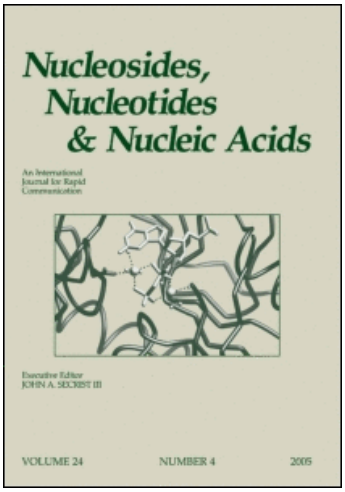

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SYNTHESIS OF C-5'-*nor*-DIDEOXYCARBANUCLEOSIDES STRUCTURALLY RELATED TO NEPLANOCIN C

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Abstract Purine carbanucleosides built on a 6-oxabicyclo[3.1.0]hexane template were synthesized from readily available 2-cyclopentenone employing a Mitsunobu reaction to incorporate the base onto the carbocyclic ring. Both adenosine and guanosine analogues exhibited moderate antiviral activity.

INTRODUCTION

In solution, the furanose ring of nucleosides exists in a dynamic equilibrium between the 2'-*exo*/3'-*endo* conformation (Northern) and the facing 2'-*endo*/3'-*exo* conformation (Southern) as defined by the concept of the pseudorotational cycle.[1,2] However, in the solid state only one of these Northern or Southern conformations is found, and one of these conformations would be exclusively responsible for molecular recognition with a specific target enzyme. As the biological activity in nucleosides is strongly modulated by the sugar conformation, it is quite desirable to fix the sugar conformation to correlate the biological activity with the preferred solution conformer. The replacement of the furanose ring oxygen by a methylene group brings about a special family of nucleoside analogues: carbanucleosides.[3-5] These compounds display a wide

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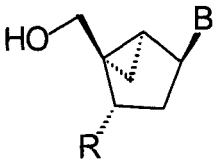
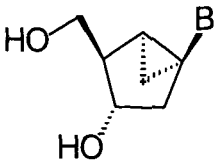


1, R = H, B = adenine
2, R = H, B = guanine
3, R = H, B = thymine
4, R = H, B = uracil
5, R = H, B = cytosine
6, R = OH, B = adenine
7, R = OH, B = guanine
8, R = OH, B = thymine
9, R = OH, B = uracil
10, R = OH, B = cytosine

Northern Geometry



11, B = adenine
12, B = guanine
13, B = thymine
14, B = uracil
15, B = cytosine

Southern Geometry

FIGURE 1. Carbanucleosides locked in the N and S conformation

range of biological properties, especially as antiviral and antitumor agents,[6-7] and present greater metabolic stability because they are not recognized by phosphorylases and hydrolases. However, their conformations in solution are far from the typical North and South geometries observed in normal nucleosides due to the lack of the anomeric effect and *gauche* interactions.[8] However, if carbocyclic nucleosides are built on a rigid bicyclo[3.1.0]hexane system as a pseudosugar moiety, it is possible to obtain carbanucleosides either in the North or the South geometry that mimic quite well the puckering of normal nucleosides (Figure 1).[9-15] This bicyclo[3.1.0]hexane system, in the absence of severe van der Waals interactions, always presents a boat-like preferred conformation.[10,16-18] It is of interest to point out that in this restricted system, the relative position of the base and the hydroxymethyl group determines the actual geometry of the carbanucleoside analogue (Figure 1). Several conformationally restricted carbocyclic nucleosides have been prepared with all normal bases. Some of the Northern analogues proved to be extremely potent antiviral agents[19-21] while the Southern derivatives exhibited vanishing inhibitory action. Moreover, conformationally restricted carbocyclic analogues of AZT have been prepared and the 5'-triphosphate locked in the Northern

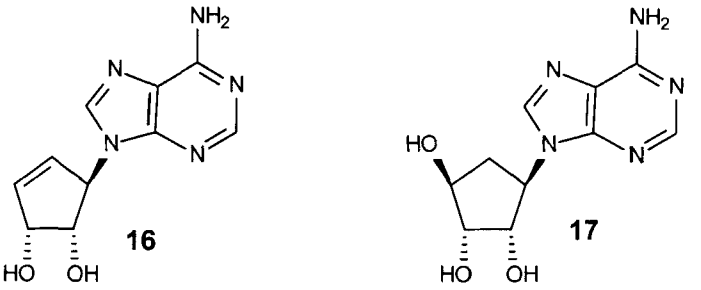
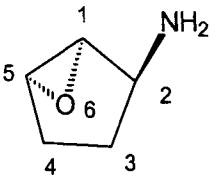


