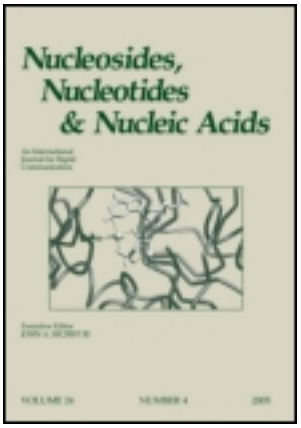

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of Cyclobutane Nucleosides

Abdelaziz Ebead [a], Rene Fournier [a] & Edward Lee-Ruff [a]

[a] Department of Chemistry, York University, Toronto, Ontario, Canada

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SYNTHESIS OF CYCLOBUTANE NUCLEOSIDES

Abdelaziz Ebead, Rene Fournier, and Edward Lee-Ruff
Department of Chemistry, York University, Toronto, Ontario, Canada

□ *2-(6-Chloropurinyl)-3-benzoyloxymethylcyclobutanone can be prepared by reaction of 6-chloropurine with 3-benzoyloxymethyl-2-bromocyclobutanone. The* N*-alkylation gave both* N-9 *and* N-7 *regioisomers. Both regioisomers upon hydride reduction followed by aminolysis gave the corresponding adenine nucleoside analogues. However, the* N-7 *series led to the hypoxanthine analogues as byproducts.*

Keywords Carbocyclic nucleosides; cyclobutane nucleosides; cyclobutanone

INTRODUCTION

Structurally modified nucleosides represent an important class of medicinal compounds, which have been found to behave as therapeutic agents and are currently used in pharmaceuticals as antitumour, antiviral, and antibiotic agents.[1–4] Carbocyclic nucleosides are structurally related to ribonucleosides but have the ring oxygen replaced with a methylene group[5] rendering these more hydrolytically stable toward cellular phosphorylases and hydrolyases. Their structural similarity makes these suitable substrates for the same target enzymes as the ribonucleoside analogues. The observation of potent antiviral activity of the natural occurring oxetane nucleoside, Oxetanocin A[6], prompted the development and commercialization of carbocyclic cyclobutane Oxetanocin analogues (e.g., Cyclobut-A, Lobucavir, or Cyclobut-G), which have been prepared and shown to possess increased bioavailability as a result of their enhanced stability towards hydrolysis.[7]

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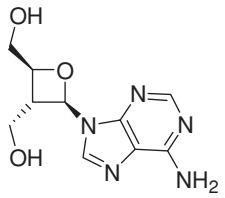
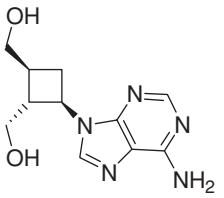
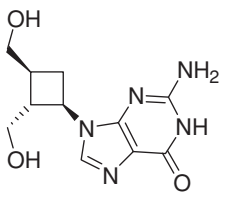
Address correspondence to Edward Lee-Ruff, Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada. E-mail: leeruff@yorku.ca



Oxetanocin A



Cyclobut-A

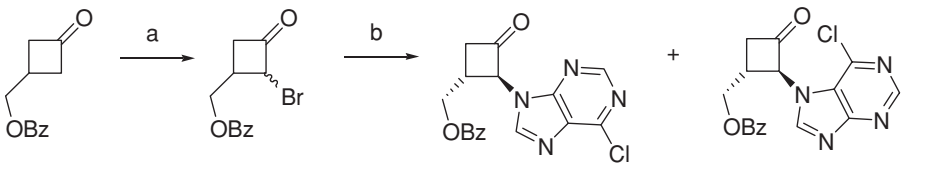


Cyclobut-G, Lobucavir

Our group has been interested in using cyclobutanones as synthetic intermediates by exploiting their unique chemistry as a result of their inherent strain. We have shown that appropriately substituted derivatives can act as glycosyl donors by way of photoisomerization to a transient oxacarbene, which on N-H insertion to nucleobases give, deoxyribonucleosides.[8] During the course of these investigations we became interested in introducing nucleobases at the α-position in order to investigate their ground and excited state reactivity for the purpose of using these as potential nucleoside synthesis starting points.[9] In the current study, we report on the preparation of α-adeninylcyclobutanols and related cyclobutane nucleoside analogues from the corresponding cyclobutanones. The latter series of compounds can also serve as precursors to the divergent synthesis of acyclic, cyclopropane, and isonucleoside analogues of interest as potential antiviral agents. This would be accomplished by exploiting some of the unique photochemistry of cyclobutanones.[10]

RESULTS AND DISCUSSION

The *N*-alkylation of cylobutanones by nucleobases can be achieved by way of α-bromocyclobutanones. We chose 3-benzoyloxycyclobutanone **1**[9] as our substrate for the biologically relevant protected hydroxymethyl substituent in the final product. Bromination of **1** was carried out in chloroform solution giving 65% of a stereoisomeric mixture of **2** (2.2:1), which could not be separated, but used for the *N*-alkylation step with 6-chloropurine under basic conditions. Surprisingly, two regioisomeric components **3** and **4** were produced in 35 and 17%, respectively. The remaining mixture consisted of unreacted **1** (20%) and minor components which were not characterized. The major isomer was identified as the *trans N-9* alkylated cyclobutanone **3** from the single crystal x-ray analysis (Figure 1), while the minor component was assigned the *trans N-7* alkylated derivative **4** from the X-ray diffraction analysis of one of the reduced products derived from this ketone (vide infra).



