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Chemoenzymatic synthesis and antiviral evaluation of conformationally constrained and 3′-methyl-branched carbanucleosides using both enantiomers of the same building block

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Abstract—Starting from both enantiomers of a readily available building block, a straightforward enantioselective approach to constrained 3′-methyl-2′,3′-α-oxirane-fused and 3′-methyl-3′,4′-α-oxirane-fused carbanucleosides bearing different purine base analogues is described. The title compounds were evaluated as potential antiviral agents against important viruses. None of the new compounds had significant antiviral activity at a concentration of 100 μg/mL, which was the highest concentration tested.

1. Introduction

According to the concept of pseudorotational cycle,[1,2] the sugar moiety of nucleosides rapidly equilibrates in solution between two extreme forms of ring pucker close to a 2′-*exo*/3′-*endo*, the north (N), and the facing 2′-*endo*/3′-*exo*, the south (S), conformations. Preference for any of these specific conformations is determined by the interplay of interactions resulting from anomeric and *gauche* effects.[3–5] However, in the crystalline structure, only one of these two conformers is present and, moreover, when a nucleoside binds to its target enzyme, only the north (N) or south (S) range takes part in drug–receptor interactions.[6] Consequently, as the conformation in solution may be unlike that found in the crystalline state, any structure-biological activity correlation would be flawed unless the crystal and the solution conformation are the same. In this respect, it has been reported that an oxirane-fused or cyclopropane-fused ring can confer a remarkable rigidity to the sugar ring of nucleosides.[7–9]

Carbanucleosides are derivatives in which the endocyclic oxygen of the nucleoside sugar ring has been replaced by a methylene group.[10–14] These analogues display remarkable metabolic stability since they are unaffected by phosphorylases and hydrolases that cleave the glycosidic bond of natural nucleosides.[15–18] They are also recognized by the same enzymes that recognize normal nucleosides displaying, correspondingly, a wide range of biological properties.[19] However, removal of the furanose oxygen causes the cyclopentane ring to adopt an unusual 1′-*exo* conformation with respect to the characteristic conformations observed in the furanose moiety.[4,20] One of the strategies that can be used in carbocyclic nucleosides to regain the ring pucker characteristic of typical nucleosides is to construct them on a rigid cyclopropane-fused[21–28] or oxirane-fused[29–34][3.1.0]bicyclic scaffold. In our ongoing search for antiviral nucleoside analogues we have synthesized two series of constrained and alkyl-branched carbonucleosides built on a 6-oxabicyclo[3.1.0]hexane template.[35]

Since the oxabicyclo[3.1.0]hexane template is known to exist rigidly in a boat-like shape,[29] these synthesized derivatives are able to maintain identical conformation in the crystalline state and in solution and thereby help define the role of sugar puckering in nucleosides by stabilizing the active receptor bound conformation. In this respect, the aim of this article is to describe in a full paper the synthesis and antiviral evaluation of novel conformationally constrained α-2′,3′-oxirane-fused and α-3′,4′-oxirane-fused (neplanocin B scaffold)

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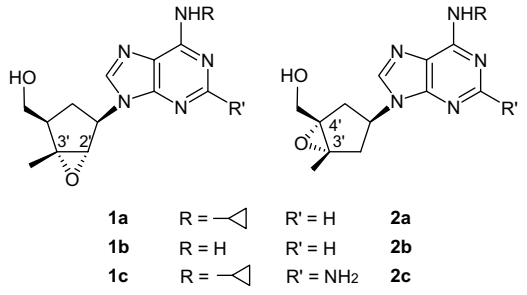


Figure 1. Structure of target compounds **1a**–**c** and **2a**–**c**.

carbanucleosides substituted at the 3′-C-position of the carbasugar ring with a methyl group (Fig. 1).

2. Results and discussion

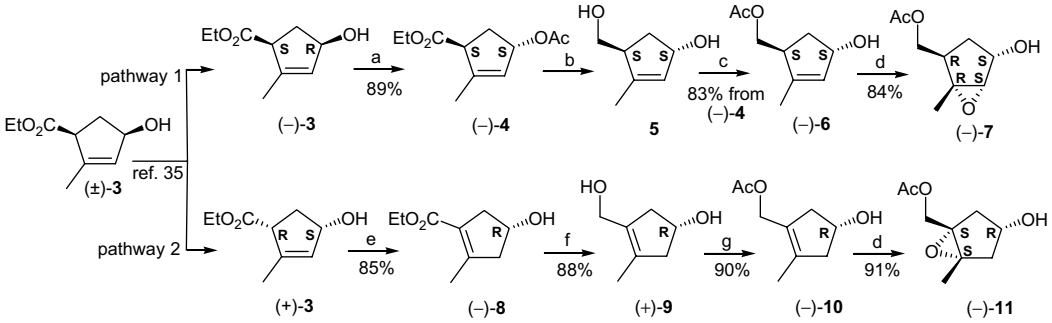
2.1. Synthesis

Both enantiomers of the same building block, ethyl *cis*-4-hydroxy-2-methylcyclopent-2-en-1-carboxylate, [**3**], easily obtained through enzymatic kinetic resolution of the racemic,[35] are the convenient entry points of our approach (Scheme 1). The inversion of the alcohol configuration of (−)-**3** (pathway 1) was efficiently accomplished using a Mitsunobu reaction.[36,37] Derivative (−)-**3** was treated with acetic acid in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine to give the corresponding inverted acetate (−)-**4** in 89% yield. Carboethoxy acetate (−)-**4** was readily converted to the diol **5** by exposure to lithium aluminum hydride, but attempts to acylate unequivocally the primary hydroxyl group under classical and convenient chemical conditions[38] failed, due to the unstability of alcohol **5**. This problem was solved by lipase-catalyzed monoacylation. In this case, biocatalysts are particulary attractive because of their chemo-, regio-, and stereoselectivity, and because enzyme-catalyzed reactions are carried out under mild conditions which minimize chemical problems with labile starting materials or products.[39] Screening experiments were made using five commercially available lipases: PPL (porcine pancreas, Fluka), CRL (*Candida rugosa* type VII, Sigma), RML (*Rhizomucor miehei*, Lipozyme RM IM, Novo Nordisk), PFL (*Pseudomonas fluorescens*, lipase AK, Amano Pharmaceutical), and CAL-B (*Candida antartica* B, Novozyme 435, Novo Nordisk). Effectively, exposure of crude **5** to PPL (porcine pancreas lipase) and vinyl acetate at room temperature for 4 h led to the expected primary acetate (−)-**6** as the sole product in 83% yield for two steps. This compound underwent hydroxyl-directed epoxidation[40,41] by treatment with *m*-chloroperbenzoic acid (*m*-CPBA) at 0 °C in CH_2Cl_2 to afford the key α-epoxide (−)-**7** in 84% yield.