FIGURE 2. Chemical structure of two representative 5'-*nor*-carbanucleosides

conformation was solely responsible for reverse transcriptase inhibition.[22] In addition, potent antiviral activity has been found in 5'-*nor*-carbanucleosides as inhibitors of *S*-adenosylhomocysteine hydrolase, namely the truncated analogue of neplanocin A **16**[23,24] and 5'-*nor*-aristeromycin **17**[25-27] (Figure 2). As the N geometry seems to be the active conformation, it was of interest to explore the antiviral activity of conformationally restricted carbanucleosides built on a very simple 6-oxa-bicyclo[3.1.0]hexane template locked in the Northern conformation.

RESULTS AND DISCUSSION

A straightforward convergent approach for the preparation of carbocyclic purine derivatives (compounds **18** and **19**) was envisioned starting from the readily available 2-cyclopenten-1-one (**20**). Thus, **20** was treated with sodium borohydride in the presence of cerium chloride,[28] at low temperature to afford the allylic alcohol **21** in good yield, which was transformed into epoxy alcohol **22** by treatment with *m*-chloroperbenzoic acid. The course of the epoxidation reaction was directed by the hydroxyl group and occurred with high regioselectively affording only one diasteromer according to the Henbest rule.[29] Reaction of the epoxy alcohol **22** with 6-chloropurine under Mitsunobu[30-32] conditions produced the desired carbocyclic nucleoside derivative yielding exclusively the *N*-9 alkylated product (compound **23**). Treatment of **23** with methanolic ammonia gave the desired carbocyclic analogue of adenosine **18**. The presence of the epoxide group produced a similar effect to the cyclopropyl moiety [9,10] on the template as deduced from the analysis of the proton nuclear magnetic resonance spectrum. Therefore, the



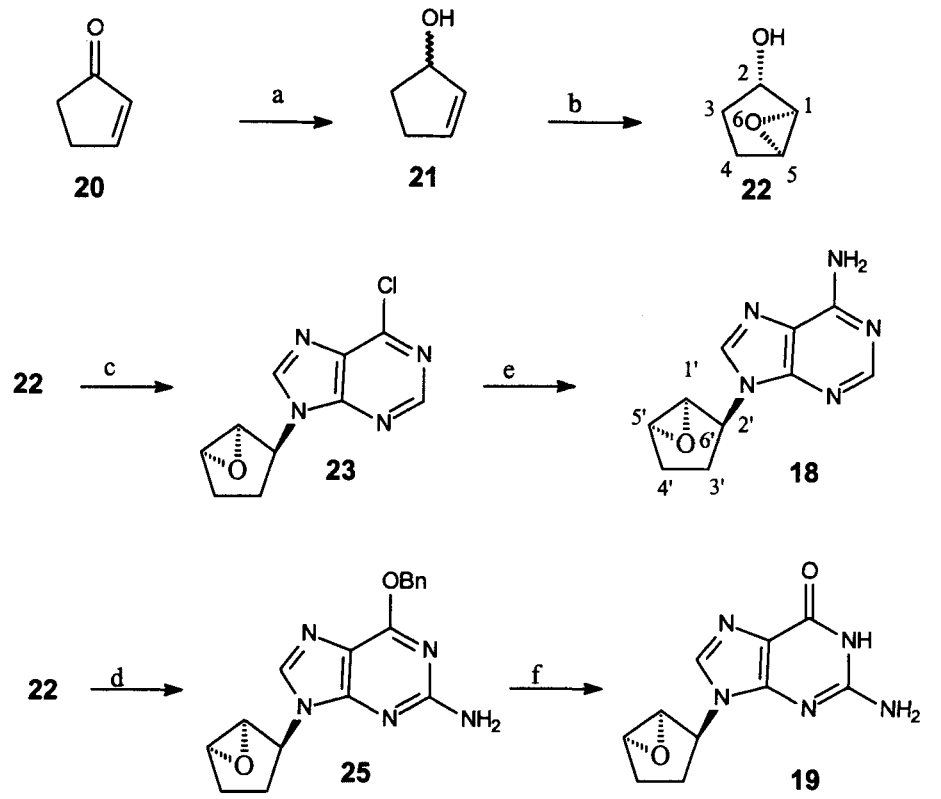
26

FIGURE 3. Cyclopentylamine derivative bearing the oxabicyclo[3.1.0] system for *ab initio* calculations