1 **2** **3** **4**

a. $Br_2/CHCl_3$; b. 6-chloropurine/KOH/CH_3CN

The crystal structure of **3** indicated co-crystallization with its corresponding hydrate (Figure 1). Alkylation at *N-7* is known to take place in competition with *N-9* alkylation by way of the delocalized anion. MO calculations of the 6-chloropurinyl anion indicate relative charges of −0.37 and −0.59 at the *N-7* and *N-9* centers, respectively (vide infra), which is consistent with the larger abundance of ketone **3**. The predominant formation of the *trans*-ketones is the result of thermodynamic control of the *N*-alkylation under basic conditions. None of the *cis*-ketones was detected.

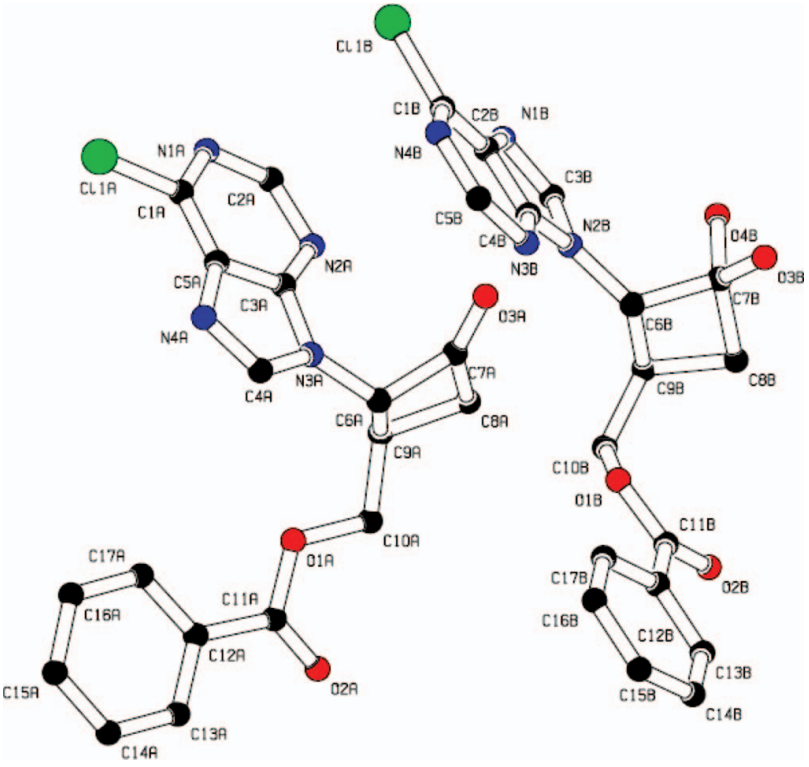
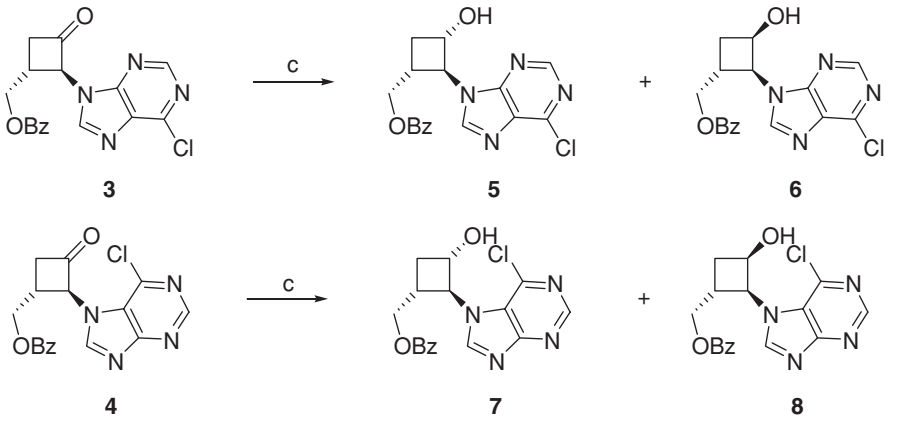


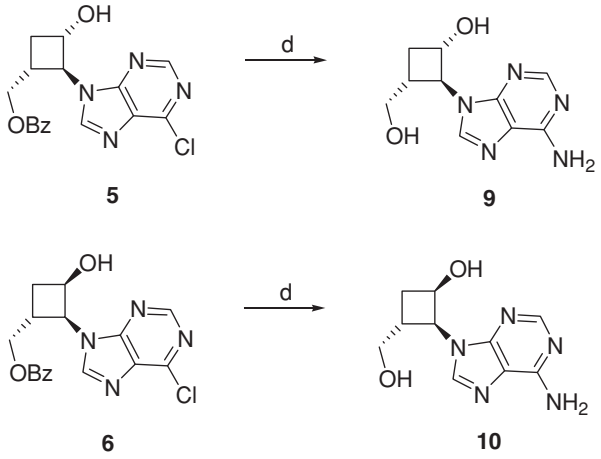
FIGURE 1 Crystal structure of ketone **3** and its hydrate.