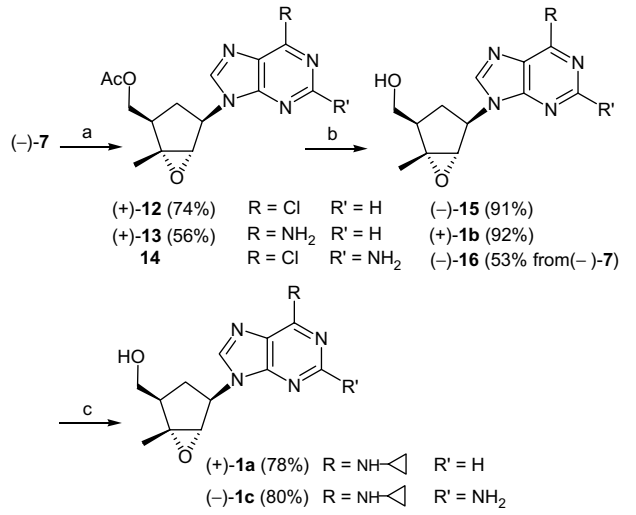
Synthesis of the target molecule (−)-**11** is outlined in pathway 2. Double bond isomerization of the enantiomeric alcohol (+)-**3** with EtONa/EtOH led to hydroxyl-ester (−)-**8** in 85% yield after silica gel column chromatography. At this stage, reduction of (−)-**8** with lithium aluminum hydride was difficult because of competing partial reduction of the carbon–carbon double bond. With this outcome, selective reduction of the carboxylate group was conveniently achieved by using diisobutylaluminum (DIBAL-H) at −80 °C in toluene as reducing agent to afford (+)-**9** in 88% yield. Like previously, exposure of (+)-**9** to RML (*R. miehei* lipase) and vinyl acetate at room temperature for 4 h gave the expected allylic acetate (−)-**10** (90% yield), and treatment of (−)-**10** with *m*-CPBA led to the key epoxide (−)-**11** in 91% yield.

Starting from enantiopure compound (−)-**7**, the synthesis of the target carbocyclic nucleosides **1a**–**c** is illustrated in Scheme 2, following the protocol previously described by us in a preliminary communication from racemic **7**.[42]

The synthesis of the target carbocyclic nucleosides **2a**–**c** was achieved as presented in Scheme 3. In a first attempt, Mitsunobu condensation of (−)-**11** with 6-chloropurine afforded the expected derivative **17** but, unfortunately, as a mixture contaminated with inseparable triphenylphosphine oxide. With this outcome, it was anticipated that the separation might be improved by first incorporating the cyclopropylamino group at the 6-position of the chloropurine in order to change the relative polarities. Effectively, condensation of 6-(cyclopropylamino)purine, [from 6-chloropurine, excess cyclopropylamine in refluxing ethanol], with (−)-**11** under the Mitsunobu conditions afforded pure (+)-**18** as the sole product in 75% yield, after efficient and convenient silica gel chromatography separation from triphenylphosphine oxide. Subsequent deprotection of the acetyl



Scheme 1. Reagents and conditions: (a) PPh_3 (1.3 equiv), DIAD (1.3 equiv), AcOH (1.3 equiv), THF, 0 °C, 1 h; (b) $LiAlH_4$ (2 equiv), ether, −20 °C to 0 °C, 1 h; (c) vinyl acetate, PPL (porcine pancreas lipase), rt, 4 h, (d) *m*-CPBA (1.3 equiv), CH_2Cl_2, 0 °C then rt, 2 h; (e) EtONa (1.0 equiv), EtOH, rt, 20 h; (f), DIBAL-H (3.0 equiv), −80 °C, toluene, 1 h; (g) vinyl acetate, RML (*R. miehei* lipase), rt, 2 h.



Scheme 2. Reagents and conditions: (a) Ph_3P (1.5 equiv), DIAD (1.5 equiv), nucleobase (1.5 equiv); i—6-chloropurine, THF, 0 °C then rt, 12 h; ii—adenine, THF; 0 °C to rt 12 h then 40 °C 4 h; iii—2-amino-6-chloropurine, THF, 0 °C to rt 12 h then 40 °C 4 h; (b) NH_3 (7 N in methanol), rt; (c) cyclopropylamine–THF (1:5), 12 h, 50 °C.

group with methanolic ammonia afforded the target molecule (+)-**2a** in 90% yield.

Preparation of the carbocyclic nucleoside (+)-**2b** was accomplished from (−)-**11** in two steps. Compound (−)-**11** was treated with adenine under the Mitsunobu conditions to give (+)-**19** in 63% yield, which was deprotected with methanolic ammonia to afford the target compound (+)-**2b** in 92% yield. It must be noted that, in this case, the optimal temperature for the Mitsunobu reaction was found to be room temperature, since at 40 °C like for **13** (Scheme 2), undesired by-products are formed and the yield is decreased. To synthesize the carbocyclic nucleoside (+)-**2c**, compound (−)-**11** was treated with 2-amino-6-chloropurine under Mitsunobu conditions to afford **20**, contaminated with inseparable triphenylphosphine oxide here also. To solve this problem, we turned our attention toward the possibility of forming the 6-cyclopropylamino derivative, like precedence, and to directly couple it with (−)-**11**. Unfortunately, 2-amino-6-(cyclopropylamino)purine, [from 2-amino-6-chloropurine, excess cyclopropylamine in refluxing ethanol], led to the formation of complex mixtures and the outcome of the reaction could not be clearly established. However, and to our delight, triphenylphosphine oxide present with **20** was conveniently eliminated during the next ammonia deprotective step by column chromatography. Thus, submission of **20** to methanolic ammonia afforded pure (+)-**21** in 70% yield (two steps from (−)-**11**), which was reacted with cyclopropylamine in THF to give the target molecule (+)-**2c** in 92% yield. All the compound structures were assigned based on ^1H and ^{13}C NMR and elemental analysis.

