SYNTHESIS OF NOVEL CONFORMATIONALLY LOCKED CARBOCYCLIC NUCLEOSIDES DERIVED FROM 5,5- AND 6,6-BIS(HYDROXYMETHYL)BICYCLO[2.2.1]HEPTAN-2-OL

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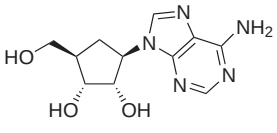
(1*R**,2*R**,3*R**,4*S**)-3-Amino-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol (**13**) was prepared from (bicyclo[2.2.1]hept-5-ene-2,2-diyl)dimethyl dibenzoate (**7**) via *cis*-diol **8**, cyclic sulfate **10**, and azide **12**. (1*R**,2*R**,3*S**,4*S**)-3-Amino-6,6-bis(hydroxymethyl)bicyclo[2.2.1]-heptan-2-ol (**18**) and (1*R**,2*S**,3*S**,4*S**)-3-amino-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol (**19**) were obtained by addition of chromyl azide to double bond of **7**, chromatographic separation, debenzoylation and hydrogenation of resulting azides **14** and **16**. The amines **13**, **18**, and **19** were used to build (1*R**,2*R**,3*R**,4*S**)- (**21a**), (1*R**,2*R**,3*S**,4*S**)-3-(6-chloro-9*H*-purin-9-yl)-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol (**21b**), and (1*R**,2*S**,3*S**,4*S**)-3-(6-chloro-9*H*-purin-9-yl)-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol (**21c**), respectively. Ammonolysis of these compounds led to 6-amino-9*H*-purine derivatives **22a**–**22c**. 6-(Dimethylamino)-9*H*-purine analogues **23a**–**23c** and 6-(cyclopropylamino)-9*H*-purine analogues **24a**–**24c** were prepared by aminolysis of **21a**–**21c**. Reaction of amines **13**, **18**, and **19** with ethyl *N*-((2*E*)-3-ethoxymethacryloyl)carbamate afforded thymine derivatives **28a**–**28c**.

Keywords: Azides; Amines; Cyclic sulfates; Nucleosides; Carbocyclic nucleosides; Purines; Pyrimidines; Nucleobases; Alkenes; Azidohydroxylation; Antivirals.

Nucleoside analogues play an important role in pharmacology, mainly as antiviral and antitumoral drugs. Carbocyclic nucleoside analogues have also attracted attention since the natural compounds aristeromycin[1] (**1**) and neplanocin A[2] (**2**) were found to exhibit significant biological effects. Carbocyclic nucleosides in comparison with the furanose-derived analogues have increased resistance to enzymatic degradation as well as decreased toxicity[3]. Prominent synthetic carbocyclic nucleosides are the anti-HIV compounds carbovir[4] (**3**) and abacavir[5] (Ziagen™) (**4**). The class of carbocyclic nucleoside analogues still possesses a large and unexploited potential for development of new pharmaceuticals.



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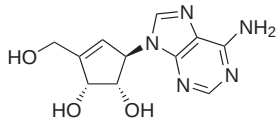

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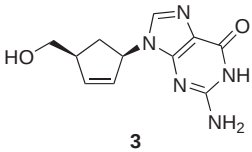

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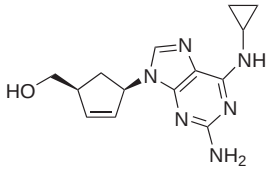

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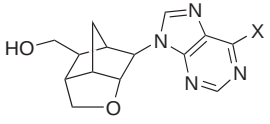
Synthesis of novel conformationally locked carbocyclic nucleosides with the 2-oxabicyclo[2.2.1]heptane ring system (as precursors of locked carbocyclic nucleic acids) was recently described[6]. Bisphosphate of the 2-iodo-(6-methylamino)purine analogue containing this ring system displayed potent binding affinity at the human $P2Y_1$ receptor[7].

The bicyclo[2.2.1]heptane (norbornane) ring, like oxabicyclo[2.2.1]heptane, is a conformationally locked carbapentofuranose and/or carbahexopyranose ring systems. Recently, we reported the synthesis of novel racemic conformationally locked carbocyclic purine nucleoside analogues derived from 5-oxatricyclo[4.2.1.$0^{3,7}$]nonane-3-methanol[8]. Only chloropurine (**5a**) and (cyclopropyl)purine (**5b**) derivatives exhibit certain activity in tests for anti-HIV-1 and -HIV-2 activity in human T-lymphocyte (CEM) cells. However, their activity corresponds with their cytotoxicity.



5a, X = Cl
5b, X = HN

This study concerns syntheses of novel carbocyclic nucleosides derived from 5,5- and 6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol. The target compounds, which are shown in Fig. 1, were synthesized from commercially available bicyclo[2.2.1]hept-5-ene-2,2-dimethanol (**6**).

Alcohol **6** was benzoylated and then *cis*-hydroxylated with OsO_4 in the yield 87% of *cis*-diol **8**. 4-Methylmorpholine 4-oxide was used as donor of oxygen[9]. The diol **8** was treated with thionyl chloride in ether at room temperature to give a mixture of sulfites **9** (95%). The mixture of stereoisomers,

which differ in orientation of the S=O bond, was not separated; the ratio of isomers (1:1) was determined by ^{1}H NMR spectroscopy. The mixture of sulfites **9** was converted to sulfate **10** following the procedure of Gao and Sharpless[10]. Treatment of sulfate **10** with lithium azide in dimethylformamide at 150 °C for 8 h afforded, after hydrolysis with a mixture of tetrahydrofuran, sulfuric acid, and water, azido derivative **11** (77%), which was deprotected with methanolic sodium methoxide to give free azide **12** (78%). Hydrogenation of azide **12** using palladium hydroxide on carbon as catalyst gave amine **13** (85%) (Scheme 1).

Steroidal alkenes have been reported[11] to give vicinal *trans*-hydroxy azides upon treatment with the in situ generated chromyl azide from sodium azide and chromium trioxide in acetic acid. An analogous reaction of an alkene with azidotrimethylsilane and chromium trioxide in dichloromethane led to α-azidoketones[12]. The reaction of alkene **7** with sodium azide and chromium trioxide in acetic acid was intended as an alternative

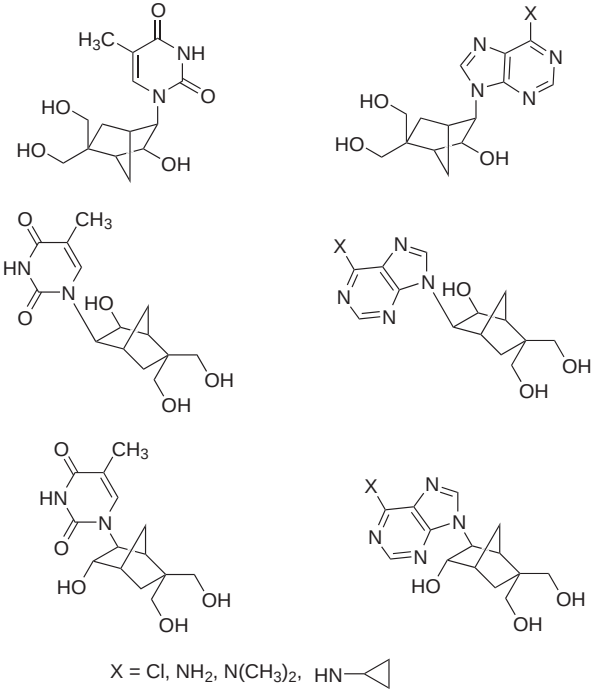
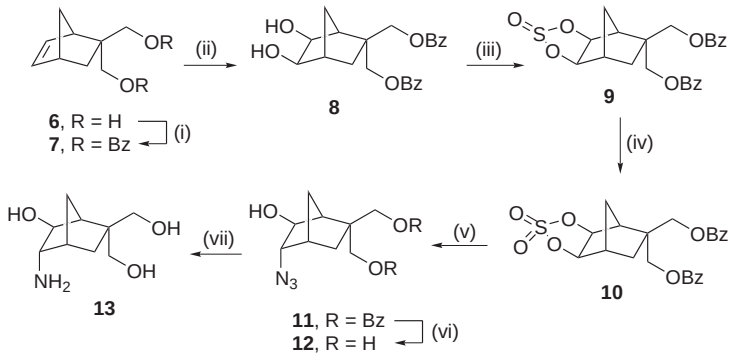


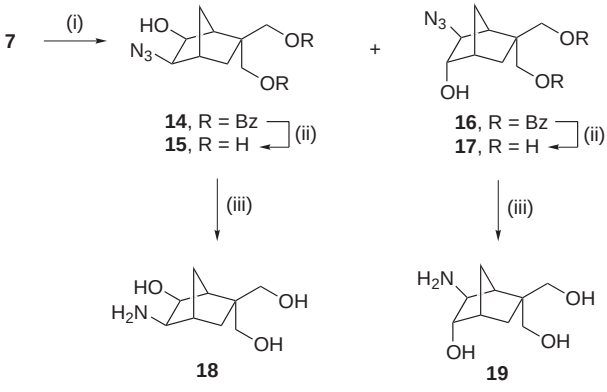
FIG. 1
Novel carbocyclic nucleosides



(i) BzCl/pyridine, 91%; (ii) OsO_3/4-methylmorpholine 4-oxide/acetone/H_2O, 87%; (iii) $SOCl_2$/ether, 95%; (iv) $NaIO_4$/$RuCl_3$/MeCN/CCl_4/H_2O, 90%; (v) LiN_3/DMF, 150 °C, 77%; (vi) 0.1 M MeONa/MeOH, 78%; (vii) H_2, $Pd(OH)_2$/C, 85%

SCHEME 1

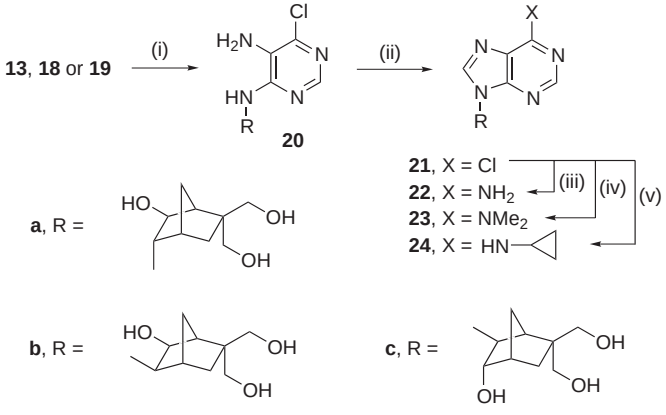
way for the preparation of azide **11**. But, surprisingly, this reaction afforded azides **14** (37%) and **16** (15%) as main products besides of a non-separable mixture of many minor by-products as a result of the ring-inverting Wagner–Meerwein rearrangement (for some examples of the rearrangement, cf. lit.[13]). Deprotection of azides **14** and **16** with methanolic sodium methoxide followed by hydrogenation on palladium hydroxide gave amines **18** (83%) and **19** (76%), respectively (Scheme 2).