Reduction of ketones **3** and **4** was carried out with sodium cyanoborohydride, with **3** giving a mixture of diastereomers **5** and **6** (2:1 ratio), and **4** giving diastereomers **7** and **8** (1:1). The stereochemistry of both diastereomers **5** and **6** obtained from the *N-9* alkylated ketone **3** was based on 2D-NOESY experiments and the differences in off-diagonal correlations of the diasterotopic ring methylene protons with the proximal ring protons for each diastereomer. For **5,** a strong correlation was observed for the C-1 and C-3 protons in the NOESY spectrum, which was absent for epimer **6**. For the stereochemical assignments of diastereomers **7** and **8**, the latter formed suitable crystals for x-ray structure analysis giving a structure, which is consistent with the *cis*-1,2-*trans*-2,3-substitution assignment (Figure 2).



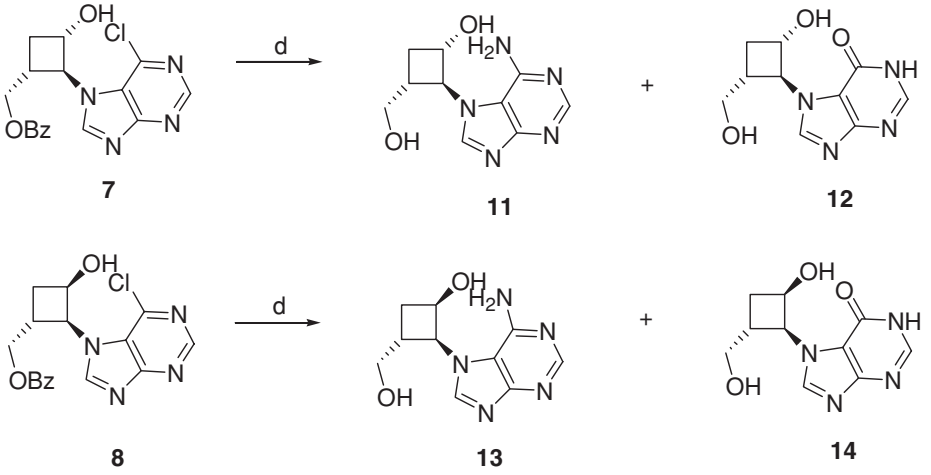
c. $NaCNBH_3$/MeOH/0 °C

The final target nucleoside **9** and **10** were prepared from alcohols **5** and **6**, respectively by reaction with concentrated ammonium hydroxide. Under



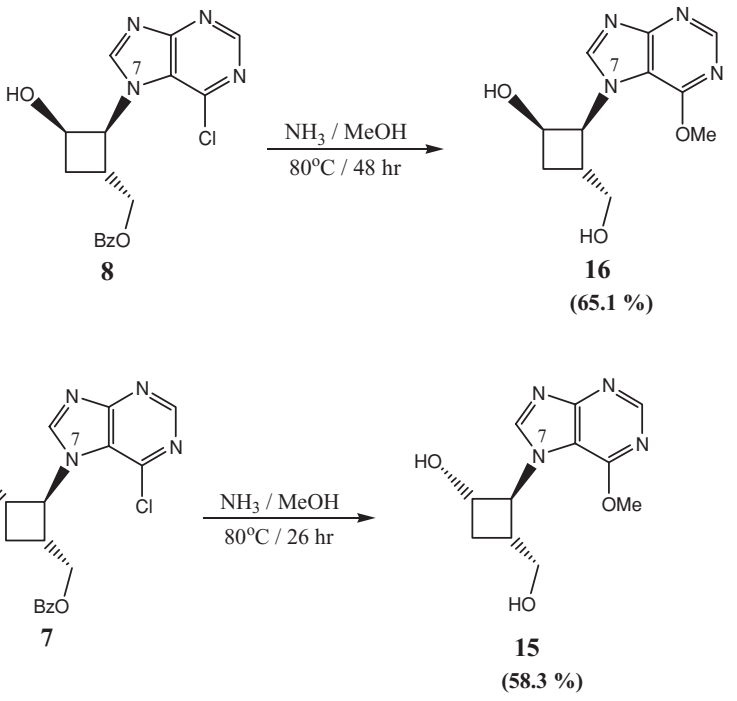
these conditions debenzoylation and aminolysis of the 6-chloropurinyl moiety occurs simultaneously with good to excellent yields (96% for **9** and 71% for **10**).

The aminolysis of the *N-7* series of alcohols **7** and **8** under the same conditions gave the corresponding nucleoside analogues **11** and **13**, respectively, as major products but this was accompanied by the formation of significant amounts of the hypoxanthine nucleosides **12** and **14**, respectively. The formation of hypoxanthines is likely due to competing hydrolysis of the 6-chloropurine moiety with ammonium hydroxide solutions. The first formed phenol product from nucleophilic aryl substitution by water undergoes tautomerization to give the more stable carbonyl form.[11]



d. NH_4OH/30 hours, room temperature

In order to circumvent formation of the hydrolysis byproduct the aminolysis was performed in methanolic ammonia solution. However, under these conditions **7** and **8** did not produce any of the adenine nucleoside derivatives **11** and **13** but resulted in the exclusive formation of the methanolysis products **15** and **16**. It is interesting to note that no solvolysis products were observed for the *N-9* series under the aminolysis conditions. This difference is likely due to the more sterically accessible 6-chloropurine nucleofugal site of the *N-9* series as compared to the *N-7* series. In addition, the hydroxycyclobutyl group hydrogen bonds better to methanol (or water) than to ammonia. This bonding serves a guide to introduce the solvent (methanol or water) to the more proximal chlorine bearing carbon in the *N*-7 series **7** and **8**. In an attempt to convert the 6-methoxypurinyl diol **16** to the adenine **13**, the reaction with concentrated ammonium hydroxide produced only **14**.



