

Enantiomeric Synthesis of L- (or 1*S*,2*R*,3*S*,5*S*)-Bicarbo-cyclic[3.1.0] Nucleosides[§]

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Abstract: The total synthesis of L- (or 1*S*,2*R*,3*S*,5*S*)-bicarbocyclic nucleosides (**8–15**) has been accomplished. The key intermediate **3** was synthesized in two steps from the known chiral compound **1** through a stereoselective cyclopropanation under Furukawa conditions and its X-ray structure has been determined. The derivative **4** was utilized to obtain thymine derivative (**8**). Amino exocyclic pyrimidine (**9–12**) and purine (**13–15**) bicarbocyclic L-nucleosides were obtained from the (1*S*,2*R*,3*S*,5*S*)-2-(3-aminobicyclo[3.1.0]hex-2-yl)ethanol (**7**). © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

During the most recent period, the pharmaceutical importance of carbocyclic nucleoside analogues has prompted the design and syntheses of many examples of these compounds showing activities against HIV, HBV, HSV types 1 and 2.^{1–3} Among them, 6-(cyclopropylamino)purine analogue of carbovir⁴, 1592U89 (abacavir), is the most interesting compound, currently undergoing clinical trials as anti-HIV agents. Recently, a number of L nucleosides have been synthesized, among which (–)-(2′*R*,5′*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytidine (3TC),⁵ β-L-2′,3′-dideoxy-5-fluorocytidine (L-FddC)⁶ and β-L-2′-fluoro-5-methyl-1-(arabinofuranosyl)uracil (L-FMAU)⁷ have shown to be the most promising as antiviral agents. Finally, interest in the influence of sugar conformation on biological activity has prompted several studies in which small rings are fused onto the sugar.^{8–10} As part of our drug discovery program, we have previously reported the enantiomeric synthesis of carbocyclic L-nucleosides.^{11–12} A preliminary account of L-bicarbo-cyclic nucleosides has recently been reported by us.¹³ We now report herein a full account of the synthesis of purine, pyrimidine and exocyclic pyrimidine bicarbocyclic L-nucleosides. The choice of the exocyclic pyrimidine nucleosides was based on the biological properties of natural parent compound, clitocine, isolated from the mushroom *Clytocybe inversa*¹⁴ and synthesized by several working groups.¹⁵ More, the exocyclic pyrimidine nucleosides have been used as a template for antiviral compounds and purine analogues.¹⁶

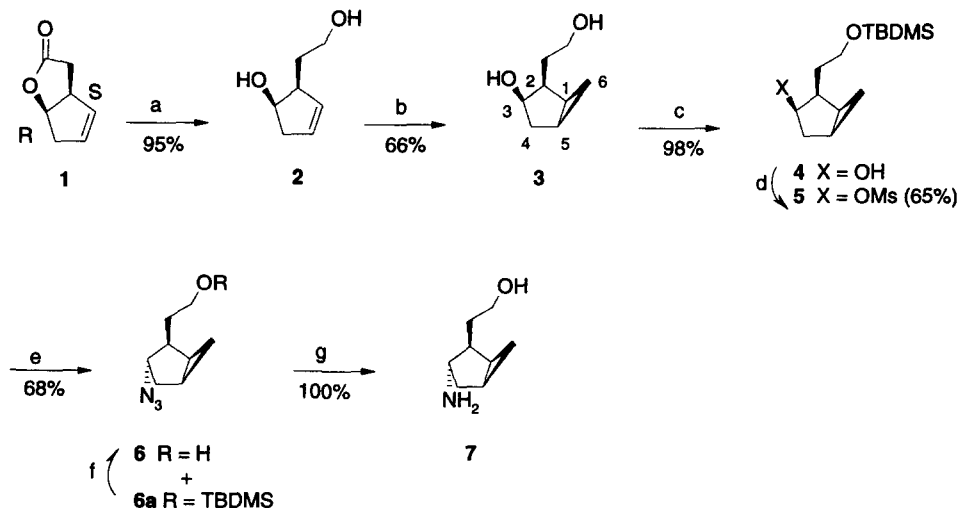
Result and Discussion

Compound **3** was prepared from (1*R*,5*S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one (**1**) using a modified version of Simmons-Smith reaction^{17a,b} (Scheme 1). One of the most useful features of the Furukawa reaction^{17b} is the

[§] This paper is dedicated to the memory of Professor Gordon Shaw

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diastereoselective delivery of the incoming methylene group. The only (1*S*,2*R*,3*R*,5*S*)-**3** was isolated with 100% diastereoisomeric excess in 63% yield (from **1**).