(i) CrO_3/NaN_3/AcOH, 37% of **14**, 15% of **16**; (ii) 0.1 M MeONa/MeOH, 83% of **15**, 79% of **17**; (iii) H_2/$Pd(OH)_2$/C, 83% of **18**, 76% of **19**

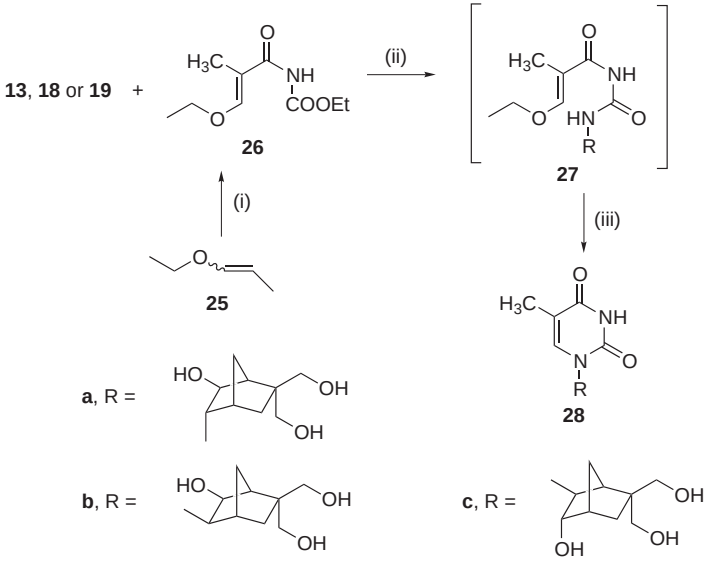
SCHEME 2

Conversion of amine **13**, **18** or **19** to the 6-chloropurine derivatives was performed by described procedures[8,14]. Coupling of the amines with 4,6-dichloropyrimidin-5-amine in ethanol in the presence of triethylamine gave pyrimidinylamino derivative **20a** (74%), **20b** (81%), and **20c** (84%). Ring closure of **20a**–**20c** with triethyl orthoformate in the presence of concentrated hydrochloric acid gave 6-chloropurine derivatives **21a** (79%), **21b** (89%), and **21c** (89%), respectively. The chloropurines were ammonolysed with liquid ammonia at 75 °C to give adenine derivatives **22a** (79%), **22b** (86%), and **22c** (84%) which, in turn, were treated with dimethylammonium *N*,*N*-dimethylcarbamate to afford 6-(dimethylamino)purine **23a** (95%), **23b** (85%), and **23c** (84%) or aminolysed with cyclopropylamine to yield 6-(cyclopropylamino)purine **24a** (89%), **24b** (88%), and **24c** (84%) (Scheme 3). The reactions of amine **13**, **18**, and **19** with acylcarbamate **26** in 1,4-dioxane at 100 °C (Scheme 4) yielded compounds **27a**–**27c** which were, without isolation, treated with Dowex 50 (H^+) to give thymine derivatives **28a** (48%), **28b** (34%), and **28c** (57%). Acylcarbamate **26** was prepared from 1-ethoxyprop-1-ene by the treatment with chlorocarbonyl isocyanate followed by ethanol using the procedure described for ethyl *N*-((2*E*)-3-ethoxy-2-ethylprop-2-enoyl)carbamate[15].



(i) 4,6-dichloropyrimidin-5-amine/TEA/ETOH, 100 °C, 74% of **20a**, 81% of **20b**, and 84% of **20c**; (ii) 1. $CH(OEt)_3$/HCl, 2. THF/H_2O/HCl, 89% of **21a**, 79% of **21b**, and 89% of **21c**; (iii) NH_3 (l), 75 °C, 79% of **22a**, 86% of **22b**, and 84% of **22c**; (iv) $Me_2NCOO^-Me_2NH^+$, 95% of **23a**, 85% of **23b**, and 84% of **23c**; (v) cyclopropylamine, 89% of **24a**, 88% of **24c**, and 86% of **24c**

SCHEME 3



(i) 1. ClCONCO/Et_3N, 2. EtOH, 68%; (ii) 1,4-dioxane;
(iii) Dowex 50 (H^+), 48% of **28a**, 34% of **28b**, and 50% of **28c**

SCHEME 4

The structure of the prepared compounds was determined by ^1H and ^{13}C NMR spectroscopy. Coupling constants *J*(H,H) were obtained by using decoupling experiments. Assignment of the signals to protons and carbon atoms in NMR spectra of the key intermediates **12**, **15**, and **17** was performed by HSQC. The structure of these compounds was determined on the basis of the observed long-range interactions C–H (HMBC). The found strong long-range C–H interactions in HMBC experiments are given in Fig. 2. The literature[16] shows the following values of coupling constants *J*(2,3) and *J*(1,2) of 2,3-substituted norbornanes: *J*(2 exo,3 exo) = 9–10 Hz, *J*(2 endo,3 endo) = 6–7 Hz, *J*(2 exo,3 endo) = 2.5–5 Hz, *J*(1,2 exo) = 3–4 Hz, and *J*(1,2 endo) = 0–2 Hz. The following values of corresponding coupling constants were found for the prepared compounds: *J*(2 endo,3 exo) = 1.5–2.2 Hz and *J*(1, 2endo) ≈ 1.0 Hz for compounds **12**, **13**, **20a**, **21a**, **22a**, **23a**, **24a**, and **28a**, *J*(2 endo,3 endo) = 5.9–6.1 Hz and *J*(1,2 endo) = 1.0–1.5 Hz for compounds **15**, **18**, **20b**, **21b**, **22b**, **23b**, **24b**, and **28b**, and *J*(2 exo,3 endo) = 1.7–2.8 Hz and *J*(1,2 exo) = 4.2–4.6 Hz for compounds **17**, **19**, **20c**, **21c**, **22c**, **23c**, **24c**, and **28c**.

In conclusion, novel racemic conformationally locked carbocyclic nucleoside analogues of adenine, 6-(dimethylamino)purine, 6-(cyclopropylamino)purine, and thymine derived from 5,5- and 6,6-bis(hydroxymethyl)-bicyclo[2.2.1]heptan-2-ol were prepared from commercially available bicyclo-[2.2.1]hept-5-ene-2,2-dimethanol. The target compounds **21a**–**21c**, **22a**–**22c**, **23a**–**23c**, **24a**–**24c**, and **28a**–**28c** were tested for inhibition of cell growth of the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 240), human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2), human promyelocytic leukemia HL60 cells (ATCC CCL 240), and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). None of the compounds exhibited significant activity[17].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Mass spectra were recorded on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian UNITY 500 instrument (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) in hexadeuteriodimethyl sulfoxide (referenced to the solvent signal). Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol UV 254 foils (Kavalier, Votice). Solvents were evaporated at 2 kPa and bath temperature 36–60 °C; the compounds were dried at 13 Pa and 50 °C.

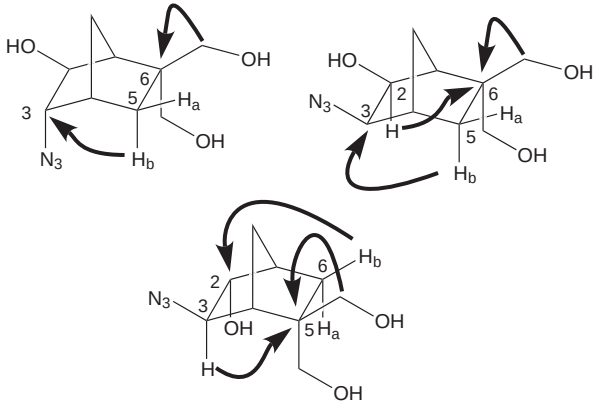


FIG. 2
Strong long-range C–H interactions in HMBC experiments

(Bicyclo[2.2.1]hept-5-ene-2,2-diyl)dimethyl Dibenzoate (**7**)

Benzoyl chloride (5.6 ml, 48 mmol) was added to a stirred and cooled solution of norbornene derivative **6** (3.08 g, 20 mmol) in pyridine (40 ml) and the mixture was left at room temperature overnight. Water (3 ml) was then added and, after 15 min, the solvent was evaporated. The residue was partitioned between ethyl acetate (200 ml) and water (100 ml). The organic phase was washed with water (100 ml), 5% hydrochloric acid (50 ml), 10% aqueous $KHCO_3$ (3 × 100 ml), dried over anhydrous sodium sulfate, and the solvent was evaporated. Crystallization of the residue from ethanol–petroleum ether afforded 6.60 g (91%) of dibenzoate **7**, m.p. 63–65 °C. For $C_{23}H_{22}O_4$ (362.4) calculated: 76.22% C, 6.12% H; found: 76.16% C, 6.11% H. FAB MS, *m/z*: 363 [M + H]. ^{1}H NMR: 1.01 dd, 1 H, *J*(6b,7b) = 2.6, J_{gem} = 12.3 (H-6b); 1.42 dm, 1 H, J_{gem} = 8.8 (H-7b); 1.69 dd, 1 H, *J*(6a,1) = 3.7 (H-6a); 1.72 dm, 1 H (H-7a); 2.90 m, 1 H (H-1); 2.95 m, 1 H (H-4); 4.02 d, 1 H and 4.22 d, 1 H, J_{gem} = 11.0 (CH_2O); 4.51 s, 2 H (CH_2O); 6.15 dd, 1 H, *J*(3,2) = 5.7, *J*(3.4) = 3.0 (H-3); 6.29 dd, 1 H, *J*(2,1) = 3.0 (H-2); 7.48 m, 4 H, 7.63 m, 2 H, and 7.95 m, 4 H (H-arom.). ^{13}C NMR: 32.94 (C-6); 42.20 (C-1); 46.01 (C-4); 46.30 (C-5); 47.00 (C-7); 134.42 (C-2); 138.05 (C-3); 128.89, 4 C, 129.32, 4 C, 113.47, 129.81, 129.82, 133.49, 165.66, and 165.79 (arom.).

((1*R**,4*S**,5*S**,6*R**)-5,6-Dihydroxybicyclo[2.2.1]heptane-2,2-diyl)dimethyl Dibenzoate (**8**)

A mixture of the bicyclo[2.2.1]heptene derivative **7** (10.87 g, 30 mmol), acetone (600 ml), water (60 ml), an aqueous solution of 4-methylmorpholine 4-oxide (50%, 42 ml), and osmium tetroxide (30 mg) was stirred at room temperature overnight. The resulting solution was evaporated and the residue was partitioned between ethyl acetate (400 ml) and water (300 ml). The aqueous layer was extracted with ethyl acetate (300 ml) and the collected acetate layers were washed with water (200 ml), dried over anhydrous sodium sulfate, and evaporated. Crystallization of the residue from ethanol afforded 10.33 g (87%) of **8**, m.p. 124–125.5 °C. For $C_{23}H_{24}O_6$ (396.4) calculated: 69.68% C, 6.10% H; found: 69.46% C, 5.98% H. FAB MS, *m/z*: 397 [M + H]. ^{1}H NMR: 1.06 dd, 1 H, *J*(3b,7a) = 2.1, J_{gem} = 13.2 (H-3b); 1.45 dd, 1 H, *J*(3a,4) = 4.8 (H-3a); 1.49 dm, 1 H, J_{gem} = 10.6 (H-7b); 1.79 dm, 1 H (H-7a); 2.02 brdq, 1 H, *J*(4,1) ≈ *J*(4,7a) ≈ *J*(4,7b) = 1.5 (H-4); 2.19 m, 1 H (H-1); 3.67 brdt, 1 H, *J*(5,7b) = 1.2 (H-5); 3.96 brddd, 1 H, *J*(6,7b) = 1.2, *J*(6,5) = 5.7, *J*(6,OH) = 4.6 (H-6); 4.16 d, 1 H and 4.41 d, 1 H, J_{gem} = 11.5 (CH_2O); 4.22 d, 1 H and 4.31 d, 1 H, J_{gem} = 11.1 (CH_2O); 4.64 d, 1 H, *J*(OH,5) = 5.4 (5-OH); 4.78 d, 1 H (6-OH); 7.46 t, 2 H, 7.49 t, 2 H, 7.62 t, 1 H, 7.64 t, 1 H, 7.92 d, 2 H, and 7.95 d, 2 H (H-arom.). ^{13}C NMR: 30.75 (C-7); 33.10 (C-3); 42.87 (C-2); 43.84 (C-4); 47.57 (C-1); 65.40 (CH_2O); 67.56 (CH_2O); 68.69 (C-5); 73.10 (C-6); 128.88, 2 C, 128.90, 2 C, 129.28, 2 C, 129.35, 2 C, 129.72, 129.74, 133.50, and 133.54 (C-arom.); 165.68 (C=O); 165.80 (C=O).

