.66 m, 1 H, 7.69 m, 1 H and 8.00 m, 4 H (arom.). ^{13}C NMR: 33.51 (C-7); 37.94 (C-2); 43.54 (C-1); 49.89 (C-4); 52.50 (C-3); 63.46 (C-5); 64.28 (2-CH_2); 72.75 (C-6); 128.97, 129.09, 129.37, 129.47, 129.50, 129.78, 133.64 and 133.89 (arom.); 165.25 (6-O-CO); 165.70 (2-CH_2-O-CO).

[(1*R**,4*S**,5*S**,6*R**)-6-Azido-5-(benzoyloxy)bicyclo[2.2.1]hept-2-en-2-yl]-methyl Benzoate (**14a**) and
[(1*S**,4*R**,5*R**,6*S**)-5-Azido-6-(benzoyloxy)bicyclo[2.2.1]hept-2-en-2-yl]-methyl Benzoate (**14b**)

1,8-Diazabicyclo[5.4.0]undec-7-ene (4.2 ml, 18 mmol) was added to a solution of bromo derivative **13a** or **13b** (4.70 g, 10 mmol) in hexamethylphosphoramide (20 ml). The mixture was heated to 80 °C in argon atmosphere for 4.5 h, then diluted with ethyl acetate (150 ml), washed with water (4 × 100 ml), dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (250 g) in toluene–ethyl acetate (30:1).

[(1R,4S*,5S*,6R*)-6-Azido-5-(benzoyloxy)bicyclo[2.2.1]hept-2-en-2-yl]methyl benzoate* (**14a**): Yield 2.72 g (70%). M.p. 89–90 °C (methanol). For $C_{22}H_{19}N_3O_4$ (389.4) calculated: 67.86% C, 4.92% H, 10.79% N; found: 68.08% C, 4.82% H, 10.66% N. ^{1}H NMR: 1.79 dp, 1 H, J_{gem} = 9.4, *J*(7a,1) = *J*(7a,4) = *J*(7a,5) = *J*(7a,6) = 1.7 (H-7a); 2.00 dm, 1 H, J_{gem} = 9.3 (H-7b); 2.96 m, 1 H (H-1); 3.01 m, 1 H (H-4); 4.01 dd, 1 H, *J*(6,5) = 6.1, *J*(6,7a) = 1.6 (H-6); 4.93 ddd, 1 H, *J*(5,6) = 6.0, *J*(5,7a) = 1.8, *J*(5,4) = 0.8 (H-5); 4.94 dd, 1 H, *J*(CH^{a}H,3) = 1.5 and 4.99 dd, 1 H, *J*(CH^{b}H,3) = 1.9, J_{gem} = 14.3 (CH_2O); 6.15 m, 1 H (H-3); 7.56 m, 4 H, 7.67 m, 2 H and 8.01 m, 4 H (arom.). ^{13}C NMR: 43.43 (C-7); 46.29 (C-4); 47.67 (C-1); 61.21 (C-6); 62.30 (CH_2O); 73.78 (C-5); 129.06, 129.44, 129.58, 129.68, 133.71 and 133.78 (arom.); 131.04 (C-3); 146.72 (C-2); 165.62 and 165.65 (C=O).

[(1S,4R*,5R*,6S*)-5-Azido-6-(benzoyloxy)bicyclo[2.2.1]hept-2-en-2-yl]methyl benzoate* (**14b**): Yield 2.66 g (68%) of a solid foam. For $C_{22}H_{19}N_3O_4$ (389.4) calculated: 67.86% C, 4.92% H, 10.79% N; found: 67.84% C, 4.98% H, 10.54% N. ^{1}H NMR: 1.80 dm, 1 H, J_{gem} = 9.4 (H-7a); 2.00 dm, 1 H, J_{gem} = 9.3 (H-7b); 2.95 m, 1 H (H-4); 3.03 m, 1 H (H-1); 3.93 dd, 1 H, *J*(5,6) = 6.0, *J*(5,7a) = 1.5 (H-5); 4.94 m, 2 H (CH_2O); 5.07 dm, 1 H, *J*(6,5) = 6.0 (H-6); 6.20 m, 1 H (H-3); 7.55 m, 4 H, 7.67 m, 2 H and 8.01 m, 4 H (arom.). ^{13}C NMR: 43.62 (C-7); 47.04 (C-4); 47.21 (C-1); 62.07 (C-5); 62.28 (CH_2O); 73.18 (C-6); 129.05, 129.09, 129.45, 129.47, 129.60, 129.68, 133.73 and 133.81 (arom.); 133.25 (C-3); 145.01 (C-2); 165.63 and 165.70 (C=O).