Reagents: (a) DIBAL-H, THF, -78 °C; (b) ZnEt₂, CH₂I₂, CH₂Cl₂, 0 °C; (c) TBDMSCl, imidazole, THF, 0 °C; (d) MsCl, pyridine, 50 °C; (e) NaN₃, DMF, 70 °C; (f) nBu₄NF/THF, rt; (g) H₂, 10% Pd/C, MeOH.

Scheme 1

The structure and stereochemistry of the bicyclic derivative **3** was confirmed by NMR as well as X-ray crystallography. Crystallization from dichloromethane/pentane yielded white crystals suitable for X-ray analysis. An ORTEP drawing of **3** is shown in Figure 1. No intramolecular hydrogen bonding was observed.

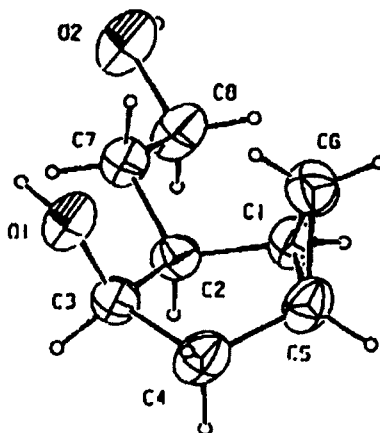
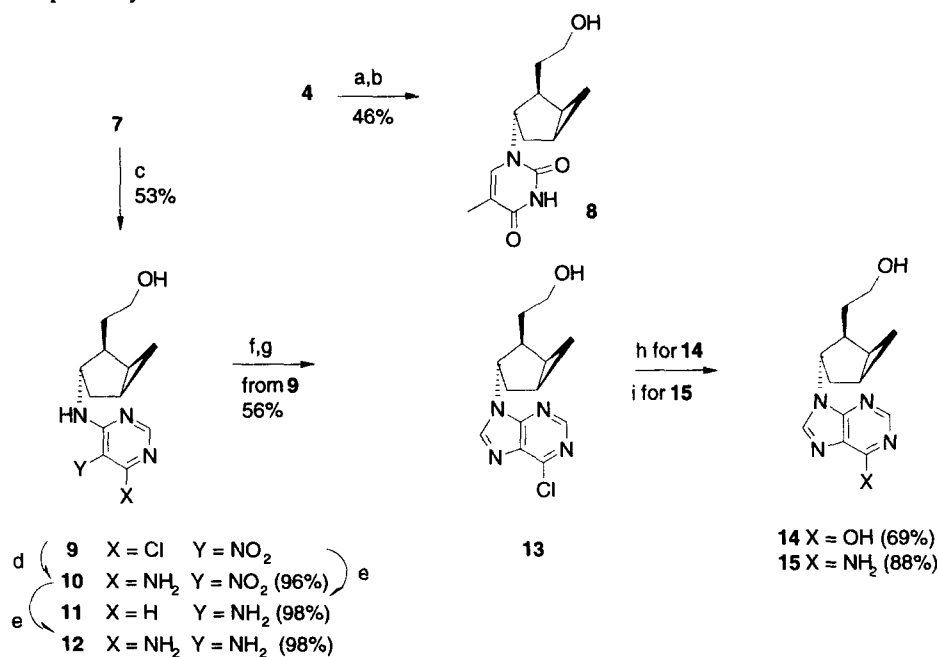


Fig 1. ORTEP Drawing of compound **3**.

Thus, the alcohol **3** was protected with *t*-butyldimethylsilyl group to yield **4** in quantitative yield. The key intermediate, bicyclo[3.1.0]hexylamine (**7**) for the synthesis of purine and exocyclic pyrimidine nucleosides, was obtained in two steps from protected bicyclo[3.1.0]hexyldiol (**4**). Thus, the silylated alcohol **4** was converted to a mixture of **6** and **6a** by the treatment of mesyl chloride followed by NaN₃. The mixture was