((3a*R**,4*R**,7*S**,7a*S**)-2-Oxohexahydro-2λ^4-4,7-methano-1,3,2-benzodioxathiole-5,5-diyl)dimethyl Dibenzoate (**9**)

Thionyl chloride (13 ml) was added to a stirred suspension of diol **8** (7.93 g, 20 mmol) in ether (130 ml) and the mixture was stirred at room temperature for 3 h. The resulting solution was evaporated and a solution of the residue in ethyl acetate (250 ml) was washed with water (100 ml) and 10% aqueous sodium hydrogencarbonate (3 × 100 ml), dried over anhydrous sodium sulfate and the solvent was evaporated. The obtained product (8.40 g, 95%) was used in the next step without purification. An analytical sample was purified by chro-

matography on a silica gel column with toluene–ethyl acetate (4:1). For $C_{23}H_{22}O_7S$ (442.5) calculated: 62.43% C, 5.01% H, 7.25% S; found: 62.59% C, 5.13% H, 7.23% S. FAB MS, *m/z*: 443 [M + H]. ^{1}H NMR: isomer A: 1.24 dd, 1 H, *J*(6b,CH_2) = 2.5, J_{gem} = 13.7 (H-6b); 1.45 dm, 1 H, J_{gem} = 11.6 (CH^aH); 1.63 dd, 1 H, *J*(6a,7) = 5.0 (H-6a); 1.74 dpent, 1 H, *J*(CH^bH,7) ≈ *J*(CH^bH,7a) ≈ *J*(CH^bH,3a) ≈ *J*(CH^bH,4) = 1.4 (CH^bH); 2.47 brdq, 1 H, *J*(7,7a) ≈ *J*(7,CH^bH) = 1.5 (H-7); 2.71 brs, 1 H (H-4); 5.18 brdd, 1 H, *J*(7a,3a) = 5.5 (H-7a); 5.29 brdd, 1 H, *J*(3a,4) = 1.0 (H-3a); isomer B: 1.16 dd, 1 H, *J*(6b,CH^aH) = 2.6, J_{gem} = 13.7 (H-6b); 1.65 dd, 1 H, *J*(6a,7) = 5.0 (H-6a); 1.78 dpent, 1 H, *J*(CH^bH,7) ≈ *J*(CH^bH,7a) ≈ *J*(CH^bH,3a) ≈ *J*(CH^bH,4) = 1.4, J_{gem} = 13.7 (CH^bH); 2.16 dm, 1 H (CH^aH); 2.52 brdq, 1 H, *J*(7,7a) ≈ *J*(7,CH^aH) = 1.5 (H-7); 2.74 brs, 1 H (H-4); 4.91 brdd, 1 H, *J*(7a,3a) = 6.1 (H-7a); 5.11 brdd, 1 H, *J*(3a,4) = 1.0 (H-3a); isomer A + isomer B: 4.11 d, 2 H and 4.51 d, 2 H, J_{gem} = 11.8 (CH_2O); 4.30 d, 2 H and 4.43 d, 2 H, J_{gem} = 12.0 (CH_2O); 4.31 d, 2 H and 4.40 d, 2 H, J_{gem} = 11.4 (CH_2O); 4.34 d, 2 H and 4.38 d, 2 H, J_{gem} = 11.4 (CH_2O); 7.46 m, 8 H, 7.92 m, 4 H, and 7.95 m, 8 H (H-arom.). The ratio A:B was found 1:1.

((3a*R**,4*R**,7*S**,7a*S**)-2,2-Dioxohexahydro-2λ^4-4,7-methano-1,3,2-benzodioxathiole-5,5-diyl)dimethyl Dibenzoate (**10**)

To a stirred ice-cool solution of sulfite **9** (7.96 g, 18 mmol) in acetonitrile (45 ml) and tetrachloromethane (23 ml), water (83 ml), sodium periodate (7.90 g) and ruthenium(III) chloride hydrate (25 mg) were added. The mixture was stirred at 0 °C for 20 min and at room temperature for 10 min. Additional amount of sodium periodate (3.94 g) was then added, the mixture was stirred at room temperature for 30 min and then diluted with ethyl acetate (500 ml). The organic layer was separated, washed with water (3 × 200 ml), dried over anhydrous sodium sulfate, and filtered through a silica gel pad (150 g). Silica gel was washed with ethyl acetate and the collected filtrates were evaporated. Crystallization of the residue from ethanol afforded 7.43 g (90%) of sulfate **10**, m.p. 152–153 °C. For $C_{23}H_{22}O_8S$ (458.5) calculated: 60.25% C, 4.84% H, 6.99% S; found: 60.07% C, 4.75% H, 6.86% S. FAB MS, *m/z*: 459 [M + H]. ^{1}H NMR: 1.27 dd, 1 H, *J*(6b,CH_2) = 2.4, J_{gem} = 13.8 (H-6b); 1.71 dd, 1 H, *J*(6a,7) = 5.2 (H-6a); 1.87 dm, 1 H (CH^aH); 2.01 dpent, 1 H, *J*(CH^bH,7) ≈ *J*(CH^bH,7a) ≈ *J*(CH^bH,3a) ≈ *J*(CH^bH,4) = 1.5, J_{gem} = 11.6 (CH^bH); 2.64 brdq, 1 H, *J*(7,7a) = 1.2, *J*(7,CH^aH) = 1.5 (H-7); 2.87 m, 1 H (H-4); 4.25 d, 1 H and 4.48 d, 1 H, J_{gem} = 12.0 (CH_2O); 4.31 d, 1 H and 4.37 d, 1 H, J_{gem} = 11.4 (CH_2O); 5.35 brdd, 1 H, *J*(7a,3a) = 5.4, *J*(7a,CH^bH) = 1.5 (H-7a); 5.51 brdd, 1 H, J(3a,4) = 1.0 (H-3a). ^{13}C NMR: 30.36 (CH_2); 30.44 (C-6); 40.86 (C-7); 42.77 (C-5); 44.54 (C-4); 64.98 (CH_2O); 67.05 (CH_2O); 83.80 (C-7a); 85.78 (C-3a); 128.84, 2 C, 128.88, 2 C, 129.40, 4 C, 129.50, 129.61, and 133.57, 2 C (C-arom.); 165.48 (C=O); 165.69 (C=O).

((1*R**,4*S**,5*R**,6*R**)-5-Azido-6-hydroxybicyclo[2.2.1]heptane-2,2-diyl)dimethyl Dibenzoate (**11**)

A solution of sulfate **10** (6.88 g, 15 mmol) and lithium azide (2.94 g, 60 mmol) in dimethylformamide (100 ml) was heated at 150 °C for 8 h and evaporated to dryness. A mixture of the residue, tetrahydrofuran (60 ml), sulfuric acid (3 ml) and water (3 ml) was stirred at room temperature overnight and then neutralized with sodium hydrogencarbonate. The mixture was partitioned between ethyl acetate (350 ml) and water (150 ml), the organic layer was separated, washed with water (2 × 100 ml), dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column (250 g) in toluene–

ethyl acetate (4:1) gave 4.84 g (77%) of azide **11**. For $C_{23}H_{23}N_3O_5$ (421.5) calculated: 65.55% C, 5.50% H, 9.97% N; found: 65.75% C, 5.65% H, 9.79% N. FAB MS, *m/z*: 422 [M + H]. ^{1}H NMR: 1.39 ddd, 1 H, *J*(3a,4) = 3.7, *J*(3a,5) = 1.2, J_{gem} = 13.4 (H-3a); 1.42 brdd, 1 H, *J*(3b,7a) = 2.1 (H-3b); 1.75 brdq, 1 H, *J*(7b,1) ≈ *J*(7b,4) = 1.7, *J*(7b,6) = 2.0, J_{gem} = 11.0 (H-7b); 1.80 brdq, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.4 (H-7a); 2.24 m, 1 H (H-1); 2.48 ddq, 1 H, *J*(4,1) = 1.4, *J*(4,5) = 4.8 (H-4); 3.74 brt, 1 H, *J*(6,5) = 2.0 (H-6); 3.79 brdq, 1 H, *J*(5,1) = 1.0 (H-5); 4.22 d, 1 H and 4.47 d, 1 H, J_{gem} = 11.5 (CH_2O); 4.26 d, 1 H and 4.36 d, 1 H, J_{gem} = 11.2 (CH_2O); 5.30 brs, 1 H (6-OH); 7.46 t, 2 H, 7.48 t, 2 H, 7.62 t, 1 H, 7.64 t, 1 H, 7.92 d, 2 H, and 7.94 d, 2 H (H-arom.). ^{13}C NMR: 28.93 (C-3); 32.92 (C-7); 39.87 (C-4); 42.89 (C-2); 48.50 (C-1); 65.26 (CH_2O); 67.56 (CH_2O); 72.23 (C-5); 73.36 (C-6); 128.86, 4 C, 129.31, 2 C, 129.42, 2 C, 129.67, 129.69, 133.52, and 133.54 (C-arom.); 165.67 (C=O); 165.83 (C=O).

((1*R**,4*S**,5*S**,6*R**)-5-Azido-6-hydroxybicyclo[2.2.1]heptane-2,2-diyl)dimethyl Dibenzoate (**14**) and ((1*R**,4*S**,5*R**,6*R**)-6-Azido-5-hydroxybicyclo[2.2.1]-heptane-2,2-diyl)dimethyl Dibenzoate (**16**)

Chromium(VI) oxide (1.1 g, 11 mmol) was added to a stirred ice-cool mixture of acetic acid (85 ml), alkene **7** (3.96 g, 10 mmol) and sodium azide (14 g). The mixture was warmed to room temperature, stirred for 30 min, filtered and evaporated. A solution of the residue in a mixture of tetrahydrofuran (40 ml), sulfuric acid (2 ml) and water (2 ml) was set aside at room temperature for 1 h and then neutralized with solid sodium hydrogencarbonate. The insoluble portion was filtered off with a Celite pad, washed with tetrahydrofuran and the collected filtrates were evaporated. A solution of the residue in ethyl acetate was left at ≈4 °C overnight and the deposited precipitate was filtered off with a Celite pad, washed with ethyl acetate and the collected filtrates were evaporated. Chromatography of the residue on silica gel (300 g) in ethyl acetate–toluene afforded 1.55 g (37%) of azide **14** and 653 mg (15%) of azide **16**.

Compound **14**: For $C_{23}H_{23}N_3O_5$ (421.5) calculated: 65.55% C, 5.50% H, 9.97% N; found: 65.82% C, 5.54% H, 9.75% N. FAB MS, *m/z*: 422 [M + H]. ^{1}H NMR: 1.15 dd, 1 H, *J*(3b,7a) = 2.6, J_{gem} = 13.2 (H-3b); 1.52 dd, 1 H, *J*(3a,4) = 4.8 (H-3a); 1.61 dpent, 1 H, *J*(7b,1) ≈ *J*(7b,5) ≈ *J*(7b,6) ≈ *J*(7b,4) = 1.5, J_{gem} = 10.7 (H-7b); 1.89 dm, 1 H, *J*(7a,1) ≈ *J*(7a,1) = 1.5 (H-7a); 2.21 brdq, 1 H, *J*(4,1) = 1.5 (H-4); 2.28 m, 1 H (H-1); 3.59 brdd, 1 H, *J*(5,4) = 1.0, *J*(5,6) = 6.0 (H-5); 4.18 d, 1 H and 4.43 d, 1 H, J_{gem} = 11.6 (CH_2O); 4.22 d, 1 H and 4.33 d, 1 H, J_{gem} = 11.2 (CH_2O); 4.25 brddd, 1 H, *J*(6,1) = 1.0, *J*(6,OH) = 5.1 (H-6); 5.30 d, 1 H (6-OH); 7.45 t, 2 H, 7.49 t, 2 H, 7.62 t, 1 H, 7.65 t, 1 H, 7.90 d, 2 H, and 7.95 d, 2 H (H-arom.). ^{13}C NMR: 32.00 (C-7); 34.33 (C-3); 42.01 (C-4); 42.69 (C-2); 48.36 (C-1); 65.42 (CH_2O); 65.50 (C-5); 67.49 (CH_2O); 70.99 (C-6); 128.88, 2 C, 128.89, 2 C, 129.28, 2 C, 129.40, 2 C, 129.68, 129.72, 133.53, and 133.56 (C-arom.); 165.68 (C=O); 165.78 (C=O).

Compound **16**: For $C_{23}H_{23}N_3O_5$ (421.5) calculated: 65.55% C, 5.50% H, 9.97% N; found: 65.75% C, 5.49% H, 9.78% N. FAB MS, *m/z*: 422 [M + H]. ^{1}H NMR: 1.32 dd, 1 H, *J*(3b,4) = 4.2, *J*(3b,5) = 1.0, J_{gem} = 12.8 (H-3b); 1.58 dm, 1 H, J_{gem} = 10.6 (H-7b); 1.69 dd, 1 H, *J*(3a,7b) = 2.1 (H-3a); 1.76 brdq, 1 H, *J*(7a,1) ≈ *J*(7a,4) ≈ *J*(7a,6) = 1.7 (H-7a); 2.32 brtq, 1 H, *J*(4,1) ≈ *J*(4,7b) = 1.5, *J*(4,5) = 4.6 (H-4); 2.36 m, 1 H (H-1); 3.64 brt, 1 H, *J*(6,1) = 0.5, *J*(6,5) = 1.8 (H-6); 3.87 brt, 1 H, *J*(5,1) = 1.0, *J*(5,6) = 1.6, *J*(5,OH) = 3.4 (H-5); 4.29 d, 1 H and 4.37 d, 1 H, J_{gem} = 11.2 (CH_2O); 4.38 d, 1 H and 4.55 d, 1 H, J_{gem} = 11.5 (CH_2O); 5.50 d, 1 H (5-OH); 7.44 d, 2 H, 7.47 d, 2 H, 7.60 t, 1 H, 7.62 t, 1 H, and 7.92 d, 4 H (H-arom.). ^{13}C NMR: 27.65 (C-3); 33.27 (C-7); 41.95 (C-4); 43.65 (C-2); 46.28 (C-1); 65.55 (CH_2O); 67.62 (C-6); 67.72

(CH_2O); 128.87, 4 C, 129.28, 2 C, 129.31, 2 C, 129.66, 2 C, 133.52, and 133.55 (C-arom.); 165.65 (C=O); 165.86 (C=O).