(1*R**,2*R**,3*S**,4*S**)-3-Azido-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (**15a**) and
(1*R**,2*R**,3*S**,4*S**)-3-Azido-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (**15b**)

Benzoate **14a** or **14b** (3.89 g, 10 mmol) was dissolved under stirring in methanolic 0.1 M sodium methoxide (40 ml), the solution was left standing at room temperature for 5 h and then neutralized with Dowex 50 (H^+). The resin was filtered off and washed with methanol. The combined filtrates were treated with a drop of triethylamine and evaporated. The residue was chromatographed on a silica gel column (150 g) in ethyl acetate–toluene (4:1).

(1R,2R*,3S*,4S*)-3-Azido-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol* (**15a**): Yield 1.5 g (83%) of a syrup. For $C_8H_{11}N_3O_2$ (181.2) calculated: 53.03% C, 6.12% H, 23.19% N; found: 53.16% C, 6.25% H, 22.93% N. ^{1}H NMR: 1.51 dp, 1 H, J_{gem} = 8.8, J(7a,1) = J(7a,4) = J(7a,2) = J(7a,3) = 1.7 (H-7a); 1.89 dt, 1 H, J_{gem} = 8.8, J(7b,1) = J(7b,4) = 1.7 (H-7b); 2.56 m, 2 H (H-1 and H-4); 3.38 dd, 1 H, J(3,2) = 5.9, J(3,7a) = 1.7 (H-3); 3.79 td, 1 H, J(2,3) = J(2,OH) = 5.5, J(2,7a) = 1.6 (H-2); 3.91 ddd, 1 H, J(CH^{a}H,OH) = 4.9, J(CH^{a}H,6) = 1.6 and 3.98 ddd, 1 H, J(CH^{b}H,OH) = 4.9, J(CH^{b}H,6) = 1.8, J_{gem} = 14.8 (CH_2O); 4.75 t, 1 H, J(OH,CH_2) = 5.4 (CH_2O**H**); 5.27 d, 1 H, J(OH,2) = 5.4 (2-OH); 5.74 m, 1 H (H-6). ^{13}C NMR: 42.70 (C-7); 47.15 (C-4); 48.90 (C-1); 58.99 (CH_2O); 61.32 (C-3); 72.38 (C-2); 128.34 (C-6); 151.59 (C-5).

(1R,2R*,3S*,4S*)-3-Azido-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol* (**15b**): Yield 1.39 g (77%) of a syrup. For $C_8H_{11}N_3O_2$ (181.2) calculated: 53.03% C, 6.12% H, 23.19% N; found: 53.07% C, 6.28% H, 22.95% N. ^{1}H NMR: 1.51 dp, 1 H, J_{gem} = 8.8, J(7a,1) = J(7a,4) = J(7a,2) = J(7a,3) = 1.7 (H-7a); 1.88 dt, 1 H, J_{gem} = 8.8, J(7b,1) = J(7b,4) = 1.7 (H-7b); 2.50 m, 1 H (H-1); 2.64 m, 1 H (H-4); 3.38 dd, 1 H, J(3,2) = 5.8, J(3,7a) = 1.9 (H-3); 3.82 td, 1 H, J(2,OH) = J(2,3) = 5.7, J(2,7a) = 1.6 (H-2); 3.91 ddd, 1 H, J(CH^{a}H,OH) = 5.3, J(CH^{a}H,5) = 1.7 and 3.99 ddd, 1 H, J(CH^{b}H,OH) = 5.4, J(CH^{b}H,5) = 2.0, J_{gem} = 14.9 (CH_2O); 4.76 t, 1 H, J(OH,CH_2) = 5.4 (CH_2O**H**); 5.24 d, 1 H, J(OH,2) = 5.5 (2-OH); 5.72 m, 1 H (H-5). ^{13}C NMR: 46.56 (C-4); 49.62 (C-1); 59.15 (CH_2O); 62.56 (C-3); 71.18 (C-2); 127.78 (C-5); 152.29 (C-6).