2.2. Biological results and conclusions

Compounds **1a**–**c** and **2a**–**c** were evaluated for their antiviral activity in human embryonic lung (HEL) cells [herpes simplex virus type 1 (HSV-1, strain KOS), herpes simplex virus type 2 (HSV-2, strain G), vaccinia virus, vesicular stomatitis virus, thymidine kinase-deficient (TK-) HSV-1 (strain KOS, ACV^r)], Vero cells (parainfluenza type 3 virus, reovirus type 1, Sindbis virus, Coxsackie B4 virus, Punta Toro virus), HeLa cells (vesicular stomatitis virus, Coxsackie B4 virus, respiratory syncytial virus), and Madin Darby canine kidney cells (influenza A H3N2, influenza A H1N1, and influenza B). In none of these cases significant antiviral activity or cytotoxicity was witnessed at a concentration of 100 μg/mL, which was the highest concentration tested.

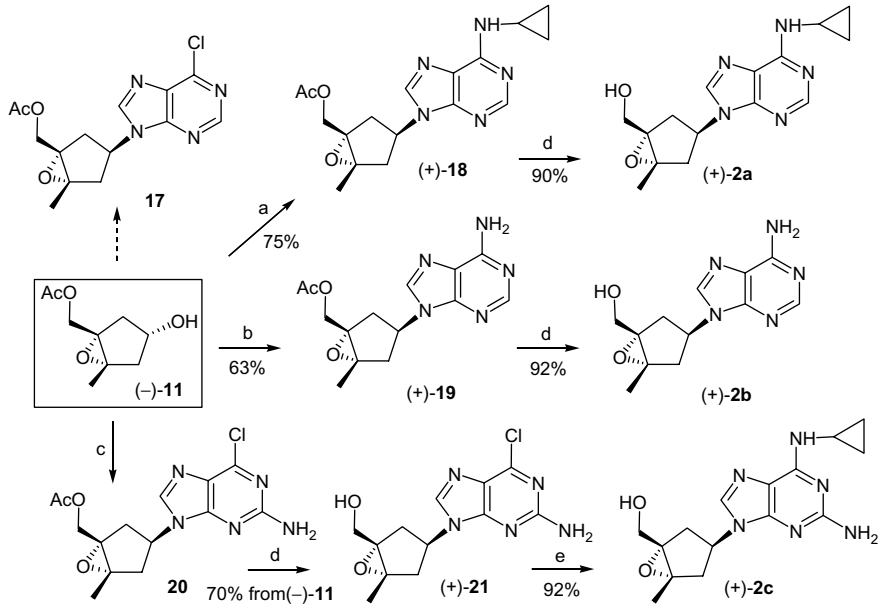
In summary, enantioselective synthesis of conformationally constrained and 3′-methyl-branched carbanucleosides **1a**–**c** and **2a**–**c** was achieved starting from both enantiomers of the same building block obtained by enzymatic kinetic resolution. Synthesized compounds were tested as potential antiviral agents. None of these compounds showed any antiviral activity.

3. Experimental

3.1. General chemical procedures

All air and/or water sensitive reactions were carried out under an argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. All corresponding glassware was oven-dried (80 °C) and/or carefully dried in line with a flameless heat gun. All solvents were distilled under an argon atmosphere: THF from a blue solution of sodium-benzophenone ketyl radical prior to use; CH_2Cl_2 and toluene from CaH_2. Routine monitoring of reactions was performed using Merck Silica gel 60 F_{254}, aluminum supported TLC plates; spots were visualized using a UV light and ethanolic acidic *p*-anisaldehyde solution or ethanolic phosphomolybdic solution, followed by heating. Purification by means of column chromatography was performed with Silica gel 60 (230–400 mesh) and gradients of Et_2O/petroleum ether or CH_2Cl_2/MeOH as eluent, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, MeOH-d_4 or DMSO-d_6 solutions on Bruker AM-500, Bruker AM-400 or Bruker AM-300 spectrometers. Chemical shifts (δ) in ppm are reported using residual non-deuterated solvents as internal reference. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Microanalyses were performed at our University. Melting points are uncorrected. Infrared spectra were obtained as films or KBr pellets using a Perkin-Elmer 1600 FTIR spectrophotometer.

3.1.1. (1*S*,4*S*)-4-Acetoxy-2-methyl-cyclopent-2-enecarboxylic acid ethyl ester (−)-4. A stirred solution of (−)-**3** (1.00 g, 5.88 mmol), acetic acid (0.44 mL, 7.68 mmol), and PPh_3 (2.00 g, 7.62 mmol) in THF (40 mL) was immersed in an ice bath and DIAD (1.52 mL, 7.72 mmol) was slowly added to maintain the temperature below 10 °C. Upon completion of the addition, the mixture was allowed to warm to rt and stirred for 1 h. The solvent was removed in vacuo, and the residue was directly chromatographed to afford (−)-**4** (1.11 g, 89%) as a colorless oil. $[\alpha]_D^{25} = -231$ (*c* 1.0, $CHCl_3$). IR (neat): *v* 3031, 1763,



Scheme 3. Reagents and conditions: (a) Ph_3P (1.5 equiv), DIAD (1.5 equiv), 6-cyclopropylaminopurine (1.5 equiv), THF, 0 °C then rt, 12 h; (b) Ph_3P (1.5 equiv), DIAD (1.5 equiv), adenine (1.5 equiv), THF, rt, 12 h; (c) Ph_3P (1.5 equiv), DIAD (1.5 equiv), 2-amino-6-chloropurine (1.5 equiv), THF, 0 °C, rt 12 h then 40 °C 4 h; (d) NH_3 (7 N in methanol), rt; (e) cyclopropylamine–THF (1:5), 50 °C, 12 h.