Deprotection of Benzoates **11**, **14**, and **16**

A solution of benzoate **11**, **14** or **16** (4.21 g, 10 mmol) in 0.1 M methanolic sodium methoxide (45 ml) was set aside at room temperature overnight. The solution was neutralized with Dowex 50 (H^+), the resin was filtered off, washed with methanol, and the collected filtrates and washings were evaporated. The precipitated crystals were filtered off and washed with ether.

(1R,2R*,3R*,4S*)-3-Azido-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**12**): Yield 1.67 g (78%), m.p. 112–113.5 °C. For $C_9H_{15}N_3O_3$ (213.2) calculated: 50.69% C, 7.09% H, 19.71% N; found: 50.75% C, 7.25% H, 19.69% N. FAB MS, *m/z*: 214 [M + H]. ^{1}H NMR: 0.94 dd, 1 H, *J*(5b,7a) = 2.6, J_{gem} = 12.9 (H-5b); 1.07 ddd, 1 H, *J*(5a,3) = 1.6, *J*(5a,4) = 4.3 (H-5a); 1.48 ddt, 1 H, *J*(7b,1) ≈ *J*(7b,4) = 1.7, *J*(7b,2) = 2.2, J_{gem} = 10.5 (H-7b); 1.62 ddt, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.5, *J*(7a,5b) = 2.6 (H-7a); 1.87 brs, 1 H (H-1); 2.29 br tq, 1 H, *J*(4,1) = 1.5, *J*(4,3) = 4.8 (H-4); 3.18 dd, 1 H, *J*(CH,OH) = 5.2 and 3.41 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.4 (CH_2O); 3.24 dd, 1 H, *J*(CH,OH) = 5.4 and 3.50 dd, 1 H, *J*(CH,OH) = 4.0, J_{gem} = 10.6 (CH_2O); 3.67 brdq, 1 H, *J*(3,1) = 1.0, *J*(3,2) = 1.5 (H-3); 3.75 brdt, 1 H, *J*(2,1) = 1.0, *J*(2,OH) = 3.9 (H-2); 4.40 dd, 1 H (CH_2O**H**); 4.50 t, 1 H, *J*(CH_2,OH) = 5.4 (CH_2O**H**); 5.00 d, 1 H (2-OH). ^{13}C NMR: 28.35 (C-5); 32.88 (C-7); 39.80 (C-4); 45.48 (C-6); 48.16 (C-1); 61.78 (CH_2O); 64.79 (CH_2O); 72.88 (C-3); 73.22 (C-2).

(1R,2R*,3S*,4S*)-3-Azido-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**15**): Yield 1.76 g (83%), m.p. 81–82 °C. For $C_9H_{15}N_3O_3$ (213.2) calculated: 50.69% C, 7.09% H, 19.71% N; found: 50.68% C, 7.26% H, 19.52% N. FAB MS, *m/z* (rel.%): 214 (100) [M + H], 165 (21). ^{1}H NMR: 0.68 brdd, 1 H, *J*(5b,7a) = 2.4, J_{gem} = 12.8 (H-5b); 1.19 dd, 1 H *J*(5a,4) = 4.6 (H-5a); 1.34 brdpent, 1 H, *J*(7b,1) ≈ *J*(7b,2) ≈ *J*(7b,3) ≈ *J*(7b,4) = 1.5, J_{gem} = 10.3 (H-7b); 1.73 brdq, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.7 (H-7a); 1.91 brs, 1 H (H-1); 2.08 brdq, 1 H, *J*(4,1) = 1.5 (H-4); 3.13 dd, 1 H, *J*(CH,OH) = 5.0 and 3.38 dd, 1 H, *J*(CH,OH) = 5.5, J_{gem} = 10.7 (CH_2O); 3.14 dd, 1 H, *J*(CH,OH) = 5.2 and 3.43 dd, 1 H, *J*(CH,OH) = 4.3, J_{gem} = 10.7 (CH_2O); 3.29 brdd, 1 H, *J*(3,2) = 6.1, *J*(3,7b) = 1.6 (H-3); 4.23 ddt, *J*(2,1) = 1.0, *J*(2,7b) = 1.5, *J*(2,OH) = 5.1 (H-2); 4.47 t, *J*(OH,CH_2) = 4.7 (CH_2O**H**); 4.50 t, *J*(OH,CH_2) = 5.3 (CH_2O**H**); 4.98 d, 1 H (2-OH). ^{13}C NMR: 32.05 (C-7); 33.97 (C-5); 42.17 (C-4); 45.29 (C-6); 48.01 (C-1); 62.22 (CH_2O); 64.85 (CH_2O); 66.07 (C-3); 71.24 (C-2).

(1R,2S*,3S*,4S*)-3-Azido-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**17**): Yield 1.69 g (79%), m.p. 137–138 °C. For $C_9H_{15}N_3O_3$ (213.2) calculated: 50.69% C, 7.09% H, 19.71% N; found: 50.70% C, 7.20% H, 19.53% N. FAB MS, *m/z*: 214 [M + H]. ^{1}H NMR: 1.03 ddd, 1 H, *J*(6b,1) = 4.4, *J*(6b,2) = 1.2, J_{gem} = 12.6 (H-6b); 1.20 dd, 1 H, *J*(6a,7b) = 2.3 (H-6a); 1.38 ddt, 1 H, *J*(7b,1) = *J*(7b,4) = 1.5, J_{gem} = 10.5 (H-7b); 1.51 ddt, 1 H, *J*(7a,1) = *J*(7a,4) = 1.6, *J*(7a,3) = 2.7 (H-7a); 1.95 m, 1 H (H-4); 2.15 brtq, 1 H, *J*(1,2) = 4.6 (H-1); 3.19 dd, 1 H, *J*(CH,OH) = 5.1 and 3.45 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.4 (CH_2O); 3.39 dd, 1 H, *J*(CH,OH) = 5.6 and 3.43 dd, 1 H, *J*(CH,OH) = 4.3, J_{gem} = 10.9 (CH_2O); 3.60 brt, 1 H, *J*(3,2) = 1.7, *J*(3,4) = 1.0 (H-3); 3.77 ddq, 1 H, *J*(2,4) = 1.2, *J*(2,OH) = 3.7 (H-2); 4.44 dd, 1 H (CH_2O**H**); 4.55 t, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 5.22 d, 1 H (2-OH). ^{13}C NMR: 26.83 (C-6); 33.25 (C-7); 42.04 (C-1); 45.84 (C-4); 46.25 (C-5); 61.80 (CH_2O); 65.16 (CH_2O); 67.69 (C-3); 77.77 (C-2).

Preparation of Amines **13**, **18**, and **19**

Hydrogen was bubbled through a stirred mixture of azide **12**, **15** or **17** (1.49 g, 7 mmol), methanol (25 ml), and palladium hydroxide on carbon (20% Pd, 75 mg) for 3 h. The catalyst was filtered off and washed with methanol. The collected filtrates and washings were evaporated. The residue was crystallized from ethanol.

(1R,2R*,3R*,4S*)-3-Amino-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**13**): Yield 1.11 g (85%), m.p. 151–154 °C. For $C_9H_{17}NO_3$ (187.2) calculated: 57.73% C, 9.15% H, 7.48% N; found: 57.62% C, 9.17% H, 7.19% N. FAB MS, *m/z*: 188 [M + H]. ^{1}H NMR: 0.85 ddd, 1 H, *J*(5a,3) = 1.1, *J*(5a,4) = 4.4, J_{gem} = 12.7 (H-5a); 1.23 dd, 1 H, *J*(5b,7a) = 2.4 (H-5b); 1.35 ddt, 1 H, *J*(7b,1) ≈ *J*(7b,4) = 1.5, *J*(7b,2) = 1.8, J_{gem} = 11.0 (H-7b); 1.57 ddt, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.3, *J*(7a,5b) = 2.4 (H-7a); 1.81 m, 1 H (H-1); 1.95 brtq, 1 H, *J*(4,1) = 1.6, *J*(4,3) = 4.4 (H-4); 2.80 brd, 1 H, *J*(3,1) = 1.0 (H-3); 3.15 d, 1 H and 3.36 d, 1 H, J_{gem} = 10.4 (CH_2O); 3.42 d, 1 H and 3.53 d, 1 H, J_{gem} = 10.6 (CH_2O); 3.48 brt, 1 H, *J*(2,3) = 1.6 (H-2); 3.50 brs, 3 H (NH_2, OH); 4.35 brs, 1 H (OH); 4.50 brs, 1 H (OH). ^{13}C NMR: 26.64 (C-5); 33.61 (C-7); 41.99 (C-4); 45.73 (C-6); 49.30 (C-1); 62.61 (CH_2O); 63.62 (C-3); 65.94 (CH_2O); 76.37 (C-2).

(1R,2R*,3S*,4S*)-3-Amino-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**18**): Yield 1.09 g (83%), m.p. 154–156 °C. For $C_9H_{17}NO_3$ (187.2) calculated: 57.73% C, 9.15% H, 7.48% N; found: 57.76% C, 9.24% H, 7.37% N. FAB MS, *m/z*: 188 [M + H]. ^{1}H NMR: 0.61 dd, 1 H, *J*(5b,7a) = 2.4, J_{gem} = 12.6 (H-5b); 1.13 dd, 1 H, *J*(5a,4) = 4.5 (H-5a); 1.17 dpent, 1 H, *J*(7b,1) ≈ *J*(7b,2) ≈ *J*(7b,3) ≈ *J*(7b,4) = 1.5, J_{gem} = 10.2 (H-7b); 1.53 brdq, 1 H (H-7a); 1.77 brdq, 1 H, *J*(4,1) = 1.6 (H-4); 1.82 brs, 1 H (H-1); 2.71 brdd, 1 H, *J*(3,7b) = 1.6 (H-3); 3.13 d, 1 H and 3.38 d, 1 H, J_{gem} = 10.4 (CH_2O); 3.17 d, 1 H and 3.42 d, 1 H, J_{gem} = 10.6 (CH_2O); 3.40 brs, 2 H (NH_2); 3.77 brd, *J*(2,1) = 1.3 (H-2); 4.40 brs, 3 H (3 × OH). ^{13}C NMR: 30.90 (C-7); 34.97 (C-5); 44.98 (C-4); 45.51 (C-6); 47.38 (C-1); 56.55 (C-3); 62.29 (CH_2O); 65.06 (CH_2O); 68.30 (C-2).

(1R,2S*,3S*,4S*)-3-Amino-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**19**): Yield 934 mg (76%), m.p. 180–182 °C. For $C_9H_{17}NO_3$ (187.2) calculated: 57.73% C, 9.15% H, 7.48% N; found: 57.52% C, 9.30% H, 7.38% N. FAB MS, *m/z*: 188 [M + H]. ^{1}H NMR: 0.89 ddd, 1 H, *J*(6b,1) = 4.4, *J*(6b,2) = 1.3, J_{gem} = 12.4 (H-6b); 1.19 dd, 1 H, *J*(6a,7b) = 2.3 (H-6a); 1.33 ddt, 1 H, *J*(7b,1) = *J*(7b,4) = 1.7, J_{gem} = 10.4 (H-7b); 1.56 ddt, 1 H, *J*(7a,1) = *J*(7a,4) = 1.7 (H-7a); 1.61 m, 1 H (H-4); 2.01 brtq, 1 H, *J*(1,2) = 4.6, *J*(1,4) = 1.5 (H-1); 2.72 brt, 1 H, *J*(3,2) = 2.2 (H-3); 3.17 d, 1 H and 3.41 d, 1 H, J_{gem} = 10.4 (CH_2O); 3.40 brs, 2 H (NH_2); 3.45 d, 1 H and 3.52 d, 1 H, J_{gem} = 10.4 (CH_2O); 3.46 brd, 1 H (H-2); 4.25 brs, 1 H, 4.45 brs, 1 H, and 4.65 brs, 1 H (3 × OH). ^{13}C NMR: 26.86 (C-6); 32.37 (C-7); 42.20 (C-1); 46.27 (C-5); 49.35 (C-4); 56.81 (C-3); 62.46 (CH_2O); 65.78 (CH_2O); 81.62 (C-2).