(1*R**,2*R**,3*S**,4*S**)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-5-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**17a**) and
(1*R**,2*R**,3*S**,4*S**)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-6-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**17b**)

A solution of azido derivative **15a** or **15b** (1.45 g, 8 mmol) in tetrahydrofuran (15 ml) was added dropwise to a stirred 1.0 M solution of lithium aluminium hydride in tetrahydrofuran (23 ml) at 0 °C under argon atmosphere. The mixture was stirred at 0 °C for 5 h, the excess of hydride was decomposed by slow addition of water. Then solid CO_2 was added to adjusted pH of the mixture to ~8. The mixture was filtered with a Celite pad, the filter was washed with methanol (3 × 30 ml) and the combined filtrates were evaporated. The residue was dissolved in ethanol (10 ml), the insoluble portion was filtered off with a Celite pad and the filtrate was evaporated. A solution of amine **16a** or **16b**, obtained in this way, 4,6-dichloropyrimidin-5-amine (1.15 g, 7 mmol), and triethylamine (2.1 ml) in ethanol (21 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 (60 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) and crystallized from ethyl acetate.

(1R,2R*,3S*,4S*)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-5-(hydroxymethyl)bicyclo[2.2.1]-hept-5-en-2-ol* (**17a**): Yield 423 mg (19%, based on **15a**). M.p. 170–171 °C. For $C_{12}H_{15}ClN_4O_2$ (282.7) calculated: 50.98% C, 5.35% H, 12.54% Cl, 19.82% N; found: 51.18% C, 5.50% H, 12.28% Cl, 19.59% N. ^{1}H NMR: 1.47 dm, 1 H, J_{gem} = 8.7 (H-7a); 2.00 dt, 1 H, J_{gem} = 8.7,

J(7b,1) = *J*(7b,4) = 1.6 (H-7b); 2.52 m, 1 H (H-4); 2.60 m, 1 H (H-1); 3.75 m, 1 H (H-2); 3.89 m, 1 H (H-3); 3.98 ddd, 1 H, *J*(CH^{a}H,OH) = 5.2, *J*(CH^{a}H,6) = 1.7 and 4.16 ddd, 1 H, J_{gem} = 15.1, *J*(CH^{b}H,OH) = 5.8, *J*(CH^{b}H,6) = 2.1 (CH_2O); 4.75 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 5.10 bs, 2 H (NH_2); 5.18 d, 1 H, *J*(OH,2) = 4.4 (2-OH); 5.72 m, 1 H (H-6); 6.34 d, 1 H, *J*(NH,3) = 7.3 (NH); 7.73 s, 1 H (H-2′). ^{13}C NMR: 42.75 (C-7); 47.21 (C-4); 49.07 (C-1); 52.16 (C-3); 59.25 (CH_2O); 69.56 (C-2); 123.78 (C-5′); 126.47 (C-6); 137.48 (C-6′); 146.33 (C-2′); 152.64 (C-4′); 153.10 (C-5).