treated with a solution of $n\text{Bu}_4\text{NF}/\text{MeOH}$ and the bicyclo[3.1.0]hexylazide (**6**) was reduced by hydrogenation to provide the amine **7** (44% from **4**). Thymidine analogue **8** was obtained by *N*-alkylation of thymine with the silylated alcohol **4** under Mitsunobu¹⁸ conditions and afforded after deprotection the desired nucleoside **8** in 46% yield (Scheme 2). The structure of **8** was firmly established based on UV and NMR data. The UV max at 272 nm is typical of N^1 -alkylation with methyluracil; the signal for CH-N-moiety is found in the ^{13}C -NMR spectrum at $\delta = 42.16$ ppm; finally, the ^1H -NMR signal at $\delta = 11.24$ ppm ($\text{DMSO}-d_6$, D_2O exchangeable) can be assigned to the N^3 -proton. In order to confirm the structure of the isolated **8**, an analytical sample was successfully obtained by Mitsunobu reaction of **4** with N^3 -benzoylthymine¹⁹ and subsequent deprotections. For the exocyclic pyrimidine analogues, the reaction of **7** with 4,6-dichloro-5-nitropyrimidine gave **9** in 53% yield. The treatment of **9** with methanolic ammonia or hydrogenolysis gave the derivatives **10** and **11** in 96% and 98% yield, respectively. Further reduction of the nitro group of **10** afforded the diamino **12** in 98% yield. Derivatives (**9**–**12**) must be regarded as nucleosides derivatives of the natural exocyclic amino nucleoside, clitocine.^{14–15} Finally, purine nucleosides were synthesized by the reported methods²⁰ from **8**. The selective reduction of the nitro group of **9** followed by cyclization with triethylorthoformate gave the 6-chloropurine derivative (**13**) in 56% yield. The treatment of **13** with mercaptoethanol and sodium methoxide or with ammonia in refluxing methanol gave the protected hypoxanthine (**14**) or adenine (**15**) derivatives in 69% and 88% yield respectively.



Reagents: (a) thymine, PPh_3 , DEAD, THF; (b) $n\text{Bu}_4\text{NF}/\text{THF}$, rt; (c) 4,6-dichloro-5-nitropyrimidine, Et_3N , CH_2Cl_2 , 0 °C; (d) MeOH/NH_3 , rt; (e) H_2 , Pd/C, MeOH; (f) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, EtOH, 50 °C; (g) triethylorthoformate, HCl 12M; (h) $\text{HSCH}_2\text{CH}_2\text{OH}$, NaOCH_3 , MeOH, reflux; (i) NH_3 , MeOH, 90 °C.

Scheme 2

EXPERIMENTAL

General

Commercially available chemicals and solvents were reagent grade and used as received. Melting points (mp) were determined on a Büchi (Tottoli) and were uncorrected. All reactions were monitored by thin-layer chromatography carried out on silica gel alumina plates (0.25 mm). Silica gel chromatography was performed on silica gel 60 (230–400 mesh) using the indicated solvents. Proton NMR spectra were recorded on a Bruker AVANCE DPX 250 Fourier Transform spectrometer for 250 MHz, in the indicated solvents; signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were recorded on Perkin-Elmer SCIEX API-300 (heated nebulizer) spectrometer. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the CNRS, Vernaison, and are within $\pm 0.4\%$ of the theoretical values.

(1*S*,2*R*)-2-(2-Hydroxycyclopent-4-enyl)ethanol (2). A solution of (1*R*,5*S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** (1 g, 8.05 mmol) dissolved in dry THF (25 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. The lactone **1** was reduced by slowly adding a 1M solution of DIBAL-H in THF (24.1 mL, 24.1 mmol). The reaction mixture was allowed to warm to room temperature for 6 h and quenched by slowly adding MeOH (20 mL). The mixture was then neutralized with 1M HCl and the solvent was removed under reduced pressure. The residual solid was filtered, washed with EtOAc (4 x 100 mL), and the combined filtrate was evaporated *in vacuo* to give a residue which was purified by column chromatography (silica gel- $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to give **2** as a colorless oil (982 mg, 95%). $[\alpha]_{\text{D}}^{20} +71.0\text{ }^{\circ}$ (c 1, MeOH); ^1H NMR (CDCl_3) δ 5.70 (m, 1H), 5.55 (m, 1H), 4.50 (td, 1H, $J = 6.3\text{ Hz}$, 2.5 Hz), 4.00 (broad s, D_2O -exchangeable), 3.76 (m, 1H), 3.67 (m, 1H), 2.69 (m, 1H), 2.60–2.31 (m, 2H), 1.80 (m, 2H). Its physical data were identical to the known compound.²¹