signal corresponding to the pseudoanomeric proton (H-2') was observed as a doublet centered at 5.14 ppm with a coupling constant close to 7 Hz indicating that two torsion angles among the pseudoanomeric protons and the neighbor hydrogen atoms were close to 90°. In addition, molecular modeling studies on a model compound, cyclopentyl amine **26** (Figure 3) agreed with the observed multiplicity. Therefore, the lowest energy conformer of **26** presented torsion angles $\phi_{H1'\text{-}C1'\text{-}C1'a\text{-}H1'a} = -71°$, $\phi_{H1'\text{-}C1'\text{-}C2'\text{-}H2'\alpha} = 29°$ and $\phi_{H1'\text{-}C1'\text{-}C2'\text{-}H2'\beta} = 90°$ and calculated coupling constants of 2.2, 7.2, and 1.2 Hz, respectively, which are in agreement with the observed proton NMR spectra. The *ab initio* energy calculations of optimized conformers were performed with the program Gaussian 94 employing a 6-31G* basis set.[33]

The carbocyclic analogue of guanosine **19** was prepared employing the epoxy alcohol **22** *via* a Mitsunobu-coupling reaction with 2-amino-6-benzyloxypurine (compound **24**) to afford the carbocyclic guanosine precursor **25**. As it was the case for the adenosine analogue, formation of *N*-7 alkylated product was not detected. Cleavage of the benzyl group by catalytic transfer hydrogenation yielded the desired carbocyclic 5'-*nor*-guanosine derivative (Scheme 1). The carbocyclic adenosine derivative **18** proved to be a relatively good inhibitor of herpes simplex virus type 1 in a dose dependent manner. Compound **18**, at a concentration of 50 μM, was able to reduce virus-induced cytopathogenicity by 14%, while at 200 μM exhibited 26% inhibition. The guanosine derivative **19** was only active at the highest concentration assayed (200 μM) showing an inhibitory effect close to 30% (Table 1). Similar inhibitory activity was found against herpes simplex virus type 2 (data not shown). Drugs **18** and **19** also showed weak activity

SCHEME 1



Reagents and conditions: a) $NaBH_4/CeCl_3$, MeOH, 30 min, 81%; b) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h, 82%; c) 6-chloropurine, PPh_3, DEAD, THF, rt, overnight, 70%; d) 2-amino-6-benzyloxypurine (**24**), PPh_3, DEAD, THF, rt, overnight, 28%; e) NH_3/MeOH, 70 °C, 5 h, 82%; f) HCO_2NH_4, Pd/C, MeOH, 65 °C, 3 h, 46%.

TABLE 1. Antiherpetic activity of Cabanucleosides against Herpes Simplex Virus Type-1

Compd. 18	% Inhibition	Compd. 19	% Inhibition
25 μM	0.00	25 μM	0.00
50 μM	13.7	50 μM	0.00
100 μM	16.4	100 μM	0.00
200 μM	26.0	200 μM	28.7

against human cytomegalovirus with an ED_{50} values of 333 μM and 266 μM, respectively. In conclusion, purine carbanucleosides having a quite simple pseudosugar moiety still exhibited modest to weak antiviral activity demonstrating that a specific sugar conformation plays a critical role in their biological activity.

BIOLOGICAL ASSAYS

Cell and viruses

Vero (African green monkey kidney) cell line was grown in MEM (minimum essential medium), supplemented with 5% bovine serum. The human diploid foreskin fibroblast cell line PH was provided by Dr. G. Carballal (CEMIC, Buenos Aires, Argentina)and propagated in MEM supplemented with 10% fetal calf serum. Herpes simplex virus type 1 (HSV-1) strain F, Herpes simplex virus type 2 (HSV-2) strain G, and Human Cytomegalovirus (HCMV) strain Davis were obtained from the American Type Culture Collection (Rockville, USA).

Antiviral assays

Antiviral activity was evaluated by two methods: reduction of virus plaque formation for HSV-1 and HSV-2, and inhibition of cytophatic effect (CPE) for HCMV.