(1R,2R*,3S*,4S*)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-6-(hydroxymethyl)bicyclo[2.2.1]-hept-5-en-2-ol* (**17b**): Yield 501 mg (22%, based on **15b**). M.p. 199 °C (decomp.). For $C_{12}H_{15}ClN_4O_2$ (282.7) calculated: 50.98% C, 5.35% H, 12.54% Cl, 19.82% N; found: 50.68% C, 5.15% H, 12.71% Cl, 19.61% N. ^{1}H NMR: 1.47 dm, 1 H, J_{gem} = 8.8 (H-7a); 1.97 dt, 1 H, J_{gem} = 8.8, *J*(7b,1) = *J*(7b,4) = 1.6 (H-7b); 2.55 m, 1 H (H-1); 2.61 m, 1 H (H-4); 3.79 m, 1 H (H-2); 3.90 dt, 1 H, *J*(3,NH) = *J*(3,2) = 6.8, *J*(3,7a) = 1.8 (H-3); 3.96 ddd, 1 H, *J*(CH^{a}H,OH) = 5.3, *J*(CH^{a}H,5) = 1.7 and 4.03 ddd, 1 H, J_{gem} = 14.7, *J*(CH^{b}H,OH) = 5.6, *J*(CH^{b}H,5) = 1.9 (CH_2O); 4.76 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 5.08 bs, 2 H (NH_2); 5.32 d, 1 H, *J*(OH,2) = 4.4 (2-OH); 5.85 m, 1 H (H-5); 6.36 d, 1 H, *J*(NH,3) = 7.1 (NH); 7.74 s, 1 H (H-2′). ^{13}C NMR: 42.95 (C-7); 46.80 (C-4); 49.94 (C-1); 53.41 (C-3); 59.37 (CH_2O); 68.30 (C-2); 123.78 (C-5′); 129.24 (C-5); 137.72 (C-6′); 146.48 (C-2′); 150.74 (C-6); 152.61 (C-4′).

(1*R**,2*R**,3*S**,4*S**)-5-(Chloromethyl)-3-(6-chloro-9*H*-purin-9-yl)-bicyclo[2.2.1]hept-5-en-2-ol (**18a**) and
(1*R**,2*R**,3*S**,4*S**)-6-(Chloromethyl)-3-(6-chloro-9*H*-purin-9-yl)-bicyclo[2.2.1]hept-5-en-2-ol (**18b**)

Concentrated hydrochloric acid (1.4 ml) was added to a stirred mixture of compound **17a** or **17b** (226 mg, 0.8 mmol) and triethyl orthoformate (14 ml), the resulting solution was stored at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (5 ml). To the stirred solution, 0.5 M hydrochloric acid (5 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 × 8 ml). The combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (20 g) in ethyl acetate–toluene and then crystallized from ethanol–ether.

(1R,2R*,3S*,4S*)-5-(Chloromethyl)-3-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-ol* (**18a**): Yield 110 mg (44%). M.p. 173.5–175 °C. For $C_{13}H_{12}C_{12}N_4O$ (311.2) calculated: 50.18% C, 3.89% H, 22.79% Cl, 18.01% N; found: 50.11% C, 3.65% H, 22.68% Cl, 17.76% N. FAB MS, *m/z* (%): 313/311 (78/100) [M + H], 157/155 (70/18) [6-chloropurine + H]. ^{1}H NMR: 1.82 dm, 1 H, J_{gem} = 9.5 (H-7a); 2.37 dm, 1 H, J_{gem} = 9.4 (H-7b); 2.80 m, 1 H (H-1); 3.25 m, 1 H (H-4); 4.04 m, 1 H (H-2); 4.43 m, 2 H (CH_2Cl); 4.70 dd, 1 H, *J*(3,2) = 6.1, *J*(3,7) = 1.2 (H-3); 5.16 d, 1 H, *J*(OH,2) = 4.6 (OH); 6.20 d, 1 H, *J*(6,1) = 2.1 (H-6); 8.69 s, 1 H (H-8′); 8.76 s, 1 H (H-2′). ^{13}C NMR: 42.50 (CH_2Cl); 44.86 (C-7); 47.13 (C-4); 49.75 (C-1); 56.94 (C-3); 69.51 (C-2); 130.63 (C-5′); 134.00 (C-6); 146.72 (C-8′); 148.46 (C-5); 148.75 (C-6′); 151.45 (C-2′); 153.18 (C-4′).