(1*R**,2*R**,3*R**,4*S**)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-6,6-bis(hydroxymethyl)-bicyclo[2.2.1]heptan-2-ol (**20a**)

A solution of amine **13** (562 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (984 mg, 6 mmol), and triethylamine (1.8 ml) in ethanol (18 ml) was heated in a pressure vessel at 100 °C for 48 h and, after cooling, the precipitated crystals were filtered off and washed with ethanol and ether. 580 mg (61%) of pyrimidine **20a** was obtained. Chromatography of the mother liquors on a silica gel column in ethyl acetate–acetone–ethanol–water (90:15:11:9) afforded 120 mg (13%) of the same compound, m.p. 263–265 °C. For $C_{13}H_{19}ClN_4O_3$ (314.8) calculated: 49.60% C, 6.08% H, 11.26% Cl, 17.80% N; found: 49.50% C, 6.26% H, 11.11% Cl, 17.58% N. FAB MS, *m/z* (rel.%): 317/315 (37/100) [M + H], 281 (44). ^{1}H NMR: 0.89 dd, 1 H,

J(5b,7a) = 2.2, J_{gem} = 13.2 (H-5b); 0.97 ddd, 1 H, *J*(5a,3) = 1.6, *J*(5a,4) = 4.4 (H-5a); 1.49 brdq, 1 H, *J*(7b,1) ≈ *J*(7b,2) ≈ *J*(7b,4) = 1.6, J_{gem} = 10.5 (H-7b); 1.68 dm, 1 H (H-7a); 1.94 m, 1 H (H-1); 2.53 brtq, 1 H, *J*(4,1) ≈ *J*(4,7a) = 1.6, *J*(4,3) = 4.4 (H-4); 3.20 dd, 1 H, *J*(CH,OH) = 5.2 and 3.46 dd, 1 H, *J*(CH,OH) = 5.5, J_{gem} = 10.6 (CH_2O); 3.43 dd, 1 H, *J*(CH,OH) = 5.6 and 3.57 dd, 1 H, *J*(CH,OH) = 4.3, J_{gem} = 10.6 (CH_2O); 3.70 m, 1 H, *J*(3,2) = 2.2, *J*(3,NH) = 4.5 (H-3); 3.93 brdq, 1 H, *J*(2,1) = 1.0, *J*(2,OH) = 3.8 (H-2); 4.40 dd, 1 H (CH_2O**H**); 4.53 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.60 d, 1 H (2-OH); 5.21 brs, 2 H (NH_2); 6.61 d, 1 H (NH); 7.74 s, 1 H (H-2′). ^{13}C NMR: 27.63 (C-5); 32.83 (C-7); 39.45 (C-4); 45.93 (C-6); 48.10 (C-1); 62.53 (CH_2O); 65.35 (C-3); 65.50 (CH_2O); 73.35 (C-2); 123.94 (C-5′); 136.97 (C-4′); 145.69 (C-2′); 152.22 (C-6′).

(1*R**,2*R**,3*S**,4*S**)-3-[(5-Amino-6-chloropyrimidin-4-yl)amino]-6,6-bis(hydroxymethyl)-bicyclo[2.2.1]heptan-2-ol (**20b**) and (1*R**,2*S**,3*S**,4*S**)-3-[(5-Amino-6-chloropyrimidin-4-yl)-amino]-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol (**20c**)

A solution of amine **18** or **19** (562 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (984 mg, 6 mmol), and triethylamine (1.8 ml) in ethanol (18 ml) was heated in a pressure vessel at 100 °C for 6 days and, after cooling, was taken down. The residue was chromatographed on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (180:30:23:417) and crystallized from ethanol.

Compound **20b**: Yield 764 mg (81%), m.p. 220–222 °C. For $C_{13}H_{19}ClN_4O_3$ (314.8) calculated: 49.60% C, 6.08% H, 11.26% Cl, 17.80% N; found: 49.35% C, 6.21% H, 11.12% Cl, 17.59% N. FAB MS, *m/z* (rel.%): 317/315 (36/100) [M + H]. ^{1}H NMR: 0.79 dd, 1 H, *J*(5b,7a) = 2.4, J_{gem} = 12.7 (H-5b); 1.20 dd, 1 H, *J*(5a,4) = 4.4 (H-5a); 1.31 brdpent, 1 H, *J*(7b,1) ≈ *J*(7b,2) ≈ *J*(7b,3) ≈ *J*(7b,4) = 1.5, J_{gem} = 10.2 (H-7b); 1.81 dm, 1 H (H-7a); 1.95 m, 1 H (H-1); 1.99 brdq, 1 H, *J*(4,1) = 1.3 (H-4); 3.19 dd, 1 H, *J*(CH,OH) = 5.1 and 3.42 dd, 1 H, *J*(CH,OH) = 5.4, J_{gem} = 10.4 (CH_2O); 3.25 dd, 1 H, *J*(CH,OH) = 5.2 and 3.51 dd, 1 H, *J*(CH,OH) = 4.2, J_{gem} = 10.6 (CH_2O); 3.89 ddd, 1 H, *J*(3,2) = 6.1, *J*(3,7b) = 1.3, *J*(3,NH) = 7.2 (H-3); 4.18 brdd, 1 H, *J*(2,1) ≈ *J*(2,7b) = 1.0 (H-2); 4.48 t, 1 H (CH_2O**H**); 4.51 t, 1 H (CH_2O**H**); 4.94 d, *J*(OH,2) = 4.6 (2-OH); 5.02 brs, 2 H (NH_2); 6.38 d, 1 H (NH); 7.74 s, 1 H (H-2′). ^{13}C NMR: 31.85 (C-5); 34.52 (C-7); 42.42 (C-1); 45.44 (C-6); 47.93 (C-4); 57.31 (C-3); 68.64 (C-2); 123.63 (C-5′); 137.67 (C-4′); 146.51 (C-2′); 152.55 (C-6′).

Compound **20c**: Yield 840 mg (84%), m.p. 144–146 °C (hydrate), 250–252.5 °C. For $C_{13}H_{19}ClN_4O_3 \cdot H_2O$ (332.8) calculated: 46.92% C, 6.36% H, 10.65% Cl, 16.84% N; found: 46.93% C, 6.41% H, 10.79% Cl, 16.67% N. FAB MS, *m/z* (rel.%): 317/315 (35/100) [M + H], 281 (24). ^{1}H NMR: 1.18 ddd, 1 H, *J*(6b,1) = 4.4, *J*(6b,2) = 1.2, J_{gem} = 12.8 (H-6b); 1.29 dd, 1 H, *J*(6a,7b) = 2.0 (H-6a); 1.46 dm, 1 H, J_{gem} = 10.6 (H-7b); 1.51 ddt, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.3, *J*(7a,3) = 2.6 (H-7a); 1.79 m, 1 H (H-4); 2.18 brtq, 1 H, *J*(1,2) = 4.4, *J*(1,4) ≈ *J*(1,7) = 1.3 (H-1); 3.17 dd, 1 H, *J*(CH,OH) = 5.4 and 3.46 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.4 (CH_2O); 3.60 dd, 1 H, *J*(CH,OH) = 3.5 and 3.68 dd, 1 H, *J*(CH,OH) = 8.8, J_{gem} = 11.2 (CH_2O); 3.71 dt, 1 H, *J*(3,2) = 2.8, *J*(3,NH) = 5.6 (H-3); 3.94 brq, 1 H, *J*(2,4) = 1.2, *J*(2,OH) = 3.4 (H-2); 4.46 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 4.48 dd, 1 H (CH_2O**H**); 4.89 d, 1 H (2-OH); 5.20 brs, 2 H (NH_2); 6.86 d, 1 H (NH); 7.69 s, 1 H (H-2′). ^{13}C NMR: 26.72 (C-6); 32.93 (C-7); 42.11 (C-1); 46.42 (C-4); 47.13 (C-5); 58.55 (C-5); 62.63 (CH_2O); 64.56 (CH_2O); 78.18 (C-2); 124.11 (C-5′); 136.50 (C-4′); 145.25 (C-2′); 151.32 (C-6′).

Preparation of 6-Chloropurine Analogues **21a**, **21b**, and **21c**

Concentrated hydrochloric acid (0.7 ml) was added to a stirred mixture of compound **20a** (315 mg, 1 mmol), **20b** (315 mg, 1 mmol) or **20c** (333 mg, 1 mmol) and triethyl orthoformate (15 ml), the resulting solution was set aside at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (9 ml). To the stirred solution, 0.5 M hydrochloric acid (9 ml) was added, the mixture was stirred at room temperature for 3 h and then neutralized with solid sodium hydrogencarbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (3 × 7 ml). The collected organic phases were dried over anhydrous sodium sulfate and evaporated.

(1R,2R*,3R*,4S*)-3-(6-Chloro-9H-purin-9-yl)-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**21a**): The residue was crystallized from water. Yield 305 mg (89%), m.p. 141–142 °C (hydrate), 198–199.5 °C. For $C_{14}H_{17}ClN_4O_3 \cdot H_2O$ (342.8) calculated: 49.05% C, 5.59% H, 10.34% Cl, 16.34% N; found: 49.25% C, 5.62% H, 10.38% Cl, 16.41% N. FAB MS, *m/z* (rel.%): 327/325 (38/100) [M + H]. ^{1}H NMR: 0.57 dd, 1 H, *J*(5b,7a) = 2.3, J_{gem} = 13.7 (H-5b); 1.07 ddd, 1 H, *J*(5a,3) = 1.6, *J*(5a,4) = 4.6 (H-5a); 1.70 brdq, 1 H, *J*(7b,1) ≈ *J*(7b,4) = 1.6, *J*(7b,2) = 2.0, J_{gem} = 10.5 (H-7b); 1.83 dm, 1 H (H-7a); 2.10 m, 1 H (H-1); 3.15 overlapped (H-4); 3.15 dd, 1 H, *J*(CH,OH) = 5.5 and 3.38 dd, 1 H, *J*(CH,OH) = 5.5, J_{gem} = 10.5 (CH_2O); 3.22 dd, 1 H, *J*(CH,OH) = 5.3 and 3.40 dd, 1 H, *J*(CH,OH) = 4.5, J_{gem} = 10.6 (CH_2O); 4.29 brdt, 1 H, *J*(3,1) = 1.0, *J*(3,2) = 2.2, *J*(3,4) = 4.3 (H-3); 4.44 dd, 1 H (CH_2O**H**); 4.53 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 4.91 brdt, 1 H, *J*(2,1) = 1.0, *J*(2,OH) = 3.9 (H-2); 5.22 d, 1 H (2-OH); 8.77 s, 1 H and 8.81 s, 1 H (H-2′, H-8′). ^{13}C NMR: 27.73 (C-5); 32.48 (C-7); 40.29 (C-4); 45.85 (C-6); 48.55 (C-1); 62.18 (CH_2O); 64.67 (CH_2O); 69.54 (C-3); 70.33 (C-2); 131.40 (C-5′); 147.02 (C-8′); 149.28 (C-6′); 151.51 (C-2′); 152.83 (C-4′).