1751, 1131 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.66 (m, 1H), 5.56 (m, 1H), 4.12 and 4.08 (*AB*X_3, J = 10.8, 7.2 Hz, 2H), 3.50 (m, 1H), 2.55 (ddd, J = 14.4, 7.6, 4.9 Hz, 1H), 2.02 (ddd, J = 14.4, 8.5, 3.2 Hz, 1H), 1.95 (s, 3H), 1.75 (d, J = 1.1 Hz, 3H), 1.20 (AB*X*$_3$, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (C), 170.7 (C), 145.1 (C), 127.2 (CH), 79.6 (CH), 60.7 (CH_2), 52.8 (CH), 35.2 (CH_2), 21.1 (CH_3), 15.3 (CH_3), 14.1 (CH_3). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.91; H, 7.62.

3.1.2. Acetic acid (1*S*,4*S*)-4-hydroxy-2-methyl-cyclopent-2-enylmethyl ester (−)-6. A solution of (−)-**4** (600 mg, 2.83 mmol) in dry diethyl ether (30 mL) was slowly added at −20 °C to a stirred slurry of $LiAlH_4$ (215 mg, 5.67 mmol) in dry diethyl ether (30 mL). After 1 h at 0 °C, Celite (10 g) and $Na_2SO_4{\cdot}10H_2O$ (10 g) were added and the solution was allowed to warm to rt and stirred for a further 1 h. The reaction mixture was filtered through a pad of $MgSO_4$ and concentrated. The oily residue was used for the next reaction without further purification. The crude diol **5** and PPL (60 mg) in 60 mL of vinyl acetate were magnetically stirred at rt for 4 h while monitoring the progress of the reaction by TLC. After completion of the reaction, the mixture was filtered, the solvent was removed in vacuo and the residue was directly chromatographed to give 397 mg (83%) of pure (−)-**6** as a colorless oil. $[\alpha]_D^{25} = -103.2$ (*c* 1.0, $CHCl_3$). IR (neat): ν 3329, 1756, 1142 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.50 (br s, 1H), 4.80–4.71 (m, 1H), 4.04 and 3.95 (*AB*X, J = 10.9, 6.2, 4.9 Hz, 2H), 2.93 (m, 1H), 2.08–1.99 (AB*X*, m, 1H), 1.99 (d, J = 0.7 Hz, 3H), 1.87 (ddd, J = 13.6, 8.0, 3.4 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (C), 144.6 (C), 130.2 (CH), 75.8 (CH), 66.1 (CH_2), 46.2 (CH), 38.6 (CH_2), 20.8 (CH_3), 15.1 (CH_3). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.85; H, 8.26.

3.1.3. Acetic acid (1*R*,2*R*,4*S*,5*S*)-4-hydroxy-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-ylmethyl ester (−)-7. To a stirred solution of (−)-**6** (1.00 g, 5.88 mmol) in CH_2Cl_2 (20 mL) was added *m*-CPBA (1.73 g, 7.68 mmol, 77 wt% in water) at 0 °C. The solution was allowed to warm to rt. After stirring for 2 h, the mixture was poured into a solution of Na_2SO_3 (2 g, 45.8 mmol) and was extracted with CH_2Cl_2. The organic extracts were combined, washed with a saturated solution of $NaHCO_3$, dried, filtered, and concentrated to afford after purification by column chromatography 963 mg (84%) of (−)-**7**. $[\alpha]_D^{25} = -52.1$ (*c* 1.0, $CHCl_3$). IR (neat): ν = 3321, 1752, 1148, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.27 (t, J = 7.8 Hz, 1H), 3.95 (*AB*X, J = 11.4, 5.2, 4.9 Hz, 2H), 3.28 (s, 1H), 2.79 (br s, OH), 2.38 (dt, J = 7.8, 5.0 Hz, 1H), 1.98 (s, 3H), 1.76 (dd, J = 13.4, 7.8 Hz, 1H), 1.48 (dt, J = 13.4, 7.8 Hz, 1H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (C), 72.3 (CH), 65.3 (CH), 65.0 (CH_2), 64.0 (C), 41.4 (CH), 33.1 (CH_2), 20.7 (CH_3), 15.5 (CH_3). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.91; H, 7.61.

3.1.4. (*R*)-4-Hydroxy-2-methyl-cyclopent-1-enecarboxylic acid ethyl ester (−)-8. The compound (+)-**3** (750 mg, 4.41 mmol) was dissolved in EtOH (30 mL) and a solution of EtONa (1.0 M in EtOH, 4.50 mL, 4.50 mmol) at 0 °C was added under argon. The reaction mixture was stirred for 20 h at rt, the solution was poured into a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The organic extracts were combined, dried, filtered, and concentrated. Purification by column chromatography afforded 639 mg (85%) of (−)-**8** as a clear oil. $[\alpha]_D^{25} = -17.5$ (*c* 1.0, $CHCl_3$). IR (neat): ν 3420, 1729, 1652, 1261 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.39 (tt, J = 6.3, 2.3 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 2.90 (m, 1H), 2.78 (ddq J = 18.4, 6.3, 1.2 Hz, 1H), 2.58 (br d, J = 16.8 Hz, 1H), 2.42 (br dd, J = 18.4, 0.9 Hz, 1H), 2.10 (br s, 3H), 1.26

(t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.9$ (C), 152.7 (C), 124.8 (C), 69.2 (CH), 59.8 (CH_2), 50.1 (CH_2), 43.6 (CH_2), 16.3 (CH_3), 14.3 (CH_3). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.83; H 8.33.

3.1.5. (*R*)-3-Hydroxymethyl-4-methyl-cyclopent-3-enol (+)-9. To a solution of (−)-**8** (500 mg, 2.94 mmol) in toluene (30 mL) under argon was added dropwise at −78 °C a toluene solution of diisobutylaluminum hydride (1.0 M, 10.3 mL, 10.3 mmol). The reaction mixture was stirred for 1 h at this temperature, quenched with Celite (10 g) and $Na_2SO_4{\cdot}10H_2O$ (10 g), and allowed to warm to rt. Filtration and concentration gave, after purification by column chromatography, 330 mg (88%) of pure (+)-**9** as a colorless oil. $[\alpha]_D^{25} = +3.9$ (*c* 1.0, $CHCl_3$). IR (neat): *v* 3339, 1636, 1142 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.35 (tt, $J = 6.0$, 1.7 Hz, 1H), 4.21 and 3.99 (AB, $J = 12.0$ Hz, 2H), 2.72–2.55 (m, 2H), 2.40 (br d, $J = 16.8$ Hz, 1H), 2.22 (br d, $J = 16.8$ Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.2 (C), 131.7 (C), 69.9 (CH), 58.2 (CH_2), 48.3 (CH_2), 43.8 (CH_2), 13.7 (CH_3). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.87; H, 9.39.

