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Synthesis of Bicarbocyclic Dideoxynucleosides as Potential Antiviral Agents

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Abstract: Two novel classes of bicarbocyclic dideoxynucleosides have been synthesized for antiviral studies. The key intermediates, **9** and **23**, synthesized in multiple steps from readily available monocyclic or bicyclic precursors, were coupled with the desired heterocyclic bases to afford, after further elaboration, the corresponding bicarbocyclic dideoxynucleosides. The structure and stereochemistry of the tosylate intermediates and the target bicarbocyclic dideoxynucleosides were confirmed by extensive ^{1}H and ^{13}C NMR studies including COSY, NOESY, DEPT, and selective INEPT experiments.

INTRODUCTION

Reverse transcriptase (RT) is an essential enzyme for the replication of the human immunodeficiency virus (HIV). Inhibitors of RT, which are divided into 2',3'-dideoxynucleoside analogs and non-nucleoside compounds, have been found to exhibit both *in vitro* and *in vivo* anti-HIV activities.[1,2] Among nucleoside RT inhibitors, 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxyinosine (ddI), 2',3'-didehydro-3'-deoxythymidine (d4T), and 2',3'-dideoxy-3`-thiacytidine [(-)3TC], are in clinical use for the treatment of AIDS. However, their long-term usefulness is limited because of the development of resistant strains and also by their toxicities which include bone marrow toxicity, peripheral neuropathy, pancreatitis and hepatotoxicity.[3] For this reason, the synthesis of new and distinctly different nucleosides is of considerable significance in this field.[4-6] The area of carbocyclic nucleosides as anti-HIV agents has received much less attention than that pertaining to the natural nucleosides. However, one carbocyclic nucleoside, carbovir, **1**, has shown potent anti-HIV activity through inhibition of HIV RT.[7,8] Another carbocyclic nucleoside, neplanocin A (**2**), while not showing anti-HIV activity, is an inhibitor of S-adenosyl-L-homocysteine hydrolase and has antitumor activity.[9] Also, in terms of exploration of new and distinctly different nucleosides, the area of bicarbocyclic nucleosides of anti-HIV interest has received little attention. Some bicyclic nucleosides have been developed that have moderate antiviral activity, such as 2',3'-dideoxy-2',3'-α-methylenecytidine (**3**) and bicarbocyclic nucleoside **4**.[10,11] A few bicyclic nucleosides corresponding to natural nucleoside analogs have also exhibited anti-HIV activity.[12] This paper reports on the development of

approaches to the synthesis of two new families of bicarbocyclic nucleosides.[13] A key consideration in the design of these new bicyclic nucleosides as antiviral compounds is the conformation of the bicyclic ring and its effect on the spatial relationship between N-9 or N-1 and the -CH_2OH.[14] Molecular modeling studies suggest that these distances for the bicarbocyclic nucleosides of this paper are comparable to those found in nucleosides of natural origin.