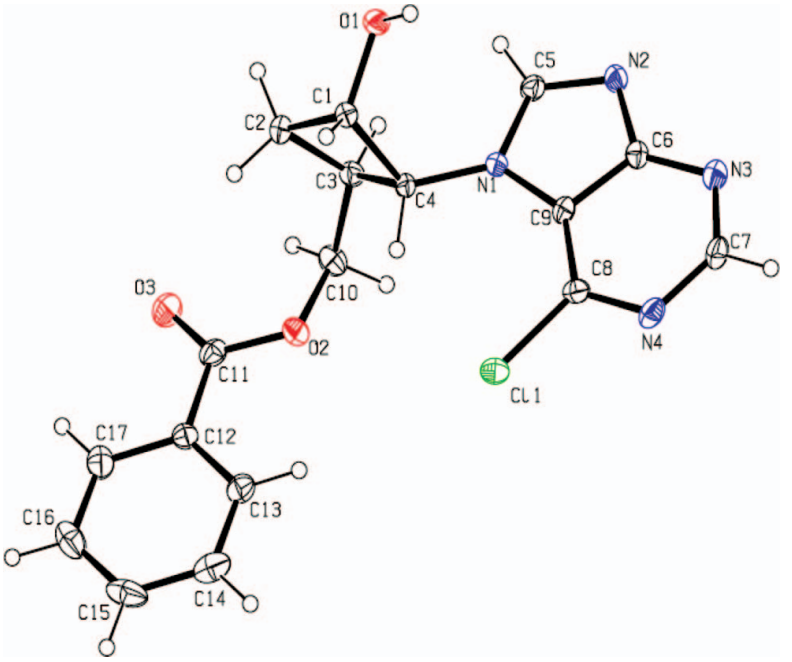


FIGURE 2 Crystal structure for cyclobutanol **8**.

CONCLUSIONS

Starting with a common cyclobutanone precursor possessing a protected hydroxymethyl pendant group, *N*-alkylation with 6-chloropurine under basic conditions generated two regioisomeric α-6-chloropurinyl cyclobutanones by way of *N-7* and *N-9* alkylation of the purinyl anion. The regioisomers are exclusively the *trans*-disubstituted derivatives. Each of the regioisomers was reduced to the corresponding cyclobutanols by hydride reduction giving the mono-protected 6-chloropurine nucleosides. Aminolysis for the *N-9* series of alcohols generated the corresponding deprotected adenine nucleoside analogues while the *N-7* series give a mixture of the adenine and hypoxanthine nucleosides. Thus a common cyclobutanone precursor can be used to produce both *N-7* and *N-9* purinyl cyclobutanone which on structural modification give both adenine and hypoxhanthine cyclobutane nucleoside analogues. All of these novel purinyl substituted cyclobutanols will be screened for biological activity as RT inhibitors for HIV.

In addition, cyclobutanones are known to undergo ring-expansion photoisomerization to a transient oxacarbene, which can be trapped in aqueous solutions giving hemiacetals. Under these conditions ketones **3** and **4** would give isoribonucleosides. Furthermore, a competitive photocycloelimination and photodecarbonylation by triplet sensitization of ketones **3** and **4** would result in acyclic and cyclopropane nucleoside analogues. Preliminary observations on the photochemistry of **3** has been recently reported by us.[10]

The unnatural *trans*-stereochemistry between the nucleobase and hydroxymethyl group in our compounds has been shown to impart biological activity in other nucleoside analogues.[12]

EXPERIMENTAL

All reactions were done in dried glassware. All solvents used for the reactions were dried and distilled. Melting points were obtained with Fisher-Johns melting point apparatus and are uncorrected. Ultraviolet (UV) spectra were determined using an Ultrospec 4300 pro UV spectrometer (GE Healthcare, Piscataway, NJ, USA). Infrared spectra were recorded on a Pye Unicam SP3-200 spectrometer as thin KBr pellets and are reported in cm^{-1}. Mass spectra were recorded on a QStar Elite spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker ARX 400 and 600 MHz superconducting NMR spectrometer. Data for ^{1}H-NMR are referenced relative to residual $CDCl_3$ proton signals at δ 7.27 ppm and to DMSO-d^6 δ at 2.50 ppm. Data for ^{13}C-NMR are referenced relative to $CDCl_3$ at δ 77.16 ppm and to DMSO-d^6 δ at 39.52 ppm. Data for ^{1}H are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet) and integration. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 ALUGRAM sheets and silica gel (40–63 μm) was

used for column chromatography. Preparative TLC was conducted using pre-dried glass plates coated with a silica gel (0–20 μm). All reagents employed were purchased from commercial sources and used without further purification.

(2-Bromo-3-oxocyclobutyl)methyl Benzoate (2)

A solution of bromine (1.25 ml, 25mmol) in 50 mL chloroform was added dropwise at 0°C to a stirred solution of cyclobutanone **1**[9] (5.1 g, 25 mmol) in 100 mL of chloroform. The solution was warmed to room temperature and stirred overnight. The reaction mixture was washed with sat. aq $NaHCO_3$, sat. NaCl and dried over $MgSO_4$. The solvent was removed under vacuum and the residue purified by column chromatography (7% ethyl acetate in hexane) to give 4.6 g (65%) of **2** as a mixture of cis and trans diastereomers (1: 2.2) as an oil.