(1*S*,2*R*,3*R*,5*S*)-2-(3-Hydroxybicyclo[3.1.0]hex-2-yl)ethanol (3). To a 10 mL of CH_2Cl_2 at $0\text{ }^{\circ}\text{C}$ was added ZnEt_2 (1 M in Hexane, 1.04 mL, 1.04 mmol) and CH_2I_2 (0.17 mL, 2.09 mmol) and maintained for 10 min. To this solution was added **2** (67 mg, 0.53 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at $0\text{ }^{\circ}\text{C}$ and quenched with saturated NH_4Cl (20 mL). After the organic layer was separated, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO_4 , filtered and evaporated. The crude product was purified by column chromatography (silica gel- hexane/EtOAc, 1:1) to give **3** (49 mg, 66%) as a white solid which recrystallize in $\text{CH}_2\text{Cl}_2/\text{pentane}$. mp $74\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} +11.5$ (c 11, CHCl_3); ^1H -NMR (CDCl_3) δ 4.20 (t, 1H, $J = 6.36\text{ Hz}$), 3.89 (m, 1H), 3.70 (td, 1H, $J = 9.78\text{ Hz}$, 3.2 Hz), 2.9 (broad s, D_2O -exchangeable), 2.23 (m, 2H), 1.86 (m, 3H), 1.26 (m, 2H), 0.67 (m, 1H), 0.32 (m, 1H); MS: m/z 143 ($\text{M}^+ + 1$); Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.92. Found : C, 67.78; H, 10.03.

(1*S*,2*R*,3*R*,5*S*)-2-(3-Hydroxybicyclo[3.1.0]hex-2-yl) ethanol *tert*-butyldimethylsilane ether (4). A solution of **3** (196 mg, 1.4 mmol), *tert*-butyldimethylsilyl chloride (311 mg, 2.1 mmol), imidazole (281 mg, 4.0 mmol) in anhydrous THF (10 mL) was stirred at $0\text{ }^{\circ}\text{C}$ for 2 h. The reaction mixture was washed successively with sat. aqueous NaHCO_3 (15 mL) and brine to neutrality. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel- hexane/EtOAc, 9:1 containing 1% Et_3N) to give **4** as a colorless oil (346 mg, 98%). $[\alpha]_{\text{D}}^{20} +17.4$ (c 13, CHCl_3); ^1H -NMR (CDCl_3) δ 4.15 (t, 1H, $J = 6.4\text{ Hz}$), 3.85 (m, 1H), 3.64 (td, 1H, $J = 10.3\text{ Hz}$, 2.4 Hz), 3.48 (s

broad, 1H), 2.18 (m, 2H), 1.84 (m, 3H), 1.22 (m, 2H), 0.90 (s, 9H), 0.67 (q, 1H, $J = 3.9$ Hz), 0.27 (m, 1H), 0.08 (s, 6H); MS: m/z 257 ($M^+ + 1$); Anal. Calcd for : $C_{14}H_{28}O_2$ Si . 0.15 AcOEt : C, 63.95; H, 10.73. Found : C, 64.00; H, 10.36.

(1S,2R,3R,5S)-2-(3-[(Methylsulfonyl)oxy]bicyclo[3.1.0]hex-2-yl) ethanol *tert*-butyl dimethyl-silane ether (5). A solution of **4** (330 mg, 1.3 mmol) in anhydrous pyridine (10 mL) was stirred at 0 °C. To this cooling mixture, methanesulfonyl chloride (150 μ L, 1.93 mmol) was added dropwise and stirring was continued for 2 h. The reaction mixture was washed successively with sat. aqueous $NaHCO_3$ (10 mL) and brine to neutrality. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by column chromatography (silica gel- hexane/EtOAc, 8:2 containing 1% Et_3N) to give **5** as a colorless syrup (282 mg, 65%). $[\alpha]_D^{20} + 8.6$ (c 8, $CHCl_3$); 1H -NMR ($CDCl_3$) δ 5.40 (m, 1H), 3.75 (m, 2H), 2.94 (m, 1H), 2.67 (m, 1H), 2.23 (m, 2H), 1.74 (m, 2H), 1.36 (m, 2H), 0.89 (s, 9H), 0.40 (m, 2H), 0.08 (s, 6H); MS: m/z 336 ($M^+ + 1$). The product was subjected to the next reaction without further purification.