(1R,2R*,3S*,4S*)-6-(Chloromethyl)-3-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-ol* (**18b**): Yield 124 mg (50%). M.p. 176–177 °C. For $C_{13}H_{12}Cl_2N_4O$ (311.2) calculated: 50.18% C, 3.89% H, 22.79% Cl, 18.01% N; found: 50.06% C, 3.75% H, 22.79% Cl, 17.86% N. FAB MS, *m/z* (%): 313/311 (71/100) [M + H], 157/155 (36/68) [6-chloropurine + H]. ^{1}H NMR: 1.81 dm,

1 H, J_{gem} = 9.6 (H-7a); 2.39 dm, 1 H, J_{gem} = 9.7 (H-7b); 2.79 m, 1 H (H-1); 3.23 m, 1 H (H-4); 4.15 m, 1 H (H-2); 4.41 m, 2 H (CH_2Cl); 4.59 dd, 1 H, *J*(3,2) = 6.2, *J*(3,7a) = 1.7 (H-3); 5.19 d, 1 H, *J*(OH,2) = 4.4 (2-OH); 6.33 m, 1 H (H-5); 8.66 s, 1 H (H-8′); 8.74 s, 1 H (H-2′). ^{13}C NMR: 42.76 (CH_2Cl); 44.78 (C-7); 46.29 (C-4); 50.89 (C-1); 57.53 (C-3); 68.25 (C-2); 130.54 (C-5′); 135.67 (C-5); 146.51 (C-6); 146.77 (C-8′); 148.74 (C-6′); 151.41 (C-2′); 153.08 (C-4′).

(1*R**,2*R**,3*S**,4*S**)-3-(6-Chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**19a**) and (1*R**,2*R**,3*S**,4*S**)-3-(6-Chloro-9*H*-purin-9-yl)-6-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**19b**)

Trifluoroacetic acid (1 ml) was added to a suspension of pyrimidine derivative **17a** or **17b** (424 mg, 1.5 mmol) in triethyl orthoformate (10 ml), the mixture was stirred at room temperature for 4 h and then evaporated. A solution of the residue in the mixture of tetrahydrofuran (10 ml) and aqueous 0.5 M HCl (10 ml) was stored at room temperature for 4 h. The solution was neutralized with solid sodium hydrogencarbonate. The organic phase was separated, the aqueous layer was extracted with tetrahydrofuran (4 × 15 ml), combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (60 g) with ethyl acetate–acetone–toluene (20:3:2) and crystallized from ether.

(1R,2R*,3S*,4S*)-3-(6-Chloro-9H-purin-9-yl)-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol* (**19a**): Yield 224 mg (51%). M.p. 179–181 °C (decomp.). For $C_{13}H_{13}ClN_4O_2$ (292.7) calculated: 53.34% C, 4.48% H, 12.11% Cl, 19.14% N; found: 53.01% C, 4.49% H, 12.26% Cl, 18.89% N. FAB MS, *m/z* (%): 295/293 (30/78) [M + H], 157/155 (37/100) [6-chloropurine + H]. ^{1}H NMR: 1.76 dp, 1 H, J_{gem} = 9.4, *J*(7a,1) = *J*(7a,2) = *J*(7a,3) = *J*(7a,4) = 1.7 (H-7a); 2.32 dm, 1 H, J_{gem} = 9.3 (H-7b); 2.75 m, 1 H (H-1); 3.11 m, 1 H (H-4); 4.00 m, 1 H (H-2); 4.05 ddd, 1 H, *J*(CH^aH,OH) = 5.1, *J*(CH^aH,6) = 1.6 and 4.11 ddd, 1 H, *J*(CH^bH,OH) = 5.6, *J*(CH^bH,6) = 1.9, J_{gem} = 14.9 (CH_2O); 4.57 dd, 1 H, *J*(3,2) = 6.2, *J*(3,7a) = 1.4 (H-3); 4.89 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 5.10 d, 1 H, *J*(OH,2) = 4.1 (2-OH); 5.89 m, 1 H (H-6); 8.65 s, 1 H (H-8′); 8.75 s, 1 H (H-2′). ^{13}C NMR: 44.14 (C-7); 46.34 (C-4); 49.24 (C-1); 57.02 (C-3); 58.99 (CH_2O); 69.98 (C-2); 128.29 (C-6); 130.66 (C-5′); 146.78 (C-8′); 148.78 (C-6′); 151.47 (C-2′); 153.21 (C-4′); 153.69 (C-5).