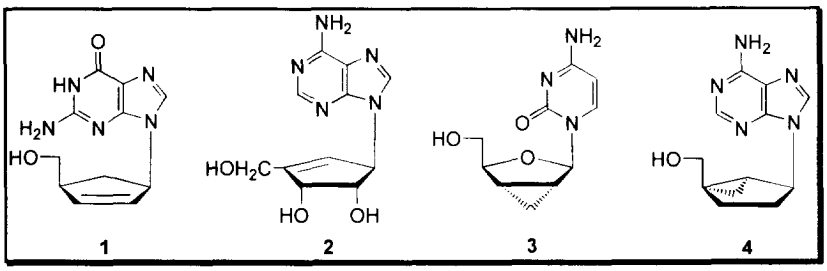


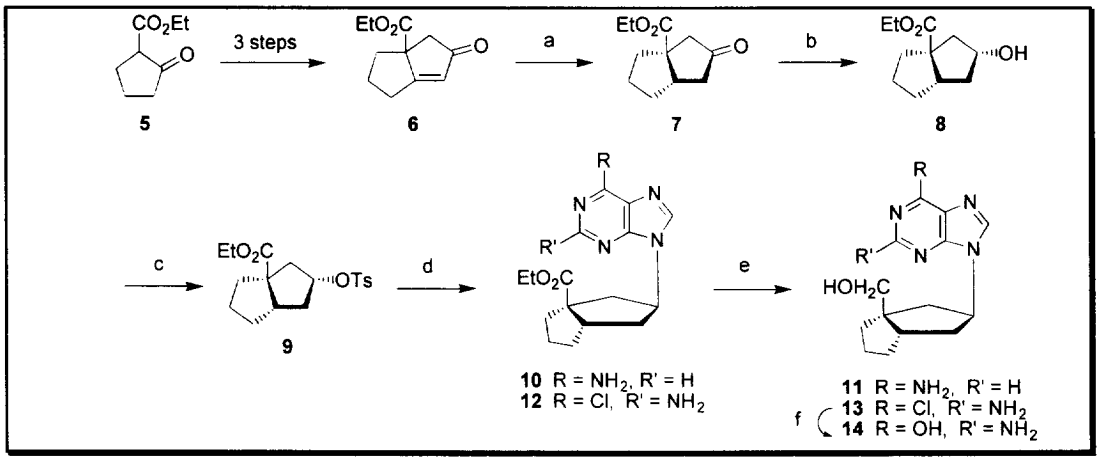
Figure 1

RESULTS AND DISCUSSION

The strategy used for the synthesis of these bicyclo[3,3,0]octanyl nucleosides involved utilization of key intermediates **9** and **23** which could be synthesized from ethyl 2-oxocyclopentan-1-carboxylate (**5**) (for **9**) and from dicyclopentadiene (**19**) (for **23**). Coupling of the appropriate nucleobase with these intermediates bearing a good leaving group would generate the corresponding racemic bicarbocyclic nucleosides with the desired stereochemistry and further elaboration of the coupling product would afford the target molecules.

Enone **6** was prepared from ethyl 2-oxocyclopentan-1-carboxylate (**5**) in three steps.[15] Ketone **7** was produced in 98% yield by hydrogenation of enone **6** using 5% palladium on activated carbon as catalyst (Scheme 1). The *cis*-fused bicyclo[3,3,0]octane derivative was the only product because addition of hydrogen occurred from the less hindered β-face to give the less-strained *cis*-fused product. Diastereoselective reduction (i.e. attack from the less hindered β-face) of ketone **7** to produce alcohol **8** (81% yield) was accomplished by using $NaBH_4/CeCl_3$ in methanol as the reducing agent. When enone **6** was directly reduced to alcohol **8** with $NaBH_4/CeCl_3$ in methanol, a mixture of two isomers, alcohol **8** (major) and its 3-epimer (minor) was produced. Alcohol **8** was converted to a key intermediate, tosylate derivative **9,** in 88% yield, by treatment with *p*-toluenesulfonyl chloride in pyridine. Coupling of tosylate **9** with adenine in DMF in the presence of K_2CO_3 and 18-crown-6 at 80 °C afforded compound **10** in 68% yield. Reduction of compound **10** with DIBAL-H in THF provided racemic bicarbocyclic dideoxyadenosine **11**. The structure and stereochemistry of **11** was confirmed by extensive NMR data. Proton assignments for the tosylate **9** and the target compound **11**

were determined on the basis of COSY two dimensional NMR spectra. The results of the NOESY studies for the tosylate **9** and dideoxyadenosine analogue **11** (Figure 2) provided additional confirmation for the structure and relative stereochemistry of these compounds. For tosylate **9**, the NOE correlations of the methylene protons (CO_2CH_2) with H-2'β, H-5', and H-8'β were observed. The NOE correlations of H-3' with H-2'β and



Scheme 1. Reagents: a) Pd/C, H_2, EtOH; b) $NaBH_4$, $CeCl_3$, MeOH; c) TsCl, pyridine; d) adenine, 18-crown-6, K_2CO_3, DMF; e) DIBAL-H, THF; f) 1 N NaOH.

H-4'β were also observed in tosylate **9**. These data indicated that H-3', H-5', and the ester group (CO_2Et) were on the same side of the molecule **9** and the tosyl group (OTs) was on the opposite side. For the bicarbocyclic dideoxyadenosine analogue **11**, NOE correlations of the methylene protons (CH_2OH) with H-2'β and H-5' were observed. NOE correlations were also observed between H-3' and H-2'α, and H-3' and H-4'α. These data indicated that the adenine group, CH_2OH, and H-5' were on the same side of molecule **11**. The NOESY experiments, coupled with the expected mechanism of the SN_2 reaction, confirm that the heterocycle base and CH_2OH in **11** are indeed on the same side of the molecule.