Major component: ^{1}H-NMR ($CDCl_3$), δ 8.04 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 4.98 (m (long rang coupling, 1H), 4.65 (dxd, J = 4.8, 11.4 Hz, 1H), 4.55 (dxd, J = 6.3, 11.7 Hz, 1H), 3.25 (dxdxdxd, J = 2.4, 9.6, 12.0, 17.4 Hz, 1H), 3.16 (m, 1H), 3.02 (m, 1H); ^{13}C-NMR ($CDCl_3$), δ 197.3, 166.3, 133.6, 129.7. 129.5, 128.7, 64.7, 50.8, 46.6, 36.2;

Minor component: ^{1}H-NMR ($CDCl_3$), δ 7.99 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 8.1 Hz, 2H), 5.27 (m (long rang coupling, 1H), 4.63 (dxd, J = 4.8, 12.6 Hz, 1H), 4.51 (dxd, J = 5.1, 11.7 Hz, 1H), 3.42 (dxdxdxd, J = 3.0, 9.3, 12.3, 17.1 Hz, 1H), 3.11 (m, 2H); ^{13}C-NMR ($CDCl_3$), δ 198.5, 166.2, 133.4, 129.8. 129.6, 128.6, 64.9, 51.7, 46.9, 28.9. IR (cm^{-1}) 1799 (C=O of ketone), 1720 (C=O of ester);

Anal. Calcd for $C_{12}H_{11}BrO_3$ for the mixture: C, 50.91; H, 3.92. Found: C, 50.89; H, 3.66. HRMS (EI) for the mixture *m/z* Calcd for $C_{12}H_{11}BrO_3$ (M^+) 281.9892, found 281.9893.

N-Alkylation of 6-Chloropurine with 2

To a mixture of 6-chloropurine (1.54 g, 10 mmol) in acetonitrile (160 mL), potassium hydroxide (0.67 g, 12 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (0.194 g, 0.6 mmol) were added and the mixture was stirred overnight at room temperature. A solution of α-bromocyclobutanone **2** (3.39 g, 12 mmol) in acetonitrile (30 mL) was added dropwise and the mixture was stirred overnight at room temperature. Insoluble material was filtered off and the solvent was removed under vacuum. The residue was purified by chromatography (70% ethyl acetate in hexane) to produce 1.25 g (35%) of *trans*-N-9 alkylated derivative **3** as a solid (m.p. 60–62°C) and 0.68 g (17%) of *trans*-N-7 alkylated derivative **4** as a solid (m.p. 75–76°C).

Benzoic acid 2-(6-chloro-purin-9-yl)-3-oxo-cyclobutylmethyl ester (3): ^{1}H-NMR ($CDCl_3$), δ 8.65 (s, 1H), 8.15 (s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 6.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 5.76 (d, J = 8.0 Hz, 1H), 4.77 (d, J = 5.2 Hz, 2H), 3.56 (m, 1H), 3.44 (m, 1H), 3.23 (dxd, J = 8.8, 18.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$), δ 196.9, 166.5, 152.2, 151.5, 151.4, 144.0, 133.8, 131.6, 129.6, 129.1, 128.7, 68.9, 65.0, 45.3, 33.3; IR (cm^{-1}) 1799 (C=O, ketone), 1716 (C=O, ester); Anal. Calcd for $C_{17}H_{13}ClN_4O_3$: C, 57.23; H, 3.67. Found: C, 56.70; H, 3.82.

Benzoic acid 2-(6-chloro-purin-7-yl)-3-oxo-cyclobutylmethyl ester (4): ^{1}H-NMR ($CDCl_3$), δ 8.85 (s, 1H), 8.38 (s, 1H), 7.82 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.8 Hz, 2H), 6.22 (d, J = 6.6 Hz,1H), 4.80 (dxd, J = 3.3, 11.7 Hz, 1H), 4.76 (dxd, J = 5.1, 11.7 Hz, 1H), 3.30 (m, 1H), 3.44 (m, 3H); ^{13}C-NMR ($CDCl_3$), δ 196.6, 166.3, 161.7, 153.0, 148.0, 142.9, 133.9, 129.5, 129.0, 128.8, 121.9, 69.8, 64.6, 44.7, 36.0; IR (cm^{-1}) 1798 (C=O, ketone), 1717 (C=O, ester); HRMS (EI) *m/z* Calcd for $C_{17}H_{13}ClN_4O_3$ (M^+) 356.0676, found 356.0679.

Reduction of Ketone 3 with $NaCNBH_3$

To a solution of ketone **3** (0.870 g, 2.44 mmol) in methanol (30 mL), sodium cyanoborohydride ($NaCNBH_3$) (0.076 g, 1.22 mmol) was added and the mixture was stirred at 0°C for 5 hours after which sat. aq. NH_4Cl (20 mL) was added and stirred for 10 minutes. The solvent was evaporated under vacuum and the organic mixture was extracted from the residue using 25% MeOH in $CHCl_3$. The solvent was evaporated and the residue was purified by column chromatography (50–70% ethyl acetate in hexane using gradient elution) giving alcohol **5** (0.306 g, 35%) as a solid (m.p. 300°C) as well as 0.158 g (18%) of alcohol **6** as a solid (m.p. 159–161°C).