In the plaque reduction assay, Vero cell monolayers grown in 24-well plates were infected with about 50 PFU (plaque forming units) of virus/well in the absence or presence of various concentrations of the compounds. After 1 h adsorption, residual inoculum was replaced by MEM containing 0.7% methylcellulose and the corresponding dose of compound. Plaques were counted after 2 days of incubation at 37 °C. The antiviral activity was calculated as the percent reduction of virus plaque formation in treated cultures with respect to untreated control cultures. The values obtained represent the mean of two independent experiments with duplicate determinations for each concentration. Acyclovir was used as positive control with an $ID_{50} = 0.16$ μM.

The anti HCMV activity was determined by a cytophatic effect reduction assay. Briefly, PH monolayers were infected in quadruplicate with HCMV at a multiplicity of infection of 0.1 in the absence or presence of various concentrations of the compounds. Cells controls were included in each experiment. After 7 days of incubation at 37 °C, the cytophatic effect was examined under an inverted microscope. The effective dose 50%

(ED_{50}), was calculated as the concentration required to reduced virus induced cytopathicity by 50%.

EXPERIMENTAL SECTION

All chemical reagents were commercially available and used without further purification. The glassware used in air and/or moisture sensitive reactions were flame-dried and carried out under a dry nitrogen atmosphere. Tetrahydrofuran was freshly distilled before use from sodium/benzophenone ketyl.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 MHz spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.00). The ^{1}H-NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. Coupling constants are reported in Hertz. ^{13}C-NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using a Nicolet Magna 550 spectrometer. Low-resolution mass spectra were obtained on a VG TRIO 2 instrument at 70 eV (direct inlet). High-resolution mass spectra were recorded on a VG ZAB BEqQ spectrometer.

Chromatographic columns were performed with E. Merck silica gel (Kieselgel 60, 230-400 mesh). Analytical thin layer chromatography was performed with 0.2 mm coated commercial silica gel plates (E. Merck, DC-Aluminum sheets, Kieselgel 60 F_{254}) and was visualized by 254 nm UV, or by immersion into an ethanolic solution of 5% H_2SO_4.

Elemental analyses were performed by UMYMFOR (Facultad de Ciencias Exactas y Naturales-CONICET). The results were within ± 0.4% of the theoretical values.

(±)-2-Cyclopenten-1-ol (21)

This compound was prepared by a slight modified procedure as previously described.[34] To a solution of 2-cyclopenten-1-one (**20**, 3.92 g, 47.80 mmol) in methanol (100 mL) in the presence of and cerium (III) chloride heptahydrate (14.96 g, 10.00 mmol), sodium borohydride (2.70 g, 17.85 mmol) was added portionwise keeping the temperature below 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then, an

aqueous saturated solution of sodium chloride (30 mL) was added. The mixture was concentrated under vacuum, extracted with ether (3 x 50 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded 3.15 g (81% yield) of pure allylic alcohol **21** as a colorless oil: R_f 0.40 (hexane-EtOAc, 4:1); ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 1 H, H-5_a), 2.25 (m, 2 H, H-5_b, H-4_a), 2.50 (m, 1 H, H-4_b), 4.88 (m, 1 H, H-1), 5.82 (dd, J = 5.6, 2.2 Hz, 1 H, H-2), 5.97 (m, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ 30.83 (C-5)$^{\#}$, 33.05 (C-4)$^{\#}$, 77.26 (C-1), 133.23 (C-3)*, 134.74 (C-2)*. ($^{\#,*}$ Signals assignment may be interchanged)

(±)-*cis*-6-Oxabicyclo[3.1.0]hexan-2-ol (22)

To a solution of alcohol **21** (3.00 g; 35.71 mmol) in methylene chloride (60 mL) was added dropwise a solution of 80% *m*-chloroperbenzoic acid (9.20 g) in methylene chloride (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The solvent was evaporated and the residue was purified by column chromatography using hexane-EtOAc (9:1) as eluant to afford 2.92 g (82% yield) of pure epoxy alcohol **22** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 1H, H-5_a), 1.63 (m, 1 H, H-4_b), 1.92 (m, 1 H, H-3_a), 2.42 (m, 1 H, H-3_b), 2.78 (br s, 1 H, -O*H*), 3.48 (m, 2 H, H-1, H-5), 4.28 (dt, J = 8.0, 1.2 Hz, 1 H, H-2), ^{13}C NMR ($CDCl_3$) δ 25.66 (C-4)$^{\#}$, 26.31 (C-3)$^{\#}$, 55.82 (C-5)$^{\bullet}$, 58.65 (C-1)$^{\bullet}$, 73.10 (C-2). ($^{\#,*}$ Signals assignment may be interchanged).