3.1.6. Acetic acid (*R*)-4-hydroxy-2-methyl-cyclopent-1-enylmethyl ester (−)-10. A mixture of (+)-**9** (600 mg, 4.68 mmol) and RML (50 mg) in 25 mL of vinyl acetate was magnetically stirred at rt for 2 h. After completion of the reaction, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the oily residue by column chromatography afforded 718 mg (90%) of pure (−)-**10** as a colorless oil. $[\alpha]_D^{25} = -2.6$ (*c* 1.0, $CHCl_3$). IR (neat): *v* 3349, 1757, 1142 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (s, 2H), 4.44 (tt, $J = 6.4$, 2.3 Hz, 1H), 2.78–2.63 (m, 2H), 2.33 (br d, $J = 14.5$ Hz, 1H), 2.27 (br d, $J = 14.5$ Hz, 1H), 2.04 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2 (C), 136.1 (C), 127.3 (C), 69.9 (CH), 60.6 (CH_2), 48.3 (CH_2), 44.5 (CH_2), 20.8 (CH_3), 13.8 (CH_3). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.19; H, 8.33.

3.1.7. Acetic acid (1*S*,3*R*,5*S*)-3-hydroxy-5-methyl-6-oxa-bicyclo[3.1.0]hex-1-ylmethyl ester (−)-11. To a stirred solution of (−)-**10** (500 mg, 2.94 mmol) in CH_2Cl_2 (30 mL) was added *m*-CPBA (860 mg, 3.82 mmol, 77 wt% in water) at 0 °C. The solution was allowed to warm to rt. After stirring for 1 h, the mixture was poured into a solution of Na_2SO_3 (960 mg, 7.64 mmol) and was extracted with CH_2Cl_2. The organic extracts were combined, washed with a saturated solution of $NaHCO_3$, dried, filtered, and concentrated to afford after purification by column chromatography 498 mg (91%) of (−)-**11**. $[\alpha]_D^{25} = -22.4$ (*c* 1.0, $CHCl_3$). IR (neat): *v* = 3352, 1755, 1144, 1041 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 4.33 and 4.12 (AB, $J = 12.3$ Hz, 2H), 4.00 (br t, $J = 4.4$ Hz, 1H), 2.09–1.99 (m partially overlapped, 4H), 2.08 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (C), 69.1 (C), 68.5 (C), 68.2 (CH), 63.2 (CH_2), 42.9 (CH_2), 39.2 (CH_2), 20.7 (CH_3), 15.1 (CH_3). Anal. Calcd for $C_9H_{14}O_4$: C 58.05, H 7.58. Found C 57.81, H 7.55.

3.1.8. Acetic acid (1*R*,2*R*,4*R*,5*S*)-4-(6-chloro-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-ylmethyl ester (+)-12. DIAD (0.72 mL, 3.62 mmol) was added dropwise to a solution of PPh_3 (950 mg, 3.66 mmol) in freshly distilled THF (50 mL) kept under an argon atmosphere at 0 °C. The mixture was stirred for 30 min and then 6-chloropurine was added (556 mg, 3.60 mmol). The mixture was stirred for an additional 30 min and then a solution of epoxide (−)-**7** (450 mg, 2.42 mmol) in dry THF (5 mL) was added slowly. The cooling bath was removed and the mixture was stirred at rt for 12 h. The volatiles were evaporated in vacuo and the resulting residue was purified by column chromatography to give the protected 6-chloropurine carbanucleoside (+)-**12** (577 mg, 74%) as a white solid. Mp 52 °C. $[\alpha]_D^{25} = +4.0$ (*c* 1.0, $CHCl_3$). IR (KBr): *v* 1742, 1238, 1136 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.22 (s, 1H), 5.16 (dd, $J = 7.6$, 1.3 Hz, 1H), 4.19 and 4.11 (*AB*X, $J = 11.7$, 5.8, 5.1 Hz, 2H), 3.77 (s, 1H), 2.71–2.55 (m, 2H), 1.99 (s, 3H), 1.96-1.87 (m, 1H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5 (C), 151.9 (CH), 151.5 (C), 151.3 (C), 143.6 (CH), 131.7 (C) 68.0 (C), 64.6 (CH_2), 64.5 (CH), 55.5 (CH), 41.2 (CH), 34.8 (CH_2), 20.8 (CH_3), 15.2 (CH_3). Anal. Calcd for $C_{14}H_{15}ClN_4O_3$: C, 52.10; H, 4.68; N, 17.36. Found: C, 52.39; H, 4.64; N, 17.40.

3.1.9. [(1*R*,2*R*,4*R*,5*S*)-4-(6-Chloro-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl]-methanol (−)-15. A solution of (+)-**12** (300 mg, 0.93 mmol) and saturated methanolic ammonia (15 mL) was stirred in a flask fitted with a rubber stopper at rt for 10 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography to give the 6-chloropurine carbanucleoside (−)-**15** (237 mg, 91%) as a white solid. Mp 68 °C. $[\alpha]_D^{25} = -5.0$ (*c* 1.0, $CHCl_3$). IR (KBr): *v* 3321, 3271, 1237 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.73 (s, 1H), 5.26 (dd, $J = 9.4$, 2.3 Hz, 1H), 4.01 and 3.82 (*AB*X, $J = 10.4$, 2.5, 2.3 Hz, 2H), 3.60 (s, 1H), 2.68 (dt, $J = 14.9$, 9.4 Hz, 1H), 2.48 (AB*X*, dq, $J = 9.4$, 2.3 Hz, 1H), 2.06 (dt, $J = 14.9$, 2.3 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8 (CH), 151.6 (C), 150.3 (C), 145.7 (CH), 130.8 (C), 69.2 (C), 65.5 (CH), 62.5 (CH_2), 54.8 (CH), 43.9 (CH), 35.5 (CH_2), 15.2 (CH_3). Anal. Calcd for $C_{12}H_{13}ClN_4O_2$: C, 51.34; H, 4.67; N, 19.96. Found: C, 50.98; H, 4.70; N, 20.01.