(1S,2R,3S,5S)-2-(3-Azidobicyclo[3.1.0]hex-2-yl)ethanol (6). A solution of **5** (270 mg, 0.81 mmol) and NaN_3 (787 mg, 12.1 mmol) in DMF (10 mL) was stirred at 70 °C for 5 h. After cooling, the mixture was diluted with EtOAc (20 mL) and washed with brine (20 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a mixture of **6** and **6a**. Without purification, this mixture was dissolved in anhydrous THF (5 mL) and stirred for 6 h with a nBu_4NF/THF 1M (807 μ L, 0.8 mmol). The mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine (20 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained residue was purified by column chromatography (silica gel- hexane/EtOAc, 80:20) to yield **6** as a colorless oil (92 mg, 68%). $[\alpha]_D^{20} + 81.3$ (c 17, $CHCl_3$); IR (NaCl) 2096 cm^{-1} 1H -NMR ($CDCl_3$) δ 3.80 (m, 2H), 3.00 (m, 1H), 2.40–1.10 (m, 5H), 0.90 (m, 2H), 0.34 (m, 1H), 0.15 (m, 1H); MS: m/z 190 ($M + Na$). The product was subjected to the next reaction without further purification.

(1S,2R,3S,5S)-2-(3-Aminobicyclo[3.1.0]hex-2-yl)ethanol (7). The azido derivative **6** (37 mg, 0.22 mmol) was dissolved in methanol (10 mL) and then introduced to a suspension of 10% Pd/C (5 mg) in methanol (6 mL). The mixture was hydrogenated in a Parr shaker at 25 psi pressure for 5 h and then filtered through celite to remove the catalyst. The solvent was evaporated to dryness to leave a residue which was purified by column chromatography (silica gel- $CH_2Cl_2/MeOH$, 9:1) to yield **7** as a white gum (32 mg, 98%). $[\alpha]_D^{20} + 55.0$ (c 16, $CHCl_3$); 1H NMR ($CDCl_3$) δ 3.54 (m, 2H), 2.46 (m, 1H), 2.16 (m, 1H), 2.00–1.50 (m, 4H), 1.23 (m, 2H), 0.20 (m, 2H); MS : m/z 142 ($M^+ + 1$).

(1S,2R,3S,5S)-2-[3-(thyminy)l)bicyclo[3.1.0]hex-2-yl]ethanol (8). To a suspension of compound **4** (80 mg, 0.31 mmol), triphenylphosphine (167 mg, 0.64 mmol) and dried thymine (81 mg, 0.64 mmol) in dried THF (3 mL) was slowly added a solution of diethyl azodicarboxylate (110 mg, 0.64 mmol) in THF (1 mL). The mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was treated with a nBu_4NF/THF 1M (400 μ L, 0.4 mmol) in THF (5 mL). The mixture was stirred at rt for 4 h, evaporated to dryness and purified by column chromatography (silica gel- $CH_2Cl_2/MeOH$, 9:1) to yield

8 as a white gum (36 mg, 46%). UV(MeOH) λ_{max} 272 nm. ^1H NMR (DMSO-*d*₆) δ 11.24 (s broad, 1H, D₂O exchangeable), 7.49 (s, 1H), 4.62 (t, 1H, D₂O exchangeable), 3.83–3.52 (m, 3H), 2.50 (m, 2H), 1.97–1.50 (m, 10H); MS: m/z 257 (M^+ +1). Anal. Calcd for C₁₃H₁₈N₂O₃: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.17; H, 7.13; N, 11.08.