(1R,2R*,3S*,4S*)-3-(6-Chloro-9H-purin-9-yl)-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**21b**): The residue was crystallized from water. Yield 265 mg (79%), m.p. 207–209 °C. For $C_{14}H_{17}ClN_4O_3 \cdot 0.5H_2O$ (333.8) calculated: 50.38% C, 5.44% H, 10.62% Cl, 16.79% N; found: 50.32% C, 5.51% H, 10.44% Cl, 16.68% N. FAB MS, *m/z* (rel.%): 327/325 (41/100) [M + H]. ^{1}H NMR: 1.03 dd, 1 H, *J*(5b,7a) = 1.7, J_{gem} = 12.9 (H-5b); 1.39 dd, 1 H, *J*(5a,4) = 4.4 (H-5a); 1.59 brdpent, 1 H, *J*(7b,1) ≈ *J*(7b,2) ≈ *J*(7b,3) ≈ *J*(7b,4) = 1.5, J_{gem} = 10.6 (H-7b); 2.06 brs, 1 H (H-1); 2.18 brdm, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.3 (H-7a); 2.53 brdq, 1 H, *J*(4,1) ≈ *J*(4,3) = 1.3 (H-4); 3.23 dd, 1 H, *J*(CH,OH) = 5.2 and 3.47 dd, 1 H, *J*(CH,OH) = 5.5, J_{gem} = 10.5 (CH_2O); 3.34 dd, 1 H, *J*(CH,OH) = 5.4 and 3.59 dd, 1 H, *J*(CH,OH) = 4.3, J_{gem} = 10.7 (CH_2O); 4.36 ddt, 1 H, *J*(2,1) = 1.2, *J*(2,3) = 5.9, *J*(2,7b) = 1.5, *J*(2,OH) = 4.5 (H-2); 4.60 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.64 t, 1 H, *J*(OH,CH_2) = 4.7 (CH_2O**H**); 4.69 brdt, 1 H (H-3); 4.75 d, 1 H (2-OH); 8.58 s, 1 H and 8.73 s, 1 H (H-2′, H-8′). ^{13}C NMR: 33.67 (C-7); 35.55 (C-5); 41.75 (C-4); 45.46 (C-6); 48.23 (C-1); 60.82 (C-3); 62.42 (CH_2O); 65.01 (CH_2O); 69.57 (C-2); 130.44 (C-5′); 146.98 (C-8′); 148.63 (C-6′); 151.29 (C-2′);152.74 (C-4′).

(1R,2S*,3S*,4S*)-3-(6-Chloro-9H-purin-9-yl)-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**21c**): The residue was chromatographed on a silica gel column (30 g) in ethyl acetate–acetone–ethanol–water (95:15:9:6). Yield 290 mg (89%), m.p. 180–183 °C. For $C_{14}H_{17}ClN_4O_3$ (324.8) calculated: 51.78% C, 5.28% H, 10.92% Cl, 17.25% N; found: 51.95% C, 5.42% H, 10.98% Cl, 17.01% N. FAB MS, *m/z* (rel.%): 327/325 (41/100) [M + H], 291 (33). ^{1}H NMR: 1.15 ddd, 1 H, *J*(6b,1) = 4.4, *J*(6b,2) = 1.0, J_{gem} = 12.8 (H-6b); 1.46 dd, 1 H, *J*(6a,7b) = 2.1 (H-6a); 1.71 brdt, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.2, *J*(7a,3) = 2.6, J_{gem} = 10.6 (H-7a); 1.86 dm, 1 H (H-7b); 2.30 m, 1 H (H-4); 2.32 brtq, 1 H, *J*(1,2) = 4.2, *J*(1,4) ≈ *J*(1,7) = 1.2 (H-1); 3.30 dd, 1 H, *J*(CH,OH) = 5.2 and 3.47 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.5 (CH_2O); 3.67 dd, 1 H,

J(CH,OH) = 5.0 and 3.47 dd, 1 H, *J*(CH,OH) = 5.0, J_{gem} = 10.6 (CH_2O); 4.48 t, 1 H, *J*(OH,CH_2) = 5.0 (CH_2O**H**); 4.50 brq, 1 H, *J*(2,3) = 2.8, *J*(2,4) = 1.0 (H-2); 4.56 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.63 brt, 1 H (H-3); 5.27 d, 1 H, *J*(OH,2) = 4.0 (2-OH); 8.79 s, 1 H and 8.89 s, 1 H (H-2′, H-8′). ^{13}C NMR: 26.83 (C-6); 33.81 (C-7); 42.41 (C-1); 46.69 (C-4); 47.34 (C-5); 61.93 (CH_2O); 62.52 (C-3); 64.54 (CH_2O); 77.55 (C-2); 131.21 (C-5′); 146.08 (C-8′); 149.21 (C-6′); 151.50 (C-2′); 152.32 (C-4′).

Ammonolysis of 6-Chloropurines **21a**, **21b**, and **21c**

Liquid ammonia (10 ml) was added to a stirred suspension of a 6-chloropurine (0.5 mmol) in methanol (2 ml) at –70 °C and the mixture was heated in an autoclave at 75 °C for 48 h. Ammonia was evaporated and the residue was crystallized from water.

(1R,2R*,3R*,4S*)-3-(6-Amino-9H-purin-9-yl)-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**22a**): Yield 124 mg (79%), m.p. 290–293 °C. For $C_{14}H_{19}N_5O_3 \cdot 0.5H_2O$ (314.4) calculated: 53.49% C, 6.41% H, 22.28% N; found: 53.69% C, 6.42% H, 22.13%N. FAB MS, *m/z* (rel.%): 306 (100) [M + H], 275 (48). ^{1}H NMR: 0.54 dd, 1 H, *J*(5b,7a) = 2.3, J_{gem} = 13.6 (H-5b); 1.07 ddd, 1 H, *J*(5a,3) = 1.6, *J*(5a,4) = 4.6 (H-5a); 1.67 brdq, 1 H, *J*(7b,1) ≈ *J*(7b,4) = 1.6, *J*(7b,2) = 2.0, J_{gem} = 10.5 (H-7b); 1.79 dm, 1 H (H-7a); 2.07 m, 1 H (H-1); 3.04 brtq, 1 H, *J*(4,1) ≈ *J*(4,7a) = 1.6, *J*(4,3) = 4.3 (H-4); 3.20 dd, 1 H, *J*(CH,OH) = 5.2 and 3.40 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.5 (CH_2O); 3.23 dd, 1 H, *J*(CH,OH) = 5.2 and 3.45 dd, 1 H, *J*(CH,OH) = 4.4, J_{gem} = 10.6 (CH_2O); 4.17 brdq, 1 H, *J*(3,1) = 1.0, *J*(3,2) = 2.2 (H-3); 4.46 dd, 1 H (CH_2O**H**); 4.52 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.78 brdt, 1 H, *J*(2,1) = 1.0, *J*(2,OH) = 3.9 (H-2); 5.12 d, 1 H (2-OH); 7.22 brs, 2 H (NH_2); 8.13 s, 1 H and 8.22 s, 1 H (H-2′, H-8′). ^{13}C NMR: 27.82 (C-5); 32.49 (C-7); 40.30 (C-4); 45.94 (C-6); 48.28 (C-1); 62.08 (CH_2O); 64.63 (CH_2O); 68.74 (C-3); 70.39 (C-2); 119.38 (C-5′); 139.97 (C-8′); 150.48 (C-4′); 152.49 (C-2′); 156.18 (C-6′).

(1R,2R*,3S*,4S*)-3-(6-Amino-9H-purin-9-yl)-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**22b**): Yield 135 mg (86%), m.p. 301–303.5 °C. For $C_{14}H_{19}N_5O_3 \cdot 0.5H_2O$ (314.4) calculated: 53.49% C, 6.41% H, 22.28% N; found: 53.28% C, 6.45% H, 21.99% N. FAB MS, *m/z* (rel.%): 306 (100) [M + H], 136 (32). ^{1}H NMR: 0.98 dd, 1 H, *J*(5b,7a) = 2.6, J_{gem} = 12.8 (H-5b); 1.35 dd, 1 H, *J*(5a,4) = 4.3 (H-5a); 1.56 brdpent, 1 H, J_{gem} = 10.5 (H-7b); 2.04 m, 1 H (H-1); 2.14 dm, 1 H (H-7a); 2.36 brdq, 1 H, *J*(4,1) ≈ *J*(4,7) = 1.5, *J*(4,5a) = 4.3 (H-4); 3.23 dd, 1 H, *J*(CH,OH) = 5.3 and 3.47 dd, 1 H, *J*(CH,OH) = 5.5, J_{gem} = 10.4 (CH_2O); 3.33 dd, 1 H, *J*(CH,OH) = 4.9 and 3.58 dd, 1 H, *J*(CH,OH) = 4.3, J_{gem} = 10.7 (CH_2O); 4.29 brddt, 1 H, *J*(2,1) ≈ *J*(2,7b) = 1.2, *J*(2,3) = 6.0, *J*(2,OH) = 4.6 (H-2); 4.56 brdt, 1 H, *J*(3,4a) ≈ *J*(3,7b) = 1.2 (H-3); 4.59 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.62 t, 1 H, *J*(OH,CH_2) = 4.6 (CH_2O**H**); 4.75 d, 1 H (2-OH); 7.12 brs, 2 H (NH_2); 8.02 s, 1 H and 8.11 s, 1 H (H-2′, H-8′). ^{13}C NMR: 33.71 (C-7); 35.85 (C-5); 42.40 (C-4); 45.46 (C-6); 48.23 (C-1); 59.74 (C-3); 62.36 (CH_2O); 64.93 (CH_2O); 69.61 (C-2); 118.13 (H-5′); 140.31 (H-8′); 150.20 (C-4′); 152.18 (C-2′); 155.96 (C-6′).

(1R,2S*,3S*,4S*)-3-(6-Amino-9H-purin-9-yl)-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-ol* (**22c**): Yield 128 mg (84%), m.p. 269–270 °C. For $C_{14}H_{19}N_5O_3$ (305.3) calculated: 55.07% C, 6.27% H, 22.94% N; found: 54.94% C, 6.42% H, 22.70% N. FAB MS, *m/z* (rel.%): 306 (100) [M + H], 136 (57). ^{1}H NMR: 1.16 ddd, 1 H, *J*(6b,1) = 4.4, *J*(6b,2) = 1.2, J_{gem} = 12.7 (H-6b); 1.43 dd, 1 H, *J*(6a,7b) = 2.0 (H-6a); 1.65 brddt, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.2, *J*(7a,3) = 2.3, J_{gem} = 10.6 (H-7a); 1.80 dm, 1 H, *J*(7b,1) ≈ *J*(7b,4) = 1.2 (H-7b); 2.09 brs, 1 H (H-4); 2.30 brtq, 1 H, *J*(1,2) = 4.2, *J*(1,4) = 1.2 (H-1); 3.27 dd, 1 H, *J*(CH,OH) = 5.3 and 3.46 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.5 (CH_2O); 3.68 dd, 1 H, *J*(CH,OH) = 4.6 and 3.76 dd, 1 H, *J*(CH,OH) = 6.2,

J_{gem} = 11.0 (CH_2O); 4.45 brt, 1 H, J(3,2) = 2.8 (H-3); 4.52 dd, 1 H (CH_2O**H**); 4.54 t, 1 H, J(OH,CH_2) = 5.4 (CH_2O**H**); 4.56 brq, 1 H, J(2,4) = 1.1, J(2,OH) = 3.9 (H-2); 5.20 d, 1 H (2-OH); 7.24 brs, 2 H (NH_2); 8.14 s, 1 H and 8.33 s, 1 H (H-2′, H-8′). ^{13}C NMR: 26.73 (C-6); 33.41 (C-7); 42.38 (C-1); 47.19 (C-4); 47.43 (C-5); 61.42 (C-3); 62.06 (CH_2O); 64.45 (CH_2O); 76.84 (C-2); 119.24 (C-5′); 139.19 (C-8′); 149.87 (C-4′); 152.43 (C-2′); 156.21 (C-6′).

Preparation of 6-(Dimethylamino)purines **23a**, **23b**, and **23c**

A chloropurine (0.5 mmol) was dissolved under stirring in dimethylammonium *N*,*N*-dimethylcarbamate (1.5 ml), the solution was set aside at room temperature for 5 h and then evaporated. The residue was crystallized from water.