3.1.10. [(1*R*,2*R*,4*R*,5*S*)-4-(6-Cyclopropylamino-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl]-methanol (+)-1a. A mixture of (−)-**15** (200 mg, 0.71 mmol) and cyclopropylamine (2 mL) in dry THF (10 mL) was stirred at rt for 3 h, and the reaction mixture was evaporated in vacuo. The resulting residue was purified by column chromatography to give the corresponding 6-cyclopropylamino carbanucleoside (+)-**1a** (167 mg, 78%) as a white solid. Mp 150 °C (dec). $[\alpha]_D^{25} = +7.1$ (*c* 1.0, MeOH). IR (KBr): *v* = 3291, 3115, 1667, 1609 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.95 (s, 1H), 6.14 (br s, 1H), 5.00 (dd, $J = 9.5$, 2.9 Hz, 1H), 3.81 and 3.72 (*AB*X, $J = 10.9$, 4.5, 3.5 Hz, 2H), 3.56 (s, 1H), 3.01 (m, 1H), 2.61 (dt, $J = 14.5$, 9.5 Hz, 1H), 2.49–2.42 (AB*X*, m, 1H), 2.25 (dt, $J = 14.5$, 2.9 Hz, 1H), 1.62 (s, 3H), 0.93–0.87 (m, 2H), 0.65–0.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (C), 152.9 (CH), 148.5 (C), 139.6 (CH), 120.0 (C),

69.3 (C), 66.2 (CH), 62.8 (CH_2), 55.6 (CH), 44.5 (CH), 34.4 (CH_2), 23.7 (CH), 15.4 (CH_3), 7.4 ($2 \times CH_2$). Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 23.24. Found: C, 59.98.; H, 6.33; N, 23.04.

3.1.11. Acetic acid (1*R*,2*R*,4*R*,5*S*)-4-(6-amino-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-ylmethyl ester (+)-13. Epoxide (−)-**7** (450 mg, 2.42 mmol) was converted to the protected adenosine carbanucleoside (+)-**13** (408 mg, 56%) as a white solid, according to the same procedure used in the preparation of (+)-**12** except stirring for 12 h at rt then 4 h at 40 °C. Mp 143 °C (dec). $[\alpha]_D^{25} = +3.0$ (*c* 1, $CHCl_3$). IR (KBr): *v* 3276, 3089, 1741, 1249 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.86 (s, 1H), 5.95 (br s, 2H), 5.06 (d, *J* = 7.9 Hz, 1H), 4.21 and 4.07 (*AB*X, *J* = 11.4, 6.2, 5.2 Hz, 2H), 3.74 (s, 1H), 2.66–2.49 (m, 2H), 1.98 (s, 3H), 1.90 (d, *J* = 13.4 Hz, 1H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (C), 155.7 (C), 153.0 (CH), 149.9 (C), 138.6 (CH), 119.8 (C), 67.9 (C), 64.8 (CH), 64.7 (CH_2), 54.9 (CH), 41.4 (CH), 34.7 (CH_2), 20.8 (CH_3), 15.3 (CH_3). Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.44; H, 5.65; N, 23.09. Found: C, 55.15; H, 5.69; N, 22.98.

3.1.12. [(1*R*,2*R*,4*R*,5*S*)-4-(6-Amino-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl]-methanol (+)-1b. Starting from (+)-**13** (200 mg, 0.66 mmol), adenosine carbanucleoside (+)-**1b** (157 mg, 92%) was prepared in the same manner as that for 6-chloropurine carbanucleoside (−)-**15**. Mp 170 °C (dec). $[\alpha]_D^{25} = +12.0$ (*c* 1.0, DMSO). IR (KBr): *v* = 3278, 3107, 1678, 1600 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.19 (s, 1H), 8.13 (s, 1H), 7.21 (br s, 2H), 4.91 (d, *J* = 7.2 Hz, 1H), 4.77 (t, *J* = 4.5 Hz, 1H), 3.79 (s, 1H), 3.55 (m, 1H), 3.38 (m, 1H), 2.27–2.18 (m, 2H), 1.88 (d, *J* = 12.6 Hz, 1H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.2 (C), 152.5 (CH), 149.6 (C), 139.2 (CH), 118.9 (C), 68.1 (C), 64.1 (CH), 61.6 (CH_2), 54.2 (CH), 44.5 (CH), 33.6 (CH_2), 15.5 (CH_3). Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 54.85; H, 5.84; N, 26.59.

3.1.13. [(1*R*,2*R*,4*R*,5*S*)-4-(2-Amino-6-chloro-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl]-methanol (−)-16. Epoxide (−)-**7** (450 mg, 2.42 mmol) was converted to the protected 2-amino-6-chloropurine carbanucleoside **14**, according to the same procedure used in the preparation of (+)-**12**. Derivative **14** was contaminated with triphenylphosphine oxide which will be eliminated during the next ammonia deprotective step. Derivative **14** was converted to 2-amino-6-chloropurine carbanucleoside (−)-**16**, according to the same procedure used in the preparation of (−)-**15**. At this stage, triphenylphosphine oxide present with **14** was conveniently eliminated by column chromatography to give pure (−)-**16** as a white solid (380 mg, 53% yield, two steps from (−)-**7**). Mp 181 °C (dec). $[\alpha]_D^{25} = -3.6$ (*c* 0.5, MeOH/$CHCl_3$, 1:1). IR (KBR): *v* 3305, 3172, 1676, 1615 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 6.87 (br s, 2H), 4.79 (dd, *J* = 7.9, 1.3 Hz, 1H), 4.73 (t, *J* = 4.7 Hz, OH), 3.78 (s, 1H), 3.47 (dt, *J* = 10.6, 4.7 Hz, 1H), 3.37 (ddd, *J* = 10.6, 5.8, 4.7 Hz, 1H), 2.29–2.15 (m, 2H), 1.89 (br d, *J* = 13.6 Hz, 1H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.9 (C), 154.2 (C), 149.5 (C), 141.6 (CH), 123.5 (C), 68.1 (C), 63.8 (CH), 61.5 (CH_2), 54.3 (CH), 44.5 (CH), 33.4 (CH_2), 15.4 (CH_3). Anal. Calcd for $C_{12}H_{14}ClN_5O_2$: C, 48.74; H, 4.77; N, 23.68. Found: C, 49.03.; H, 4.73; N, 23.71.