(1*S*,2*R*,3*S*,5*S*)-2-[3-(6-Chloro-5-nitropyrimidin-4-ylamino)bicyclo[3.1.0]hex-2-yl]ethanol (9). The intermediate **7** (84 mg, 0.60 mmol) dissolved in anhydrous CH₂Cl₂ (10 mL) was introduced to a suspension of 4,6-dichloro-5-nitropyrimidine (127 mg, 0.65 mmol) and Et₃N (125 μ L, 0.89 mmol) in anhydrous CH₂Cl₂ (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. After filtration over celite, the filtrate was evaporated to dryness under reduced pressure without heating. The obtained residue was purified by column chromatography (silica gel- hexane/EtOAc, 7:3). The desired nucleoside **9** was isolated as a yellow oil (106 mg, 60%). $[\alpha]_{\text{D}}^{20}$ +86.0 (c 10, MeOH); UV (MeOH) λ_{max} 351 nm; ^1H -NMR (MeOD-*d*₄) δ 8.30 (s, 1H), 4.10 (m, 1H), 3.67 (m, 2H), 2.30 (m, 2H), 1.76 (m, 2H), 1.65 (m, 1H), 1.35 (m, 2H), 0.35 (m, 2H). MS: m/z 298 (M^+ +1); Anal. Calcd for C₁₂H₁₅ClN₄O₃ · 0.5 EtOAc: C, 49.05; H, 5.58; N, 17.32. Found: C, 49.01; H, 5.50; N, 17.58.

(1*S*,2*R*,3*S*,5*S*)-2-[3-(6-Amino-5-nitropyrimidin-4-ylamino)bicyclo[3.1.0]hex-2-yl] ethanol (10). A solution of the intermediate **9** (51 mg, 0.17 mmol) in saturated NH₃/MeOH (10 mL) was stirred at room temperature for 1 h. The solution was concentrated under reduced pressure and the obtained residue was purified by column chromatography (silica gel- CH₂Cl₂/MeOH, 9:1) to give **10** as a yellow solid (46 mg, 96%). mp 166 °C; $[\alpha]_{\text{D}}^{20}$ +134.0 (c 6, MeOH); UV (MeOH) λ_{max} 347 nm; ^1H -NMR (MeOD-*d*₄) δ 7.93 (s, 1H), 4.11 (m, 1H), 3.70 (m, 2H), 2.33 (m, 2H), 1.77 (m, 2H), 1.63 (m, 1H), 1.48–1.37 (m, 2H), 0.36 (m, 2H). MS: m/z 280 (M^+ +1); Anal. Calcd for C₁₂H₁₇N₅O₃: C, 51.60; H, 6.13; N, 25.07. Found: C, 51.48; H, 6.11; N, 26.97.

(1*S*,2*R*,3*S*,5*S*)-2-[3-(5-Aminopyrimidin-4-ylamino)bicyclo[3.1.0]hex-2-yl]ethanol (11). The 6-chloro-pyrimidine alcohol **9** (48 mg, 0.16 mmol) was dissolved in methanol (10 mL) and then introduced to a suspension of 10% Pd/C (5 mg) in methanol (5 mL). The mixture was hydrogenated in a Parr shaker at 25 psi pressure for 5 h and then filtered through celite to remove the catalyst. The solvent was evaporated to dryness to leave a residue which was purified by column chromatography (silica gel- CH₂Cl₂/MeOH, 9:1) to yield **11** (38 mg, 98%) as a brown oil. $[\alpha]_{\text{D}}^{20}$ +60.0 (c 9, MeOH); UV (MeOH) λ_{max} 350 nm; ^1H -NMR (MeOD-*d*₄) δ 8.10 (s, 1H), 7.52 (s, 1H), 4.06 (dd, 1H, J = 9 Hz, 3Hz), 3.70 (m, 2H), 2.35 (m, 2H), 1.77 (m, 2H), 1.61 (m, 1H), 1.48–1.37 (m, 2H), 0.36 (m, 2H). MS: m/z 235 (M^+ +1); Anal. Calcd for C₁₂H₁₇N₄O: C, 61.78; H, 7.34; N, 24.01. Found: C, 61.69; H, 7.28; N, 23.97.

(1*S*,2*R*,3*S*,5*S*)-2-[3-(6-Amino-5-aminopyrimidin-4-ylamino)bicyclo[3.1.0]hex-2-yl] ethanol (12). The 6-amino-5-nitropyrimidine alcohol **9** (65 mg, 0.23 mmol) was dissolved in methanol (10 mL) and then introduced to a suspension of 10% Pd/C (10 mg) in methanol (5 mL). The mixture was hydrogenated in a Parr shaker at 25 psi pressure for 3 h and then filtered through celite to remove the catalyst. The solvent was evaporated to dryness to leave a residue which was purified by column chromatography (silica gel- CH₂Cl₂/MeOH, 9:1) to yield **12** (58 mg, 97%) as a brown gum. $[\alpha]_{\text{D}}^{20}$ +56.0 (c 7, MeOH); UV (MeOH) λ_{max} 288 nm; ^1H -NMR (MeOD-*d*₄) δ 7.70 (s, 1H), 3.73–3.50 (m, 3H), 2.23 (m, 2H), 1.75–1.52 (m, 7H), 0.33 (m,

2H). MS: m/z 250 ($M^+ + 1$); Anal. Calcd for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09. Found: C, 57.79; H, 7.64; N, 27.92.