(1R,2R*,3S*,4S*)-3-(6-Chloro-9H-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol* (**19b**): Yield 250 mg (57%). M.p. 156.5–159 °C (decomp.). For $C_{13}H_{13}ClN_4O_2$ (292.7) calculated: 53.34% C, 4.48% H, 12.11% Cl, 19.14% N; found: 53.19% C, 4.42% H, 12.24% Cl, 18.98% N. FAB MS, *m/z* (%): 295/293 (33/100) [M + H], 157/155 (74/23) [6-chloropurine + H]. ^{1}H NMR: 1.76 dp, 1 H, J_{gem} = 9.4, *J*(7a,2) = *J*(7a,3) = *J*(7a,1) = *J*(7a,4) = 1.6 (H-7a); 2.33 dm, 1 H, J_{gem} = 9.3 (H-7b); 2.70 bs, 1 H (H-1); 3.14 m, 1 H (H-4); 4.03 ddd, 1 H, J_{gem} = 14.8, *J*(CH^a,OH) = 5.5, *J*(CH^a,5) = 1.7 (CH^aH-O); 4.04 m, 1 H (H-2); 4.10 ddd, 1 H, J_{gem} = 14.8, *J*(CH^b,OH) = 5.5, *J*(CH^b,5) = 1.9 (CH^bH-O); 4.60 dd, 1 H, *J*(3,2) = 6.2, *J*(3,7a) = 1.6 (H-3); 4.82 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 5.08 d, 1 H, *J*(OH,2) = 4.5 (2-OH); 6.03 m, 1 H (H-5); 8.64 s, 1 H (H-8′); 8.74 s, 1 H (H-2′). ^{13}C NMR: 44.16 (C-7); 45.89 (C-4); 49.87 (C-1); 57.90 (C-3); 59.29 (CH_2O); 68.46 (C-2); 130.03 (C-5); 130.52 (C-5′); 146.77 (C-8′); 148.68 (C-6′); 151.35 (C-2′); 151.82 (C-6); 153.10 (C-4′).

(1*S**,2*S**,3*R**,4*R**)-3-(6-Amino-9*H*-purin-9-yl)-5-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**20a**) and
(1*R**,2*R**,3*S**,4*S**)-3-(6-Amino-9*H*-purin-9-yl)-6-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**20b**)

A solution of chloropurine derivative **19a** or **19b** (88 mg, 0.3 mmol) in liquid ammonia (5 ml) was heated in autoclave at 70 °C for 12 h. Ammonia was evaporated and the residue was crystallized from water.