3.1.14. [(1*R*,2*R*,4*R*,5*S*)-4-(2-Amino-6-cyclopropylamino-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl]-methanol. (−)-1c. Derivative (−)-**16** (200 mg, 0.68 mmol) was converted to 2-amino-6-cyclopropylamino carbanucleoside (+)-**1c** (171 mg, 80%) as white solid according to the same procedure used in the preparation of (+)-**1a** except stirring at 50 °C for 12 h. Mp 190 °C (dec). $[\alpha]_D^{25} = -4.3$ (*c* 1.0, MeOH). IR (KBr): *v* = 3305, 3172, 1676, 1615 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.76 (s, 1H), 7.28 (br d, *J* = 3.6 Hz, 1H), 5.86 (br s, 2H), 4.78 (t, 4.9 Hz, 1H), 4.72 (d, *J* = 7.2 Hz, 1H), 3.70 (s, 1H), 3.49 (dt, *J* = 10.8, 4.9 Hz, 1H), 3.30 (dt, *J* = 10.8, 4.9 Hz, 1H), 3.02 (br s, 1H), 2.27–2.07 (m, 2H), 1.86 (d, *J* = 14.0 Hz, 1H), 1.47 (s, 3H), 0.69–0.61 (m, 2H), 0.60–0.53 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3 (C), 156.1 (C), 151.5 (C), 135.3 (CH), 113.6 (C), 68.0 (C), 64.2 (CH), 61.7 (CH_2), 53.6 (CH), 44.6 (CH), 33.3 (CH_2), 24.0 (CH), 15.6 (CH_3), 6.6×2 (CH_2). Anal. Calcd for $C_{15}H_{20}N_6O_2$: C, 56.95; H, 6.37; N, 26.56. Found: C, 57.23; H, 6.39; N, 26.35.

3.1.15. Acetic acid (1*S*,3*S*,5*S*)-3-(6-cyclopropylamino-purin-9-yl)-5-methyl-6-oxa-bicyclo[3.1.0]hex-1-ylmethyl ester (+)-18. Epoxide (−)-**11** (150 mg, 0.81 mmol) was converted to the protected 6-cyclopropyl carbanucleoside (+)-**18** (208 mg, 75%), according to the same procedure used in the preparation of (+)-**12**. $[\alpha]_D^{25} = +6.0$ (*c* 1.0, MeOH). IR (neat): *v* 1742, 1238, 1136 cm^{-1}. ^1H NMR (300 MHz, MeOH-d_4): δ 8.26 (s, 1H), 8.11 (s, 1H), 4.66 (quintuplet, *J* = 8.7 Hz, 1H), 4.53 and 4.20 (AB, *J* = 12.3 Hz, 2H), 2.94 (m, 1H), 2.63 (dd, *J* = 13.6, 8.7 Hz, 1H), 2.54–2.47 (m partially overlapped, 2H), 2.51 (dd, *J* = 13.6, 8.7 Hz, 1H), 2.09 (s, 3H), 1.50 (s, 3H), 0.87 (m, 2H), 0.62 (m, 2H). ^{13}C NMR (75 MHz, MeOH-d_4): δ 172.3 (C), 157.1 (C), 153.3 (CH), 150.0 (C), 141.6 (CH), 121.2 (C) 68.2 (C), 68.1 (C), 64.5 (CH_2), 51.8 (CH), 39.0 (CH_2), 35.6 (CH_2), 24.5 (CH), 20.6 (CH_3), 15.3 (CH_3), 7.6 ($2 \times CH_2$). Anal. Calcd for $C_{17}H_{21}N_5O_3$: C, 59.46; H, 6.16; N, 20.40 Found: C, 59.81; H, 5.92; N, 20.79.

3.1.16. (1*S*,3*S*,5*S*)-3-(6-Cyclopropylamino-purin-9-yl)-5-methyl-6-oxa-bicyclo[3.1.0]hex-1-yl]-methanol (+)-2a. Starting from (+)-**18** (200 mg, 0.58 mmol), 6-cyclopropylamino carbanucleoside (+)-**2a** (158 mg, 90%) was prepared in the same manner as that for 6-chloropurine carbanucleoside (−)-**15**. Mp 143 °C. $[\alpha]_D^{25} = +8.2$ (*c* 1.0, MeOH). IR (KBr): *v* 1748, 1231, 1139 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.70 (s, 1H), 6.25 (br s, 1H), 4.60 (quintuplet, *J* = 8.5 Hz, 1H), 3.93 and 3.88 (AB, *J* = 12.4 Hz, 2H), 3.01 (m, 1H), 2.69 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.62 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.52 (d, *J* = 8.5 Hz, 2H), 1.51 (s, 3H), 0.90 (m, 2H), 0.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8 (C), 152.7 (CH), 148.9 (C), 139.5 (CH), 120.7 (C), 69.4 (C) 67.3 (C), 61.2 (CH_2), 51.3 (CH), 38.4 (CH_2), 34.2 (CH_2), 23.6 (CH), 15.2 (CH_3), 7.3 ($2 \times CH_3$). Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 23.24; Found: C, 60.11; H, 6.41; N, 22.87.