(1R,2R*,3R*,4S*)-3-[6-(Dimethylamino)-9H-purin-9-yl]-6,6-bis(hydroxymethyl)bicyclo-[2.2.1]heptan-2-ol* (**23a**): Yield 163 mg (95%), m.p. 225–227 °C. For $C_{16}H_{23}N_5O_3 \cdot H_2O$ (342.4) calculated: 56.13% C, 7.07% H, 20.45% N; found: 56.32% C, 7.12% H, 20.65% N. FAB MS, *m/z* (rel.%): 334 (100) [M + H], 215 (36). ^{1}H NMR: 0.54 dd, 1 H, J(5b,7a) = 2.3, J_{gem} = 13.7 (H-5b); 1.05 ddd, 1 H, J(5a,3) = 1.6, J(5a,4) = 4.6 (H-5a); 1.67 brdq, 1 H, J(7b,1) ≈ J(7b,4) = 1.6, J(7b,2) = 2.0, J_{gem} = 10.5 (H-7b); 1.80 dm, 1 H (H-7a); 2.08 m, 1 H (H-1); 3.02 brtq, 1 H, J(4,1) ≈ J(4,7a) = 1.5, J(4,3) = 4.2 (H-4); 3.22 dd, 1 H, J(CH,OH) = 5.5 and 3.40 dd, 1 H, J(CH,OH) = 5.5, J_{gem} = 10.5 (CH_2O); 3.23 dd, 1 H, J(CH,OH) = 5.1 and 3.46 dd, 1 H, J(CH,OH) = 4.4, J_{gem} = 10.7 (CH_2O); 3.25 brs, 6 H ($N(CH_3)_2$); 4.20 brdt, 1 H, J(3,1) = 1.0, J(3,2) = 2.1 (H-3); 4.47 dd, 1 H (CH_2O**H**); 4.52 t, 1 H, J(OH,CH_2) = 5.5 (CH_2O**H**); 4.75 brdt, 1 H, J(2,1) = 1.0, J(2,OH) = 4.0 (H-2); 5.12 d, 1 H (2-OH); 8.20 s, 1 H and 8.24 s, 1 H (H-2′, H-8′). ^{13}C NMR: 27.68 (C-5); 32.54 (C-7); 34.50 (NCH_3); 40.25 (C-4); 45.99 (C-6); 48.28 (C-1); 62.07 (CH_2O); 64.63 (CH_2O); 68.70 (C-3); 70.39 (C-2); 119.88 (C-5′); 138.73 (C-8′); 151.26 (C-4′); 151.81 (C-2′); 154.41 (C-6′).

(1R,2R*,3S*,4S*)-3-[6-(Dimethylamino)-9H-purin-9-yl]-6,6-bis(hydroxymethyl)bicyclo-[2.2.1]heptan-2-ol* (**23b**): Yield 145 mg (85%), m.p. 237–239 °C. For $C_{16}H_{23}N_5O_3 \cdot 0.5H_2O$ (342.4) calculated: 56.13% C, 7.07% H, 20.45% N; found: 56.26% C, 7.16% H, 20.40% N. FAB MS, *m/z* (rel.%): 334 (100) [M + H], 164 (67). ^{1}H NMR: 0.98 dd, 1 H, J(5b,7a) = 2.7, J_{gem} = 12.8 (H-5b); 1.36 dd, 1 H, J(5a,4) = 4.4 (H-5a); 1.55 brdpent, 1 H, J(7b,1) ≈ J(7b,2) ≈ J(7b,3) ≈ J(7b,4) = 1.3, J_{gem} = 10.5 (H-7b); 2.04 m, 1 H (H-1); 2.13 dm, 1 H (H-7a); 2.36 brdq, 1 H, J(4,1) ≈ J(4,7a) = 1.3 (H-4); 3.22 dd, 1 H, J(CH,OH) = 5.2 and 3.47 dd, 1 H, J(CH,OH) = 5.6, J_{gem} = 10.4 (CH_2O); 3.32 dd, 1 H, J(CH,OH) = 5.0 and 3.58 dd, 1 H, J(CH,OH) = 4.4, J_{gem} = 10.6 (CH_2O); 3.45 brs, 6 H ($N(CH_3)_2$); 4.30 ddt, 1 H, J(2,1) = 1.2, J(2,3) = 6.0, J(2,OH) = 4.6 (H-2); 4.58 brdt, 1 H, J(3,7a) = 1.2 (H-3); 4.58 t, 1 H, J(CH_2,OH) = 5.4 (CH_2O**H**); 4.61 t, 1 H, J(CH_2,OH) = 4.7 (CH_2O**H**); 4.70 d, 1 H (2-OH); 8.02 s, 1 H and 8.18 s, 1 H (H-2′, H-8′). ^{13}C NMR: 33.66 (C-7); 35.83 (C-5); 38.00, 2 C ($N(CH_3)_2$); 42.21 (C-4); 45.46 (C-6); 48.25 (C-1); 59.73 (C-3); 62.33 (CH_2O); 64.90 (CH_2O); 69.53 (C-2); 118.69 (C-5′); 139.15 (C-8′); 150.97 (C-4′); 151.53 (C-2′); 154.33 (C-6′).

(1R,2S*,3S*,4S*)-3-[6-(Dimethylamino)-9H-purin-9-yl]-5,5-bis(hydroxymethyl)bicyclo-[2.2.1]heptan-2-ol* (**23c**): Yield 140 mg (84%), m.p. 235–236.5 °C. For $C_{16}H_{23}N_5O_3$ (333.4) calculated: 57.64% C, 6.95% H, 21.01% N; found: 57.52% C, 6.94% H, 20.85% N. FAB MS, *m/z* (rel.%): 334 (100) [M + H], 215 (24). ^{1}H NMR: 1.18 ddd, 1 H, J(6b,1) = 4.4, J(6b,2) = 1.1, J_{gem} = 12.8 (H-6b); 1.43 dd, 1 H, J(6a,7b) = 2.1 (H-6a); 1.65 brddt, 1 H, J(7a,1) ≈ J(7a,4) = 1.2, J(7a,3) = 2.7, J_{gem} = 10.6 (H-7a); 1.73 brdm, 1 H, J(7b,1) = J(7b,4) = 1.2 (H-7b); 2.06 m, 1 H (H-4); 2.31 brtq, 1 H, J(1,2) = 4.2, J(1,4) ≈ J(1,7) = 1.3 (H-1); 3.26 dd, 1 H, J(CH,OH) = 5.3 and 3.46 dd, 1 H, J(CH,OH) = 5.6, J_{gem} = 10.5 (CH_2O); 3.45 brs, 6 H ($N(CH_3)_2$); 3.69 dd, 1 H,

J(CH,OH) = 4.5 and 3.77 dd, 1 H, *J*(CH,OH) = 6.7, J_{gem} = 11.0 (CH_2O); 4.47 brt, 1 H, *J*(3,2) = 2.7 (H-3); 4.53 overlapped (H-2); 4.53 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.53 dd, 1 H (CH_2O**H**); 5.20 d, 1 H, *J*(OH,2) = 3.9 (2-OH); 8.22 s, 1 H and 8.36 s, 1 H (H-2′, H-8′). ^{13}C NMR: 26.68 (C-6); 33.28 (C-7); 34.33, 2 C ($N(CH_3)_2$); 42.39 (C-1); 47.08 (C-4); 47.46 (C-5); 61.21 (C-3); 62.07 (CH_2O); 64.37 (CH_2O); 76.73 (C-2); 119.74 (C-5′); 137.77 (C-8′); 150.59 (C-4′); 151.77 (C-2′); 154.44 (C-6′).

Reaction of 6-Chloropurines **21a**, **21b**, and **21c** with Cyclopropylamine

A solution of a chloropurine (0.5 mmol) in cyclopropylamine (1.5 ml) was left at room temperature overnight and then was evaporated.

(1R,2R*,3R*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]-6,6-bis(hydroxymethyl)bicyclo-[2.2.1]heptan-2-ol* (**24a**): Crystallization of the residue from water yielded 154 mg (89%) of **24a**, m.p. 218–219.5 °C. For $C_{17}H_{23}N_5O_3$ (345.4) calculated: 59.12% C, 6.71% H, 20.28% N; found: 58.95% C, 6.74% H, 20.16% N. FAB MS, *m/z* (rel.%): 346 (100) [M + H], 176 (29). ^{1}H NMR: 0.54 dd, 1 H, *J*(5b,7a) = 2.0, J_{gem} = 13.7 (H-5b); 0.61 m, 2 H, 0.70 m, 2 H, and 3.02 m, 1 H (cyclopropyl); 1.06 ddd, 1 H, *J*(5a,3) = 1.5, *J*(5a,4) = 4.5 (H-5a); 1.67 dq, 1 H, *J*(7b,1) ≈ *J*(7b,4) = 1.6, *J*(7b,2) = 2.0, J_{gem} = 10.4 (H-7b); 1.80 dm, 1 H (H-7a); 2.08 m, 1 H (H-1); 3.05 brt, 1 H (H-4); 3.20 dd, 1 H, *J*(CH,OH) = 4.4 and 3.40 dd, 1 H, *J*(CH,OH) = 4.9, J_{gem} = 10.5 (CH_2O); 3.23 dd, 1 H, *J*(CH,OH) = 5.5 and 3.43 dd, 1 H, *J*(CH,OH) = 4.8, J_{gem} = 10.6 (CH_2O); 4.18 brdt, 1 H, *J*(3,1) = 1.0, *J*(3,4) = 4.2 (H-3); 4.52 t, 1 H, *J*(OH,CH_2) = 5.0 (CH_2O**H**); 4.56 t, 1 H, *J*(OH,CH_2) = 4.6 (CH_2O**H**); 4.78 brdt, 1 H, *J*(2,1) = 1.0, *J*(2,3) = 2.0, *J*(2,OH) = 3.8 (H-2); 5.12 d, 1 H (2-OH); 7.88 brs, 1 H (NH); 8.22 s, 2 H (H-2′, H-8′). ^{13}C NMR: 6.55, 2 C (2 × CH_2); 24.20 (NCH); 27.84 (C-5); 32.50 (C-7); 40.31 (C-4); 45.94 (C-6); 48.28 (C-1); 62.10 (CH_2O); 64.64 (CH_2O); 68.75 (C-3); 70.43 (C-2); 119.75 (C-5′); 139.82 (C-8′); 150.00 (C-4′); 152.41 (C-2′); 155.71 (C-6′).

(1R,2R*,3S*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]-6,6-bis(hydroxymethyl)bicyclo-[2.2.1]heptan-2-ol* (**24b**): Chromatography of the residue on a silica gel column in ethyl acetate–acetone–ethanol–water (90:15:11:9) and crystallization from ethanol–ether afforded 152 mg (88%) of **24b**, m.p. 242–244 °C. For $C_{17}H_{23}N_5O_3$ (345.4) calculated: 59.12% C, 6.71% H, 20.28% N; found: 58.92% C, 6.78% H, 20.01% N. FAB MS, *m/z* (rel.%): 346 (100) [M + H], 176 (41). ^{1}H NMR: 0.59 m, 2 H, 0.71 m, 2 H, and 3.05 m, 1 H (cyclopropyl); 0.98 dd, 1 H, *J*(5b,7a) = 1.7, J_{gem} = 12.7 (H-5b); 1.35 dd, 1 H, *J*(5a,4) = 4.2 (H-5a); 1.55 dm, 1 H, J_{gem} = 10.4 (H-7b); 2.04 m, 1 H (H-1); 2.14 dm, 1 H (H-7a); 2.36 brd, 1 H (H-4); 3.23 dd, 1 H, *J*(CH,OH) = 5.6 and 3.46 dd, 1 H, *J*(CH,OH) = 5.4, J_{gem} = 10.4 (CH_2O); 3.33 dd, 1 H, *J*(CH,OH) = 4.8 and 3.58 dd, 1 H, *J*(CH,OH) = 4.2, J_{gem} = 10.6 (CH_2O); 4.30 brdd, 1 H, *J*(2,3) = 6.0, *J*(2,OH) = 4.6 (H-2); 4.57 brd, 1 H (H-3); 4.58 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 4.61 t, 1 H, *J*(OH,CH_2) = 4.6 (CH_2O**H**); 4.72 d, 1 H (2-OH); 7.75 brs, 1 H (NH); 8.01 s, 1 H and 8.21 s, 1 H (H-2′, H-8′). ^{13}C NMR: 6.65, 2 C (CH_2); 24.13 (NCH); 33.67 (C-7); 35.82 (C-5); 42.33 (C-4); 45.44 (C-6); 48.23 (C-1); 59.73 (C-3); 62.39 (OCH_2); 64.97 (OCH_2); 69.60 (C-2); 118.49 (C-5′); 140.10 (C-8′); 149.92 (C-4′); 152.05 (C-2′); 155.55 (C-6′).