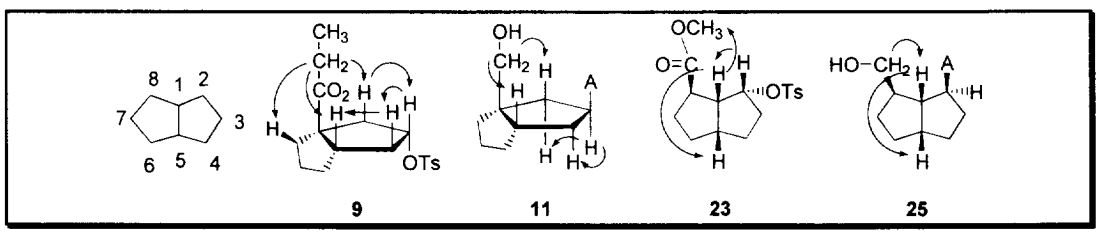
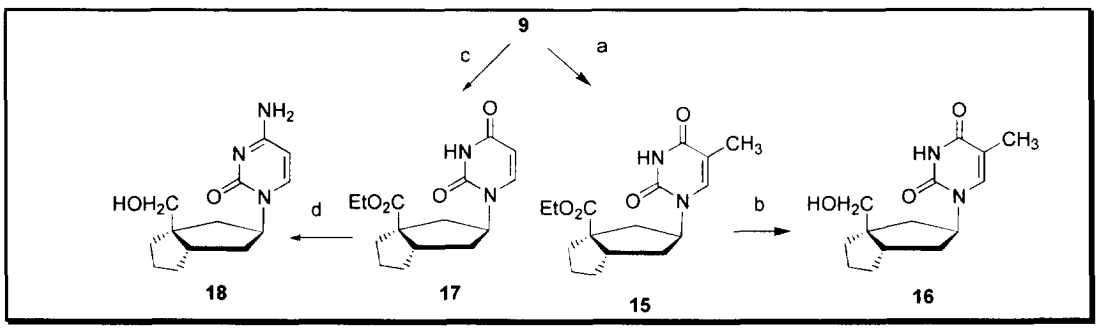


Figure 2. NOESY NMR Correlations Indicated by Arrows.

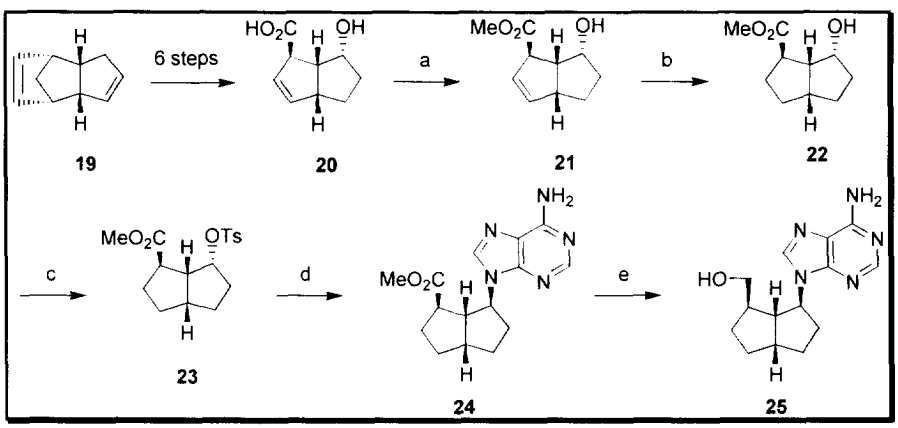
Condensation of tosylate **9** with 2-amino-6-chloropurine under the same conditions as described above gave compound **12** in 35% yield. Bicarbocyclic dideoxyguanosine analogue **14** was obtained by reduction of **12** with DIBAL-H in THF to **13** (67% yield), followed by conversion of the 6-chloro to the 6-hydroxyl group by refluxing **13** with 0.1 N aqueous NaOH (39% yield). The pyrimidine analogues, compounds **15** and **17**, were also obtained using the same coupling conditions (Scheme 2). Bicarbocyclic dideoxythymidine analogue (±) **16** was obtained by reduction of **15** with DIBAL-H in THF (67% yield). The dideoxycytidine analogue (±) **18** was obtained through treatment of the uridine derivative **17** with $POCl_3$ and 1,2,4-triazole in pyridine, followed by hydrolysis of the resulting triazole intermediate with ammonia and 1,4-dioxane, and finally reduction with DIBAL-H in THF (20% overall yield for three steps). Application of the selective INEPT ^1H–^{13}C correlations[16] confirmed the position of attachment of the bicarbocycle to the aglycone for pyrimidine analogues, **16** and **18**. Thus, irradiation of H-3' of analogues **16** or **18** led to selective enhancements of the C-2 and C-6 resonances, at 151.1 and 136.6 ppm for dideoxythymidine analogue **16**, and at 155.9 and 142.0 ppm for dideoxycytidine analogue **18**.