***Trans*, *trans*-Benzoic acid 2-(6-chloro-purin-9-yl)-3-hydroxy-cyclobutyl methyl ester (5):** ^{1}H-NMR ($CDCl_3$), δ 8.63 (s, 1H), 8.14 (s, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 6.9 Hz, 2H), 4.66 (dxd, J = 7.2, 15.0 Hz, 1H), 4.58 (m, 1H), 4.44 (m, 2H), 4.18 (S (broad), 1H (OH)), 2.85 (m, 1H), 2.58 (m, 1H), 1.90 (m, 1H); ^{13}C-NMR (CDCl3), δ 166.6, 151.9, 151.8, 151.5, 144.0, 133.8, 132.0, 129.6, 129.3, 128.8, 68.3, 65.8, 62.4, 31.7, 28.2; IR (cm^{-1}) 3240 (OH), 1717 (C=O, ester); Anal. Calcd for $C_{17}H_{15}ClN_4O_3$: C, 56.19; H, 4.21. Found: C, 56.54; H, 4.22.

***Cis*, *trans*-Benzoic acid 2-(6-chloro-purin-9-yl)-3-hydroxy-cyclobutyl methyl ester (6):** ^{1}H-NMR ($CDCl_3$), δ 8.49 (s, 1H), 8.41 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.30 (t, J = 7.8 Hz, 2H), 5.12 (dxd, J = 5.4, 9.4 Hz, 1H), 4.92 (m, 1H), 4.44 (m, 2H), 4.27 (S (broad), 1H (OH)), 3.67 (m, 1H), 2.26 (dxd, J = 3.2, 9.6 Hz, 2H); ^{13}C-NMR (CDCl3), δ 166.4, 152.0, 151.3, 150.3, 145.7, 133.5, 130.5, 129.4, 129.3, 128.6, 69.1, 65.6, 54.4, 40.2, 28.7; IR (cm^{-1}) 3240 (OH), 1717 (C=O, ester); Anal. Calcd for $C_{17}H_{15}ClN_4O_3$: C, 56.19; H, 4.21. Found: C, 56.68; H, 4.33.

Reduction of *trans*-N7 Ketone with $NaCNBH_3$

Sodium cyanoborohydride ($NaCNBH_3$) (0.088 g, 1.4 mmol) was added to a solution of ketone **4** (1.0 g, 2.8 mmol) in methanol (90 mL) and the mixture was stirred at 0°C for 6 hour followed by sat. aq. NH_4Cl (40 mL) and stirred for 10 minutes. The solvent was evaporated under vacuum and the organic mixture was extracted from the residue using 25% MeOH in $CHCl_3$. The solvent was evaporated and the residue was purified by column chromatography (75% ethyl acetate in hexane) to give 0.29 g (29%) of **7** as a solid (m.p. 195–196°C) as well as alcohol **8** (0.266 g, 26.6%) as a solid (m.p. 168–169°C).

***Trans, trans*-Benzoic acid 2-(6-chloro-purin-7-yl)-3-hydroxy-cyclobutyl methyl ester (7):** ^{1}H-NMR (DMSO-d_6), δ 9.25 (s, 1H), 8.74 (s, 1H), 7.57 (m, 3H), 7.34 (t, J = 7.8 Hz, 2H), 5.89 (d, J = 6.4 Hz, 1H (OH)), 5.12 (t, J = 8.4 Hz, 1H), 4.60 (m, 1H), 4.47 (dxd, J = 4.4, 11.2 Hz, 1H), 4.39 (dxd, J = 7.2, 11.2 Hz, 1H), 2.37, (m, 1H), 2.36 (dxd, J = 8.4, 18.4 Hz, 1H), 1.67 (dxd, J = 10.0, 18.8 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ 165.3, 161.3, 151.4, 149.2, 142.1, 133.3, 129.2, 128.6, 128.5, 121.9, 69.1, 65.3, 61.8, 34.3, 27.8; Anal. Calcd for $C_{17}H_{15}ClN_4O_3$: C, 56.19; H, 4.21. Found: C, 56.07; H, 4.42.

***Cis, trans*-Benzoic acid 2-(6-chloro-purin-7-yl)-3-hydroxy-cyclobutyl methyl ester (8):** ^{1}H-NMR (DMSO-d_6), δ 9.07 (s, 1H), 8.77 (s, 1H), 7.80 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 5.40 (s, (broad), 1H (OH)), 5.31 (dxd, J = 5.2, 8.8 Hz, 1H), 4.54 (m, 1H), 4.49 (d, J = 6.0 Hz, 2H), 3.93, (m, 1H), 2.17 (m, 1H), 1.96 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ 165.6, 161.6, 151.3, 150.1, 142.3, 133.3, 129.5, 129.0, 128.7, 122.5, 67.8, 65.6, 56.2, 36.9, 27.9; IR (cm^{-1}) 3283 (OH), 1717 (C=O, ester); Anal. Calcd for $C_{17}H_{15}ClN_4O_3$: C, 56.19; H, 4.21. Found: C, 56.41; H, 4.39.