(±)-2-(6-Chloropurin-9-yl)-6-oxabicyclo[3.1.0]hexane (23)

A suspension of 6-chloropurine (1.10 g, 7.12 mmol) and triphenylphosphine (1.86 g, 7.12 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with diethyl azadicarboxylate (1.35 mL, 8.14 mmol) at room temperature under nitrogen atmosphere. The mixture was vigorously stirred for 10 min, and a solution of epoxy alcohol **22** (740 mg, 7.40 mmol) in tetrahydrofuran (2 mL) was added in one portion. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by column chromatography eluting with hexane-EtOAc (4:1) to give 1.20 g (70% yield) of pure compound **23** that was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 1 H, H-3'$_a$), 1.94 (m, 1 H, H-4'$_a$), 2.20 (m, 2 H, H-3'$_b$, H-4'$_b$), 3.69 (d, J = 2.2 Hz, 1 H, H-1')*, 3.84 (d, J = 2.2 Hz, H-5')*, 5.25 (d, J = 6.5 Hz, 1 H, H-2'), 8.05 (s, 1 H, H-8), 8.75 (s, 1 H, H-2), ^{13}C NMR ($CDCl_3$) δ 26.03 (C-3'), 27.95 (C-4'), 55.34 (C-2'), 57.32 (C-1')*, 58.11 (C-5')*, 143.12 (C-8), 152.11 (C-2),

MS (*m/z* relative intensity) 238 (M^+, 1), 236 (M^+, 3), 209 (14), 207 (37), 183 (5), 181 (16), 157 (32), 155 (100), 119 (18), 82 (38), 81 (50), 53 (36). (* Signals assignment may be interchanged).

(±) 9-(6-oxabicyclo[3.1.0]hex-2-yl)purine-6-ylamine (18)

Compound **23** (200 mg; 0.85 mmol) was treated with methanolic ammonia (5 mL, saturated at –78 °C) and heated in sealed tube at 70 °C for 5 h. The mixture was allowed to cool to room temperature and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using CH_2Cl_2-methanol (98:2) as eluant to afford 150 mg (82% yield) of pure **18** as a white solid: mp > 270 °C; UV (MeOH) λ_{max} 262 nm; IR (KBr, cm^{-1}): 3294, 3244, 3159, 3044, 2489, 2382, 2324, 1669, 1633, 1483, 1427, 1320, 1234, 985, 835,714, 642; ^1H NMR ($CDCl_3$) δ 1.85 (m, 1 H, H-3'$_a$), 2.10 (m, 3 H, H-3'$_b$, H-4'$_a$, H-4'$_b$), 3.72 (d, J = 2.3 Hz, 1 H, H-5'), 3.80 (d, J = 2.3 Hz, 1 H, H-1'), 4.56 (br s, 2 H, -N*H*$_2$), 5.14 (d, J = 6.6 Hz, 1 H, H-2'), 8.10 (s, 1 H, H-8), 8.21 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 26.28 (C-3'), 28.68 (C-4'), 55.88 (C-2'), 58.56 (C-1')*, 59.16 (C-5')*, 140.56 (C-8), 153.84 (C-2); MS (*m/z* relative intensity) 217 (M^+, 16), 188 (83), 162 (31), 148 (11), 135 (100), 119 (9), 108 (59), 81 (30), 55 (51), 53 (48); HRMS (EI) Calcd. for $C_{10}H_{11}ON_5$: 217.0964, found 217.0960. Anal. Calcd. for $C_{10}H_{11}ON_5$: C 55.29; H 5.10; found: C 55.52, H 5.44. (* Signals assignment may be interchanged)

2-Amino-6-(benzyloxy)purine (24)

Anhydrous benzyl alcohol (5 mL) was treated with sodium (270 mg, 11.7 mmol) and the resulting suspension was vigorously stirred under nitrogen with gentle warming until the metal was completely dissolved. The solution was cooled to 0 °C and 2-amino-6-chloropurine (1.00 g, 5.9 mmol) was added. The mixture was stirred for 1 h at 100 °C , then it was diluted with CH_2Cl_2 and purified by column chromatography using CH_2Cl_2-methanol (95:5) as eluant to afford 1.26 g of pure **24** (89% yield) as a white solid: mp 209 °C; lit.[35,36] mp 204-206 °C; lit.[37] mp 202-203 °C; ^1H NMR ($CDCl_3$) δ 5.52 (s, 2 H, PhC*H*$_2$O-purine), 7.33 (m, 3 H, Ph), 7.48 (d, J = 6.9 Hz, 2 H, Ph), 7.83 (s, 1 H, H-8), MS (*m/z* relative intensity) 170 (2), 164 (8), 135 (27), 106 (11), 91 (100), 65 (44), 43 (24).