Scheme 2. Reagents: a) thymine, 18-crown-6, K_2CO_3, DMF; b) DIBAL-H, THF; c) uracil, 18-crown-6, K_2CO_3, DMF; d) 1. $POCl_3$, pyridine, 1,2,4-triazole; 2. NH_4OH, 1,4-dioxane; 3. DIBAL-H, THF.

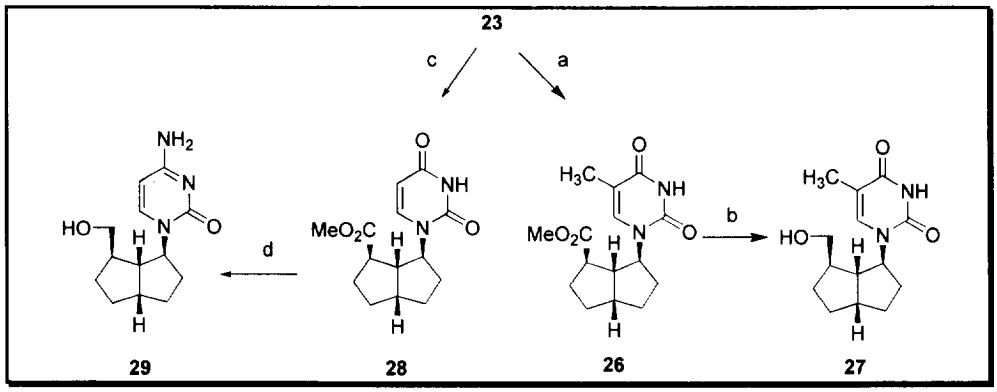
For compounds of the second series, it was discovered that hydroxyacid **20** could be prepared from dicyclopentadiene (**19**) in six steps.[17] Initially, we tried to prepare the tosylate derivative of compound **20** but this resulted in a mixture of products. The hydroxyacid **20** was then converted to its methyl ester **21** in 81% yield by treatment of **20** with diazomethane in methanol (Scheme 3). The tosylate derivative **23** was obtained by hydrogenation of hydoxyester **21** in ethanol using 5% palladium on activated carbon as catalyst, followed by treatment of compound **22** with *p*-toluenesulfonyl chloride in pyridine (83% overall yield for two steps). Condensation of the tosylate **23** with adenine in DMF in the presence of K_2CO_3 and 18-crown-6 gave the coupled product in 52% yield. Reduction of **24** with DIBAL-H in THF afforded (±) **25** (78%). Extensive NMR spectral data including 2D COSY and NOESY experiments provided strong support for the structures of

the product **25** and its key precursor **23** (Figure 2). For tosylate **23**, NOE correlations between H-1' and H-2', H-1' and H-5', H-1' and the methyl protons (CO_2CH_3) were observed. From these data, it can be concluded that H-1', H-2', H-5', and the methyl ester (CO_2Me) were on the same side of the molecule (tosylate **23**) and the tosyl group (OTs) is on the other side. For analogue **25**, NOE correlations between H-1' and H-5', H-1' and -CH_2OH were observed and no NOE correlation between H-1' and H-2' was observed. These data indicated that the adenine group, the hydroxymethyl group (CH_2OH), H-1', and H-5' were on the same side of the target molecule **25**.



Scheme 3. Reagents: a) CH_2N_2, MeOH; b) Pd/C, H_2, EtOH; c) TsCl, pyridine; d) adenine, 18-crown-6, K_2CO_3, DMF; e) DIBAL-H, THF.

Pyrimidine analogues were obtained by condensation of tosylate **23** with the desired pyrimidine base (Scheme 4). Bicarbocyclic dideoxythymidine analogue (±) **27** was prepared by coupling of tosylate **23** with thymine, followed by reduction of compound **26** with DIBAL-H in THF (67% yield). Condensation of tosylate **23** with uracil gave compound **28**. Bicarbocyclic dideoxycytidine analogue (±) **29** was synthesized by treatment of the uridine derivative **28** with $POCl_3$ and 1,2,4-triazole in pyridine, followed by hydrolysis of the resulting triazole intermediate with ammonia in 1,4-dioxane, and finally reduction with DIBAL-H in THF (22% overall yield for three steps). Selective INEPT ^1H-^{13}C correlation spectra[16] were used to confirm the position of attachment of the bicarbocycle to the aglycone for pyrimidine analogues **27** and **29**. Thus, irradiation of H-2' of the dideoxythymidine analogue **27** led to selective enhancements of the resonances for C-2 (δ 137.00 ppm) and C-6 (δ 151.91 ppm). For the dideoxycytidine analogue **29**, irradiation of H-2' led to enhancements of the signals of C-2 (δ 142.76 ppm) and C-6 (δ 156.02 ppm).