***Trans, trans*-2-(6-Amino-purin-9-yl)-3-hydroxymethyl-cyclobutanol (9):** A mixture of alcohol **5** (0.136 g, 0.38 mmol) and 130 mL of ammonium hydroxide solution (28%) was stirred at 30°C for 24 hours. The solvent was evaporated under vacuum and the residue was purified by column chromatography (15% methanol in chloroform) yielding the corresponding adenine nucleoside **9** (0.085 g, 95.5%) as a solid (m.p. 180–181°C); ^{1}H-NMR (DMSO-d_6), δ 8.24 (s, 1H), 8.14 (s, 1H), δ 7.23 (s, 2H (NH_2)), 5.56 (d, J = 6.4 Hz, 1H (OH)), 4.73 (t, J = 5.0 Hz, 1H (OH)), 4.56 (m, 1H), 4.40 (t, J = 8.2 Hz, 1H), 3.47 (t, J = 5.0 Hz, 2H), 2.54 (m, 1H), 2.21 (dxd, J = 8.6, 18.2 Hz, 1H), 1.50 (dxd, J = 9.8, 19.0 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ 156.1, 152.2, 149.7, 140.1, 119.2, 67.8, 61.8, 59.8, 35.1, 28.2; IR (cm^{-1}) 3326 (br, NH_2, OH) (OH), 3193 (NH_2); Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57. Found: C, 49.50; H, 5.99; HRMS (EI) *m/z* Calcd for $C_{10}H_{13}N_5O_2$ (M^+) 235.1069, found 235.1073; UV (EtOH) $\lambda_{max} = 261.4$ nm, $\varepsilon = 12877\ M^{-1}cm^{-1}$.

***Cis, trans*-2-(6-Amino-purin-9-yl)-3-hydroxymethyl-cyclobutanol (10):** A mixture of 110 mL of ammonium hydroxide solution (28%) and 0.130 g (0.36 mmol) of alcohol **6** was stirred for 30 hours at room temperature.

The solvent was evaporated under vacuum and the residue was purified by column chromatography (15% methanol in chloroform) to produce 0.06 g, (70.5%) of the diol **10** as a solid (m.p. 215–216°C); ^{1}H-NMR (DMSO-d_6), δ 8.22 (s, 1H), 8.11 (s, 1H), 7.17 (s, 2H (NH_2)), 5.27 (s (broad), 1H (OH)), 4.83 (dxd, J = 5.6, 8.4 Hz, 1H), 4.75 (s (broad), 1H (OH)), 4.36 (t, J = 5.2 Hz, 1H), 3.48 (m, 2H), 3.27 (m, 1H), 2.02 (m, 1H), 1.84 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ 155.9, 152.1, 149.6, 140.7, 118.5, 66.5, 61.8, 52.4, 41.2, 28.4; Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57. Found: C, 49.92; H, 6.09; HRMS (EI) *m/z* Calcd for $C_{10}H_{13}N_5O_2$ (M^+) 235.1069, found 235.1073; UV (EtOH) λ_{max} = 260.5 nm, ε = 13687 $M^{-1}cm^{-1}$.

Aminolysis of Alcohol 7

A mixture of 100 mg (0.28 mmol) of alcohol **7** and 100 mL of ammonium hydroxide solution (28%) was stirred for 22 hours at room temperature. The solvent was evaporated under vacuum and the residue was purified by chromatography (20% methanol in chloroform) to obtain 23 mg (35.1%) of the nucleoside **11** as a solid (m.p. 260–262°C) as well as 16 mg (24.3%) of the hypoxanthine nucleoside **12** as a solid (m.p. 220–222°C).

***Trans, trans*-2-(6-Amino-purin-7-yl)-3-hydroxymethyl-cyclobutanol (11):** ^{1}H-NMR (DMSO-d_6), 8.37 (s, 1H), 8.18 (s, 1H), δ 7.19 (s, 2H (NH_2)), 6.47 (d, J = 5.6 Hz, 1H (OH)), 4. 95 (t, J = 5.4 Hz, 1H (OH)), 4.47 (t, J = 8.2 Hz, 1H), 4.14 (m, 1H), 3.62 (m,1H), 3.50 (m, 1H), 2.68 (m, 1H), 2.18 (dxd, J = 8.4, 18.0 Hz, 1H), 1.59 (dxd, J = 10.0, 18.8 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ 159.8, 152.3, 151.8, 143.2, 111.1, 68.6, 60.5, 33.3, 27.6; HRMS (EI) *m/z* Calcd for $C_{10}H_{13}N_5O_2$ (M^+) 235.1069, found 235.1068; UV (H_2O) λ_{max} = 269.2 nm, ε = 7680 $M^{-1}cm^{-1}$.

7-(2-Hydroxy-4-hydroxymethyl-cyclobutyl)-1,7-dihydro-purin-6-one (12): ^{1}H-NMR (MeOH-d_4), δ 8.35 (s, 1H), 8.04 (s, 1H), 4.70 (t, J = 8.0 Hz, 1H), 4.61 (dxd, J = 8.0, 15.6 Hz, 1H), 3.71 (dxd, J = 4.6, 11.4 Hz, 1H), 3.63 (dxd, J = 6.0, 11.6 Hz, 1H), 2.64 (m,1H), 2.39 (dxd, J = 8.4, 18.8 Hz, 1H), 1.62 (dxd, J = 10.2, 18.6 Hz, 1H); ^{13}C-NMR (MeOH-d_4), δ 159.1, 156.4, 146.1, 144.6, 116.7, 70.5, 64.3, 63.6 37.9, 28.5; HRMS (ESI) *m/z* Calcd for $C_{10}H_{12}N_4O_3$ (M-H^+) 235.0831, found 235.0837; UV (H_2O) λ_{max} = 258.6 nm, ε = 8358 $M^{-1}cm^{-1}$.

Aminolysis of Alcohol 8

A mixture of 220 mL of ammonium hydroxide solution (28%) and 240 mg (0.67 mmol) of the alcohol (**8**) was stirred at room temperature for 36 hours. The solvent was evaporated under vacuum and the residue was purified by column chromatography (20% methanol in chloroform) producing 80 mg (51%) of **13** as a solid (m.p. 204–206°C) as well as 42 mg (33.6%) of the hypoxanthine derivative **14** as a solid (m.p. 230–232°C).