(1*S*,2*R*,3*S*,5*S*)-2-[3-(6-Chloro-purin-9-yl)bicyclo[3.1.0]hex-2-yl] ethanol (13). A solution **9** (100 mg, 0.34 mmol) and of $SnCl_2 \cdot 2H_2O$ (380 mg, 1.68 mmol) in EtOH (20 mL) was refluxed for 30 min. The obtained mixture was cooled and poured into cooled water (50 mL). The resulting suspension was neutralized by a saturated $NaHCO_3$ aqueous. After extraction with EtOAc (3 x 60 mL), the organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained compound [(1*S*,2*R*,3*S*,5*S*)-2-[3-(5,6-diamino-pyrimidin-4-ylamino)bicyclo[3.1.0]hex-2-yl] ethanol] was used without any further purification. A solution of the crude intermediate and 12M HCl (100 mL) in triethyl orthoformate (6 mL) was stirred at rt for 5 h. The obtained mixture was cooled, poured into cooled water, neutralized with aqueous saturated $NaHCO_3$ aqueous solution. After extraction with EtOAc (4 x 30 mL), the organic phase was dried over $MgSO_4$. The solvent was evaporated to dryness to leave a residue which was purified by column chromatography (silica gel- $CH_2Cl_2/MeOH$, 9:1) to yield **13** (52 mg, 56% from **9**) as a brown oil. UV (MeOH) λ_{max} 265 nm; 1H -NMR (MeOD- d_4) δ 8.73 (s, 1H), 8.17 (s, 1H), 3.80–3.50 (m, 3H), 2.50 (m, 2H), 1.95–1.45 (m, 7H). MS: m/z 279 and 281 ($M^+ + 1$); Anal. Calcd for $C_{13}H_{15}ClN_4O$: C, 56.02; H, 5.43; N, 20.10. Found: C, 55.83; H, 5.31; N, 19.93.

(1*S*,2*R*,3*S*,5*S*)-2-[3-(6-Hydroxypurin-9-yl)bicyclo[3.1.0]hex-2-yl] ethanol (14). A mixture of 6-chloropurine analogue **13** (70 mg, 0.25 mmol), 2-mercaptoethanol (0.7 mL, 1.0 mmol) and NaOMe (50 mg, 1 mmol) in methanol (10 mL) was refluxed overnight. The mixture was then cooled, neutralized with glacial acetic acid and concentrated under reduced pressure. The obtained residue was purified by column chromatography (silica gel- $CH_2Cl_2/MeOH$, 9:1) to yield **14** (45 mg, 69 %). UV (MeOH) λ_{max} 250 nm; 1H -NMR (MeOD- d_4) δ 8.09 (s, 1H), 7.95 (s, 1H), 3.82–3.48 (m, 3H), 2.52 (m, 2H), 2.01–1.43 (m, 7H). MS: m/z 261 ($M^+ + 1$); Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.98; H, 6.19; N, 21.52. Found: C, 59.89; H, 6.07; N, 21.48.

(1*S*,2*R*,3*S*,5*S*)-2-[3-(6-Aminopurin-9-yl)bicyclo[3.1.0]hex-2-yl] ethanol (15). A mixture of 6-chloropurine analogue **13** (70 mg, 0.25 mmol) in sat. $NH_3/MeOH$ (15 mL) was refluxed in a steel bomb for 10 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel- $CH_2Cl_2/MeOH$, 9:1) to yield **15** (57 mg, 88 %) as a solid. UV (MeOH) λ_{max} 260.5 nm; 1H -NMR (MeOD- d_4) δ 8.20 (s, 1H), 8.12 (s, 1H), 3.80–3.50 (m, 3H), 2.50 (m, 2H), 2.01–1.45 (m, 7H). MS: m/z 260 ($M^+ + 1$); Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.12; H, 6.58; N, 26.89.

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