3.1.17. Acetic acid (1*S*,3*S*,5*S*)-3-(6-amino-purin-9-yl)-5-methyl-6-oxa-bicyclo[3.1.0]hex-1-ylmethyl ester (+)-19. Epoxide (−)-**11** (150 mg, 0.80 mmol) was converted to the protected adenosine carbanucleoside (+)-**19** (153 mg, 63%) as a white solid, according to the same procedure used in the preparation of (+)-**12**. Mp 104 °C. $[\alpha]_D^{25} = +4.0$ (*c* 0.5, MeOH/$CHCl_3$, 1:1). IR (KBr): *v* 1755, 1229, 1161 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.20 (s, 1H), 8.13 (s, 1H), 7.22 (br s, 2H), 4.55 (quintuplet, *J* = 8.7 Hz, 1H), 4.51 and 4.13 (AB, *J* = 12.3 Hz, 2H), 2.57–2.38 (m, 4H), 2.07 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.2 (C), 156.1 (C), 152.3 (CH), 149.5 (C), 140.1 (CH), 119.3 (C) 66.3 (C), 66.2 (C); 63.0 (CH_2), 49.3 (CH), 37.5 (CH_2), 34.3 (CH_2), 20.6 (CH_3), 15.0 (CH_3). Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.44; H, 5.65; N, 23.09; Found: C, 55.59; H, 5.57; N, 23.41.

3.1.18. [(1*S*,3*S*,5*S*)-3-(6-Amino-purin-9-yl)-5-methyl-6-oxa-bicyclo[3.1.0]hex-1-yl]-methanol (+)-2b. Starting from (+)-**19** (200 mg, 0.66 mmol), adenosine carbanucleoside (+)-**2b** (158 mg, 92%) as a white solid was prepared in the same manner as that for 6-chloropurine carbanucleoside (−)-**15**. Mp 212 °C (dec). $[\alpha]_D^{25} = +5.4$ (*c* 0.5, MeOH/$CHCl_3$, 1:1). IR (KBr): *v* = 3278, 3107, 1678, 1600 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.20 (s, 1H), 8.13 (s, 1H), 7.22 (br s, 2H), 4.99 (t, *J* = 5.5 Hz, OH), 4.55 (quintuplet, *J* = 8.7 Hz, 1H), 3.70 and 3.61 (*AB*X, *J* = 12.1, 5.4, 5.1 Hz, 2H), 2.52–2.37 (m, 4H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.1 (C), 152.2 (CH), 149.5 (C), 140.3 (CH), 119.4 (C), 69.0 (C), 65.8 (C), 60.1 (CH_2), 49.6 (CH), 37.9 (CH_2), 34.1 (CH_2), 15.0 (CH_3). Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 55.52; H, 5.90; N, 26.68.

3.1.19. [(1*S*,3*S*,5*S*)-3-(2-Amino-6-chloro-purin-9-yl)-5-methyl-6-oxa-bicyclo[3.1.0]hex-1-yl]-methanol (+)-21. Epoxide (−)-**11** (150 mg, 0.80 mmol) was converted to the protected 2-amino-6-chloropurine carbanucleoside **20**, according to the same procedure used in the preparation of (+)-**12**. Derivative **20** was contaminated with triphenylphosphine oxide which will be eliminated during the next ammonia deprotective step. Derivative **20** was converted to 2-amino-6-chloropurine carbanucleoside (+)-**21**, according to the same procedure used in the preparation of (+)-**2a**. At this stage, triphenylphosphine oxide present with **20** was conveniently eliminated by column chromatography to give pure (+)-**21** (167 mg, 70% yield, two steps from (−)-**11** as a white solid. Mp 128 °C. $[\alpha]_D^{25} = +4.8$ (*c* 1.0, MeOH). IR (KBr): *v* 3305, 3172, 1676, 1615 cm^{-1}. ^1H NMR (300 MHz, MeOH-d_4): δ 8.13 (s, 1H), 4.58 (tt, *J* = 9.1, 8.1 Hz, 1H), 3.85 and 3.76 (*AB*, *J* = 12.3 Hz, 2H), 2.61 and 2.56 (*AB*X, *J* = 13.7, 9.1, 8.1 Hz, 2H), 2.50 and 2.46 (*AB*X, *J* = 13.8, 9.1, 8.1 Hz, 2H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, MeOH-d_4): δ 161.3 (C), 155.2 (C), 151.5 (C), 143.7 (CH), 125.3 (C), 70.6 (C), 68.0 (C), 61.9 (CH_2), 51.7 (CH), 39.0 (CH_2), 34.9 (CH_2), 15.2 (CH_3). Anal. Calcd for $C_{12}H_{14}ClN_5O_2$: C, 48.74; H, 4.77; N, 23.68. Found: C, 49.03.; H, 4.73; N, 23.71.

3.1.20. [(1*S*,3*S*,5*S*)-3-(2-Amino-6-cyclopropylamino-purin-9-yl)-5-methyl-6-oxa-bicyclo[3.1.0]hex-1-yl]-methanol (+)-2c. A mixture of (+)-**21** (100 mg, 0.34 mmol) and cyclopropylamine (1 mL) in MeOH (5 mL) was stirred at rt for 3 h, and the reaction mixture was evaporated in vacuo. The resulting residue was purified by column chromatography to give the corresponding 2-amino-6-cyclopropylamino carbanucleoside (+)-**2c** (97 mg, 92%). $[\alpha]_D^{25} = +4.4$ (*c* 1.0, MeOH). IR (neat): *v* = 3291, 3115, 1667, 1609 cm^1. ^1H NMR (300 MHz, MeOH-d_4): δ 7.79 (s, 1H), 4.51 (tt, *J* = 9.4, 8.1 Hz, 1H), 3.84 and 3.75 (*AB*, *J* = 12.3 Hz, 2H), 2.89 (m, 1H), 2.58 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.51–2.41 (m, 2H) 2.36 (dd, *J* = 13.6, 9.4 Hz, 1H), 1.46 (s, 3H), 0.82 (m, 2H), 0.58 (m, 2H). ^{13}C NMR (75 MHz, MeOH-d_4): δ 161.7 (C), 157.5 (C), 152.1 (C), 138.2 (CH), 115.0 (C), 70.6 (C), 68.0 (C), 62.0 (CH_2), 50.8 (CH), 39.5 (CH_2), 35.4 (CH_2), 24.3 (CH), 15.2 (CH_3), 7.6 × 2 (CH_2). Anal. Calcd for $C_{15}H_{20}N_6O_2$: C, 56.95; H, 6.37; N, 26.56. Found: C, 56.66; H, 6.32; N, 26.17.

3.2. Antiviral assay

Methodology used to monitor antiviral activity and cytotoxicity assay were performed as previously described.[43–45]

Acknowledgments

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