(1S,2S*,3R*,4R*)-3-(6-Amino-9H-purin-9-yl)-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol* (**20a**): Yield 42 mg (51%). M.p. 289 °C (decomp.). For $C_{13}H_{15}N_5O_2$ (273.3) calculated: 57.13% C, 5.53% H, 25.63% N; found: 56.86% C, 5.58% H, 25.36% N. FAB MS, *m/z* (%): 274 (35) [M + H], 136 (24) [adenine + H]. ^{1}H NMR: 1.72 dm, 1 H, J_{gem} = 9.2 (H-7a); 2.30 dm, 1 H, J_{gem} = 9.3 (H-7b); 2.72 m, 1 H (H-1); 2.93 m, 1 H (H-4); 3.93 m, 1 H (H-2); 4.02 ddd, 1 H, J(CH^{a}H,OH) = 5.1, J(CH^{a}H,6) = 1.6 and 4.08 ddd, 1 H, J(CH^{b}H,OH) = 5.6, J(CH^{b}H,6) = 1.8, J_{gem} = 14.9 (CH_2O); 4.45 dm, 1 H, J(3,2) = 6.2 (H-3); 4.85 t, 1 H, J(OH,CH_2) = 5.5 (CH_2O**H**); 5.03 d, 1 H, J(OH,2) = 4.7 (2-OH); 5.85 m, 1 H (H-6); 7.11 bs, 2 H (NH_2); 8.07 s, 1 H (H-8′); 8.10 s, 1 H (H-2′).

(1R,2R*,3S*,4S*)-3-(6-Amino-9H-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol* (**20b**): Yield 47 mg (56%). M.p. 264 °C (decomp.). For $C_{13}H_{15}N_5O_2 \cdot 0.5H_2O$ (282.3) calculated: 55.31% C, 5.71% H, 24.81% N; found: 55.06% C, 5.73% H, 24.64% N. FAB MS, *m/z* (%): 274 (74) [M + H], 136 (40) [adenine + H]. ^{1}H NMR: 1.72 dm, 1 H, J_{gem} = 9.2 (H-7a); 2.29 dm, 1 H, J_{gem} = 9.1 (H-7b); 2.67 m, 1 H (H-1); 2.96 m, 1 H (H-4); 3.98 m, 1 H (H-2); 4.01 ddd, 1 H, J(CH^{a}H,OH) = 5.3, J(CH^{a}H,5) = 1.4 and 4.08 ddd, 1 H, J(CH^{b}H,OH) = 5.5, J(CH^{b}H,5) = 1.7, J_{gem} = 14.8 (CH_2O); 4.49 dd, 1 H, J(3,2) = 6.2, J(3,7a) = 1.2 (H-3); 4.84 t, 1 H, J(OH,CH_2) = 5.5 (CH_2O**H**); 5.06 d, 1 H, J(OH,2) = 4.5 (2-OH); 6.01 m, 1 H (H-5); 7.13 bs, 2 H (NH_2); 8.07 s, 1 H (H-8′); 8.10 s, 1 H (H-2′). ^{13}C NMR: 44.32 (C-7); 46.56 (C-4); 50.00 (C-1); 56.83 (C-3); 59.39 (CH_2O); 68.45 (C-2); 118.27 (C-5′); 130.32 (C-5); 140.15 (C-8′); 150.63 (C-4′); 151.51 (C-6); 152.30 (C-2′); 156.01 (C-6′).

(1*R**,2*R**,3*S**,4*S**)-3-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-5-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**21a**) and
(1*R**,2*R**,3*S**,4*S**)-3-[6-(Cyclopropylamino)-9*H*-purin-9-yl]-6-(hydroxymethyl)-bicyclo[2.2.1]hept-5-en-2-ol (**21b**)

A solution of chloropurine derivative **19a** or **19b** (59 mg, 0.2 mmol) in cyclopropylamine (1 ml) was left standing at room temperature for 8 h. The mixture was evaporated and the residue was chromatographed on a silica gel column (6 g) in ethyl acetate–ethanol–acetone–water (100:15:6:4).