(1R,2S*,3S*,4S*)-3-[6-(Cyclopropylamino)-9H-purin-9-yl]-5,5-bis(hydroxymethyl)bicyclo-[2.2.1]heptan-2-ol* (**24c**): Chromatography of the residue on a silica gel column in ethyl acetate–acetone–ethanol–water (95:15:10:8) and crystallization from methanol–ether gave 153 mg (86%) of **24c**, m.p. 157.5–160 °C. For $C_{17}H_{23}N_5O_3 \cdot 0.5H_2O$ (354.4) calculated: 57.61% C, 6.83% H, 19.76% N; found: 57.74% C, 6.82% H, 19.60% N. FAB MS, *m/z* (rel.%): 346 (100) [M + H], 176 (36). ^{1}H NMR: 0.61 m, 2 H, 0.72 m, 2 H, and 3.05 m, 1 H

(cyclopropyl); 1.17 ddd, 1 H, *J*(6b,1) = 4.4, *J*(6b,2) = 1.0, J_{gem} = 12.8 (H-6b); 1.43 dd, 1 H, *J*(6a,7b) = 2.0 (H-6a); 1.65 brdt, 1 H, *J*(7a,1) ≈ *J*(7a,4) = 1.2, *J*(7a,3) = 2.6, J_{gem} = 10.6 (H-7a); 1.79 dm, 1 H (H-7b); 2.09 m, 1 H (H-4); 2.30 brtq, 1 H, *J*(1,2) = 4.2, *J*(1,4) ≈ *J*(1,7) = 1.2 (H-1); 3.26 dd, 1 H, *J*(CH,OH) = 5.3 and 3.46 dd, 1 H, *J*(CH,OH) = 5.5, J_{gem} = 10.5 (CH_2O); 3.69 dd, 1 H, *J*(CH,OH) = 4.6 and 3.77 dd, 1 H, *J*(CH,OH) = 6.1, J_{gem} = 11.0 (CH_2O); 4.46 brt, 1 H, *J*(3,2) = 2.8 (H-3); 4.52 dd,1 H (CH_2O**H**); 4.53 t, 1 H, *J*(CH_2,OH) = 5.4 (CH_2O**H**); 4.56 brq, 1 H, *J*(2,4) = 1.0, *J*(2,OH) = 3.9 (H-2); 5.20 d, 1 H (2-OH); 7.89 brs, 1 H (NH); 8.24 brs, 1 H and 8.33 s, 1 H (H-2′, H-8′). ^{13}C NMR: 6.58, 2 C (CH_2); 25.00 (NCH); 26.73 (C-6); 33.41 (C-7); 42.39 (C-1); 47.19 (C-4); 47.44 (C-5); 61.42 (C-3); 62.08 (CH_2O); 64.46 (CH_2O); 76.83 (C-2); 119.62 (C-5′); 139.01 (C-8′); 149.34 (C-4′); 152.34 (C-2′); 155.77 (C-6′).

Ethyl *N*-((2*E*)-3-Ethoxymethacryloyl)carbamate (**26**)

1-Ethoxyprop-1-ene (8.85 ml, 80 mmol) in 1,4-dioxane (40 ml) was added over 20 min to a stirred solution of chlorocarbonyl isocyanate (4.8 ml, 60 mmol) in 1,4-dioxane (55 ml) at 10 °C. The mixture was stirred for 20 min, triethylamine (8.4 ml, 60 mmol) in 1,4-dioxane (60 ml) was then added over 45 min and stirring was continued for 15 min. Anhydrous ethanol (4.3 ml, 75 mmol) was then added dropwise over 15 min followed by dioxane (120 ml) over 15 min. The mixture was stirred at 15 °C for 20 min, the solid was filtered off, washed with 1,4-dioxane (40 ml) and the combined filtrates were concentrated to 20 ml. The residue was diluted with petroleum ether (20 ml) and set aside at 5 °C for 1 h. The crystalline product was filtered off and washed with petroleum ether–1,4-dioxane (5:1, 6 ml). 8.2 g (68%) of **26** was obtained, m.p. 114–116 °C. For $C_9H_{15}NO_4$ (201.2) calculated: 53.72% C, 7.51% H, 6.96% N; found: 53.54% C, 7.55% H, 6.70% N. FAB MS, *m/z* (rel.%): 202 (100) [M + H], 113 (42), 102 (17), 85 (14). ^{1}H NMR: 1.22 t, 3 H and 1.25 t, 3 H, *J*(CH_3,CH_2) = 7.1 (2 × CH_3); 1.59 s, 3 H (2-CH_3); 4.05 q, 2 H and 4.09 q, 2 H (2 × CH_2); 7.44 s, 1 H (H-3); 10.05 s, 1 H (NH). ^{13}C NMR: 9.28, 14.45, and 15.49 (3 × CH_3); 60.67 (CH_2O); 69.45 (CH_2O); 108.00 (C-2); 151.76 (C=O); 166.72, 2 C (2 × C=O).

Preparation of Thymine Analogues **28a**, **28b**, and **28c**

A solution of amine (187 mg, 1 mmol) and acylcarbamate **26** (201 mg, 1 mmol) in 1,4-dioxane (9 ml) was heated at 100 °C for 3 h. Dowex 50 (H^+, 3 ml) was washed with 1,4-dioxane and then added to the mixture. The mixture was heated at 90 °C for 3 h, the resin was filtered off, washed with methanol and the collected filtrates were evaporated. The residue was crystallized from ethanol.

1-[(1R,2S*,3S*,4S*)-3-Hydroxy-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**28a**): Yield 142 mg (48%), m.p. 251–254 °C. For $C_{14}H_{20}N_2O_5$ (296.3) calculated: 56.75% C, 6.80% H, 9.45% N; found: 56.55% C, 6.79% H, 9.22% N. FAB MS, *m/z* (rel.%): 297 (100) [M + H], 279 (35). ^{1}H NMR: 0.80 dd, 1 H, *J*(6b′,7a′) = 2.2, J_{gem} = 13.7 (H-6b′); 1.12 ddd, 1 H, *J*(6a′,1′) = 4.6, *J*(6a′,2′) = 1.2 (H-6a′); 1.60 brdq, 1 H, *J*(7b′,1′) ≈ *J*(7b′,4′) = 1.6, *J*(7b′,3′) = 2.0, J_{gem} = 10.5 (H-7b′); 1.68 dm, 1 H (H-7a′); 1.79 d, 3 H, *J*(CH_3,6) = 1.0 (H-6); 1.99 m, 1 H (H-4′); 2.65 brtq, 1 H, *J*(1′,2′) = 4.2, *J*(1′,4′) ≈ *J*(1′,7a′) = 1.6 (H-1′); 3.20 dd, 1 H, *J*(CH,OH) = 5.3 and 3.38 dd, 1 H, *J*(CH,OH) = 5.5, J_{gem} = 10.5 (CH_2O); 3.24 dd, 1 H, *J*(CH,OH) = 5.1 and 3.53 dd, 1 H, *J*(CH,OH) = 4.3, J_{gem} = 10.7 (CH_2O); 3.82 m, 1 H (H-2′); 4.26 brdt, 1 H, *J*(3′,2′) = 2.0, *J*(3′,OH) = 3.5 (H-3′); 4.54 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.60 brt, 1 H, *J*(OH,CH_2) = 4.7 (CH_2O**H**); 4.65 d, 1 H (3′-OH); 7.57 brq, 1 H (H-6);

11.30 s, 1 H (NH). ^{13}C NMR: 12.32 (CH_3); 27.49 (C-6′); 32.73 (C-7′); 39.78 (C-1′); 46.11 (C-5′); 48.16 (C-4′); 62.36 (CH_2O); 64.91 (CH_2O); 70.26 (C-2′); 71.47 (C-3′); 107.94 (C-5); 139.67 (C-6); 152.30 (C-2); 164.02 (C-4).

1-[(1R,2R*,3S*,4S*)-3-Hydroxy-5,5-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**28b**): Yield 105 mg (34%), m.p. 200–202 °C. For $C_{14}H_{20}N_2O_5 \cdot 0.5H_2O$ (305.3) calculated: 55.07% C, 6.93% H, 9.17% N; found: 55.27% C, 6.96% H, 8.99% N. FAB MS, *m/z* (rel.%): 297 (100) [M + H], 279 (12). ^{1}H NMR: 0.83 dd, 1 H, *J*(6b′,7a′) = 2.7, J_{gem} = 12.7 (H-6b′); 1.32 dd, 1 H, *J*(6a′,1′) = 4.4 (H-6a′); 1.45 dpent, *J*(7b′,1′) ≈ *J*(7b′,2′) ≈ *J*(7b′,3′) ≈ *J*(7b′,4′) = 1.5, J_{gem} = 10.5 (H-7b′); 1.76 d, 3 H, *J*(CH_3,6) = 1.0 (CH_3); 1.90 dm, 1 H (H-7a′); 1.93 m, 1 H (H-4′); 2.26 brdq, 1 H, *J*(1′,4′) ≈ *J*(1′,7a′) = 1.5 (H-1′); 3.19 dd, 1 H, *J*(CH,OH) = 5.2 and 3.43 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.5 (CH_2O); 3.22 dd, 1 H, *J*(CH,OH) = 5.0 and 3.48 dd, 1 H, *J*(CH,OH) = 4.3, J_{gem} = 10.5 (CH_2O); 4.18 m, 2 H (H-2′, H-3′); 4.53 t, 1 H, *J*(OH,CH_2) = 5.4 (CH_2O**H**); 4.54 brt, 1 H, *J*(OH,CH_2) = 4.6 (CH_2O**H**); 7.23 brq, 1 H (H-6); 11.11 s, 1 H (NH). ^{13}C NMR: 12.61 (CH_3); 33.91 (C-7′); 36.66 (C-6′); 39.86 (C-1′); 45.69 (C-5′); 47.39 (C-4′); 61.29 (C-2′); 62.08 (CH_2O); 64.90 (CH_2O); 69.83 (C-3′); 107.04 (C-5); 139.34 (C-6); 151.83 (C-2); 164.31 (C-4).

1-[(1R,2R*,3R*,4S*)-3-Hydroxy-6,6-bis(hydroxymethyl)bicyclo[2.2.1]heptan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione* (**28c**): Yield 149 mg (50%), m.p. 223–226 °C. For $C_{14}H_{20}N_2O_5$ (296.3) calculated: 56.75% C, 6.80% H, 9.45% N; found: 56.65% C, 6.96% H, 9.19% N. FAB MS, *m/z* (rel.%): 297 (100) [M + H], 127 (92). ^{1}H NMR: 1.14 ddd, 1 H, *J*(5b′,3′) = 0.8, *J*(5b′,4′) = 4.5, J_{gem} = 12.8 (H-5b′); 1.30 dd, 1 H, *J*(5a′,7b′) = 1.7 (H-5a′); 1.45 dm, 1 H, J_{gem} = 10.6 (H-7b′); 1.59 dm, 1 H (H-7a′); 1.80 d, 3 H, *J*(CH_3,6) = 1.1; 2.01 m, 1 H (H-1′); 2.23 brtq, 1 H, *J*(4′,1′) ≈ *J*(4′,7a′) ≈ *J*(4′,7b′) = 1.6, *J*(4′,3′) = 4.0 (H-4′); 3.23 dd, 1 H, *J*(CH,OH) = 5.4 and 3.48 dd, 1 H, *J*(CH,OH) = 5.6, J_{gem} = 10.4 (CH_2O); 3.54 dd, 1 H, *J*(CH,OH) = 4.4 and 3.65 dd, 1 H, *J*(CH,OH) = 6.9, J_{gem} = 11.1 (CH_2O); 4.10 brt, 1 H, *J*(2′,1′) = 1.0, *J*(2′,3′) = 2.7, *J*(2′,7a′) = 2.0 (H-2′); 4.13 brq, 1 H, *J*(3′,1′) = 1.0, *J*(3′,OH) = 3.3 (H-3′); 4.28 dd, 1 H, *J*(OH,CH_2) = 4.4 and 6.9 (CH_2O**H**); 4.52 t, 1 H, *J*(OH,CH_2) = 5.5 (CH_2O**H**); 4.71 d, 1 H (2′-OH); 1.68 brq, 1 H (H-6); 11.39 s, 1 H (NH). ^{13}C NMR: 12.24 (CH_3); 26.84 (C-5′); 33.24 (C-7′); 42.07 (C-4′); 45.01 (C-1′); 47.82 (C-6′); 61.83 (CH_2O); 63.07 (C-2′); 64.29 (CH_2O); 76.92 (C-3′); 108.65 (C-5); 137.72 (C-6); 152.45 (C-2); 163.84 (C-4).

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