(±) 9-(6-oxabicyclo[3.1.0]hex-2-yl)-6-(phenylmethyloxy)purine-2-ylamine (25)

A suspension of 2-amino-6-benzyloxypurine (639 mg, 2.65 mmol) and

triphenylphosphine (1.043 g, 3.91 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with diethyl azadicarboxylate (0.66 mL, 3.98 mmol) under nitrogen atmosphere. The mixture was vigorously stirred for 10 min, then a solution of epoxy alcohol **22** (265 mg, 2.65 mmol) in tetrahydrofuran (2 mL) was added in one portion. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was purified by column chromatography (silica gel) employing hexane-EtOAc (7:3) as eluant to give 241 mg (28% yield) of pure compound **25** as a white solid: mp 159 °C; ^{1}H NMR ($CDCl_3$) δ 1.75-2.30 (m, 4 H, H-3'$_{a,b}$; H-4'$_{a,b}$), 3.63 (s, 1 H, H-1')*, 3.75 (s, 1 H, H-5')*, 4.94 (br s, 2 H, -NH_2), 5.04 (d, J = 6.0 Hz, 1 H, H-2'), 5.56 (s, 2 H, PhCH_2O), 7.25-7.70 (m, 5 H, Ph), 7.72 (s, 1 H, H-8), ^{13}C NMR ($CDCl_3$-CD_3OD) δ 25.44 (C-3'), 27.22 (C-4'), 53.61 (C-2'), 57.19 (C-1')*, 57.65 (C-5')*, 67.86 (PhCH_2O-purine), 127.77 (Ph), 127.86 (Ph), 128.07 (Ph), 135.95 (Ph), 136.73 (C-8), 160.74 (C-6), MS (*m/z* relative intensity) 323 (M^+, 35), 278 (25), 277 (59), 240 (18), 199 (14), 183 (11), 134 (11), 91 (100),77 (26), 55 (44), 51 (40). (* Signals assignment may be interchanged).

(±)-9-(6-oxabicyclo[3.1.0]hex-2-yl)purine-2,6-diamine (19)

To a solution of **25** (120 mg, 0.37 mmol) in methanol (30 mL) was added 10% palladium on charcoal (10 mg) and ammonium formate (1.30 g), and the reaction was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and was filtered, and the solvent was evaporated. The residue was purified by column chromatography eluting with CH_2Cl_2-methanol (95:5) to afford 40 mg (46% yield) of pure **17** as a white solid: mp >270 °C, UV (MeOH) λ_{max} 256 nm, IR (KBr, cm^{-1}) 3451, 3323, 3209, 2731, 1705, 1646, 1598, 1398, 1177, 842, 785, ^{1}H NMR (DMSO-d_6) δ 1.70-2.40 (m, 4 H, H-3'$_{a,b}$; H-4'$_{a,b}$), 3.68 (d, J = 1.5 Hz, 1 H, H-5'), 3.78 (d, J = 1.5 Hz, 1 H, H-1'), 5.03 (d, J = 6.2 Hz, 1 H, H-2'), 7.33 (br s, 2 H, -NH_2), 8.02 (s, 1 H, H-8), ^{13}C NMR (DMSO-d_6) δ 25.55 (C-3'), 27.07 (C-4'), 53.07 (C-2'), 57.04 (C-5')*, 57.46 (C-1')*, 117.10 (C-5), 135.03 (C-8), 150.76 (C-4), 153.43 (C-2), 156.66 (C-6), MS (*m/z* relative intensity) 233 (M^+, 5), 191 (6)135 (7), 69 (19), 55 (16), 44 (100); HRMS (EI) Calcd. for $C_{10}H_{11}O_2N_5$: 233.0913, found 233.0916. Anal. Calcd. for $C_{10}H_{11}O_2N_5$: C 51.50, H 4.75; found: C 51.45, H 4.91. (* Signals assignment may be interchanged).

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