(1R,2R*,3S*,4S*)-3-[(6-Cyclopropylamino)-9H-purin-9-yl]-5-(hydroxymethyl)bicyclo[2.2.1]-hept-5-en-2-ol* (**21a**): Yield 48 mg (76.5%) of a solid foam. For $C_{16}H_{19}N_5O_2$ (313.4) calculated: 61.33% C, 6.11% H, 22.35% N; found: 61.00% C, 6.17% H, 22.04% N. FAB MS, *m/z* (%): 314 (100) [M + H], 176 (56) [6-(cyclopropylamino)purine + H]. ^{1}H NMR: 0.59 m, 2 H, 0.71 m, 2 H and 3.04 bs, 1 H (cyclopropyl); 1.72 dp, 1 H, J_{gem} = 9.2, J(7a,1) = J(7a,2) = J(7a,3) = J(7a,4) = 1.6 (H-7a); 2.29 dm, 1 H, J_{gem} = 9.2 (H-7b); 2.72 m, 1 H (H-1); 2.93 m, 1 H (H-4); 3.94 m, 1 H (H-2); 4.02 ddd, 1 H, J(CH^{a}H,OH) = 5.0, J(CH^{a}H,6) = 1.4 and 4.09 ddd, 1 H, J(CH^{b}H,OH) = 5.6, J(CH^{b}H,6) = 1.7, J_{gem} = 15.0 (CH_2O); 4.46 dd, 1 H, J(3,2) = 6.2, J(3,7a) = 1.6 (H-3); 4.87 t, 1 H, J(OH,CH_2) = 5.5 (CH_2O**H**); 5.03 d, 1 H, J(OH,2) = 4.6 (2-OH); 5.86 m, 1 H (H-6); 7.78 bs, 1 H (NH); 8.07 s, 1 H (H-8′); 8.20 bs, 1 H (H-2′). ^{13}C NMR: 6.73 (CH_2 cyclopropane);

24.15 (CH cyclopropane); 44.20 (C-7); 46.80 (C-4); 49.32 (C-1); 55.77 (C-3); 58.99 (CH_2O); 69.92 (C-2); 118.76 (C-5′); 127.90 (C-6); 139.85 (C-8′); 150.11 (C-4′); 152.20 (C-2′); 153.91 (C-5); 155.61 (C-6′).

(1R,2R*,3S*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]-6-(hydroxymethyl)bicyclo[2.2.1]-hept-5-en-2-ol* (**21b**): Yield 50 mg (80%) after crystallization from water. M.p. 243–244 °C (decomp.). For $C_{16}H_{19}N_5O_2$ (313.4) calculated: 61.33% C, 6.11% H, 22.35% N; found: 61.05% C, 6.13% H, 22.09% N. FAB MS, *m/z* (%): 314 (100) [M + H], 176 (29) [6-(cyclopropylamino)purine + H]. ^{1}H NMR: 0.59 m, 2 H, 0.71 m, 2 H and 3.01 bs, 1 H (cyclopropyl); 1.72 dp, 1 H, J_{gem} = 9.3, *J*(7a,2) = *J*(7a,3) = *J*(7a,1) = *J*(7a,4) = 1.7 (H-7a); 2.29 dm, 1 H, J_{gem} = 9.3 (H-7b); 2.67 m, 1 H (H-1); 2.96 m, 1 H (H-4); 3.98 m, 1 H (H-2); 4.01 ddd, 1 H, *J*(CH^aH,OH) = 5.4, *J*(CH^aH,5) = 1.7 and 4.08 ddd, 1 H, *J*(CH^bH,OH) = 5.5, *J*(CH^bH,5) = 1.9, J_{gem} = 14.8 (CH_2O); 4.50 dd, 1 H, *J*(3,2) = 6.3, *J*(3,7a) = 1.4 (H-3); 4.85 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 5.05 d, 1 H, *J*(OH,2) = 4.5 (2-OH); 6.01 m, 1 H (H-5); 7.79 bs, 1 H (NH); 8.07 s, 1 H (H-8′); 8.20 bs, 1 H (H-2′). ^{13}C NMR: 6.73 (CH_2 cyclopropane); 24.06 (CH cyclopropane); 44.34 (C-7); 46.54 (C-4); 50.02 (C-1); 56.82 (C-3); 59.40 (CH_2O); 68.47 (C-2); 118.66 (C-5′); 130.32 (C-5); 139.98 (C-8′); 150.07 (C-4′); 151.54 (C-6); 152.21 (C-2′); 155.63 (C-6′).

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