***Cis, trans*-2-(6-Amino-purin-7-yl)-3-hydroxymethyl-cyclobutanol (13):** ^{1}H-NMR (MeOH-d_4), δ 8.54 (s, 1H), 8.30 (s, 1H), 5.04 (dxd, J = 5.6, 8.0 Hz, 1H), 4.59 (t, J = 5.2 Hz, 1H), 3.77 (dxd, J = 4.6, 11.4 Hz, 1H), 3.68 (dxd, J = 6.2, 11.4 Hz, 1H), 3.49, (m, 1H), 2.14 (m, 1H), 1.97 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ 157.2, 152.0, 150.5, 145.2, 111.2, 67.2, 62.3, 56.0, 28.0; HRMS (EI) *m/z* Calcd for $C_{10}H_{13}N_5O_2$ (M^+) 235.1069, found 235.1067; UV (H_2O) $\lambda_{max} = 268.4$ nm, $\varepsilon = 7543\ M^{-1}cm^{-1}$.

***Cis, trans*-7-(2-Hydroxy-4-hydroxymethyl-cyclobutyl)-1,7-dihydro-purin-6-one (14):** ^{1}H-NMR (MeOH-d_4), δ 8.35 (s, 1H), 8.02 (s, 1H), 5.25 (dxd, J = 5.4, 9.0 Hz, 1H), 4.54 (t, J = 5.4 Hz, 1H), 3.73 (dxd, J = 5.2, 11.6 Hz, 1H), 3.65 (dxd, J = 6.0, 11.2 Hz, 1H), 3.42, (m, 1H), 2.10 (m, 1H), 1.95 (m, 1H); ^{13}C-NMR (MeOH-d_4), δ 158.3, 158.1, 147.3, 144.5, 116.8, 69.2, 63.9, 58.0, 42.8, 28.9; IR (cm^{-1}) 3332 (br, OH), 1657 (C=N and C=O); HRMS (ESI) *m/z* Calcd for $C_{10}H_{12}N_4O_3$ (M-H^+) 235.0831, found 235.0828; UV (H_2O) $\lambda_{max} = 258.2$ nm, $\varepsilon = 8634\ M^{-1}cm^{-1}$.

Aminolysis of Alcohol 7 in Methanolic Ammonia

A mixture of 120 mg (0.33 mmol) of alcohol **7** and 25 mL of methanolic ammonia solution (7N) was stirred in sealed thick-wall round bottom flask at 80°C for 26 hours. The mixture was cooled to room temperature and the solvent was evaporated under vacuum. The residue was purified by column chromatography (15% methanol in chloroform) to produce 49 mg (58.3%) of the 6-methoxy derivative **15**. ^{1}H-NMR (MeOH-d_4), δ 8.58 (s, 1H), 8.53 (s, 1H), 4.79 (t, J = 8.2 Hz, 1H), 4.52 (dxd, J = 8.0, 15.6 Hz, 1H), 4.22 (s, 3H), 3.69 (dxd, J = 5.0, 11.4 Hz, 1H), 3.64, (dxd, J = 5.4, 11.4 Hz, 1H), 2.58 (m, 1H), 2.40 (dxd, J = 8.6, 19.0 Hz, 1H), 1.64 (dxd, J = 10.2, 19.0 Hz, 1H); ^{13}C-NMR (MeOH-d_4), δ 162.0, 158.8, 152.9, 146.7, 114.1, 71.2, 64.4, 63.5, 55.0, 37.9, 28.5; HRMS (EI) *m/z* Calcd for $C_{11}H_{14}N_4O_3$ (M^+) 250.1066, found 250.1069.

Aminolysis of Alcohol 8 in Methanolic Ammonia

A mixture of 25 mL of methanolic ammonia solution (7N) and 180 mg (0.5 mmol) of alcohol **8** was stirred in sealed thick-wall round bottom flask for 48 hours at 80°C. The mixture was cooled to room temperature and the solvent was evaporated under vacuum. The residue was purified by column chromatography (15% methanol in chloroform) obtaining 82 mg (65.1%) of the 6-methoxy derivative **16**. ^{1}H-NMR (MeOH-d_4), δ 8.57 (s, 1H), 8.53 (s, 1H), 5.11 (dxd, J = 5.2, 8.8 Hz, 1H), 4.53 (t, J = 5.4 Hz, 1H), 4.19 (s, 3H), 3.76 (dxd, J = 4.6, 11.4 Hz, 1H), 3.66, (dxd, J = 6.2, 11.4 Hz, 1H), 3.48 (m, 1H), 2.13 (m, 1H), 1.94 (m, 1H); ^{13}C-NMR (MeOH-d_4), δ 161.7, 159.3, 152.8, 147.0, 114.5, 69.0, 63.8, 58.5, 54.9, 42.0, 28.6; LC-MS: *m/z* = 251.5.

Aminolysis of 16 with NH_4OH

A mixture of 45 mg (0.18 mmol) of **16** and 30 mL of ammonium hydroxide solution (28%) was stirred in sealed thick-wall round bottom flask at 110°C for 24 hours. The reaction mixture was cooled to room temperature. Evaporation of the solvent under vacuum and purification of the residue by column chromatography (20% methanol in chloroform) produced 25 mg (59.5%) of the corresponding hypoxanthine nucleoside **14** identical in all respect with a sample prepared above.

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