Scheme 4. Reagents: a) thymine, 18-crown-6, K_2CO_3, DMF; b) DIBAL-H, THF; c) uracil, 18-crown-6, K_2CO_3, DMF; d) 1. $POCl_3$, pyridine, 1,2,4-triazole; 2. NH_4OH, 1,4-dioxane; 3. DIBAL-H, THF.

In summary, approaches to the synthesis of novel bicarbocyclic nucleosides of potential anti-HIV interest have been developed from readily available monocyclic or bicyclic precursors. The synthetic work described has generality. The structure and stereochemistry of the bicarbocyclic dideoxynucleosides were confirmed by extensive ^1H and ^{13}C NMR studies including COSY, NOESY, DEPT, and selective INEPT experiments. Antiviral activity studies are in progress and will be reported elsewhere.

EXPERIMENTAL

Melting points reported are uncorrected and were determined on a Thomas-Hoover apparatus fitted with a microscope. Ultraviolet (UV) spectra were recorded on a Gilford Response spectrophotometer. Mass spectra (MS) were obtained on a VG Trio-1 instrument. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 pulse Fourier transform instrument at 300 and 75 MHz, respectively. Chemical shift were referenced to an internal tetramethylsilane (Me_4Si) standard for ^1H NMR spectra and to the solvent ($CDCl_3$ or DMSO-d_6) for ^{13}C NMR spectra. Preparative layer chromatography was carried out on plates prepared with E. Merck PF_{254} silica gel. Column chromatography involved columns packed with 63-200 or 230-400 mesh silica gel. Elemental analyses were performed at Desert Analytics Laboratory, Tucson, Arizona and NuMega Laboratories, San Diego, California.

GENERAL SYNTHETIC PROCEDURES

Procedure A: *Glycosylation:* A mixture of dried purine or pyrimidine base (1.5 equivalent), potassium carbonate (1.5 equivalent), 18-crown-6 (1.2 equivalent), and the tosylate derivatives (**9** or **23**, 1 equivalent) in

DMF was stirred under nitrogen between 70–110 °C for 18 h. The solvent was evaporated under high-vacuum and the residue was purified by silica gel chromatography with 0-5% MeOH/$CHCl_3$ as eluant.

Procedure B: *Reduction by diisobutylaluminum hydride:* To a solution of ester nucleoside (1 equivalent) in THF under nitrogen at -30 °C was added dropwise 1.5 M diisobutylaluminum hydride (4–6 equivalent) in toluene. The reaction mixture was stirred for 4 h, during which time it was gradually warmed to room temperature and then quenched with 10% aqueous NH_4Cl, and extracted with $CHCl_3$. Combined extracts were dried over $MgSO_4$ and solvents were evaporated to give a crude product that was purified by silica gel chromatography with 0–10% MeOH/$CHCl_3$ as eluant.

Ethyl 3α-hydroxybicyclo[3,3,0]octane-1β-carboxylate (8): A suspension of enone **6**[15] (3.20 g, 16.5 mmol) and 5% palladium on activated carbon (320 mg) in 30 mL of ethanol was hydrogenated under 40 psi for 18 h. The reaction mixture was filtered with Celite, the filter cake was washed with ethanol, and the solvent was evaporated to give a crude product that was purified by silica gel chromatography with 10-20% EtOAc/hexane as eluant to give 3.15 g (98%) of ethyl 3-oxobicyclo[3,3,0]octane-1β-carboxylate (**7**) as colorless oil. Mass spectrum, m/z 196 (M^+). ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H), 1.44 (m, 1H), 1.58–1.90 (m, 3H), 2.06–2.28 (m, 3H), 2.41(m, 1H), 2.64 (ddd, J = 1.7 Hz, 9.6 Hz, and 18.7 Hz, 1H), 2.85–2.95 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.13, 25.39, 33.95, 37.21, 44.35, 45.22, 47.98, 55.98, 61.07, 176.60, 217.60.

To a solution of ketone **7** (300 mg, 1.5 mmol) and cerium(III) chloride heptahydrate (615 mg, 1.7 mmol) in 8 mL of methanol was added dropwise a solution of sodium borohydride (125 mg, 3.3 mmol) in 2 mL of methanol. The reaction mixture was stirred at room temperature for 1 h, at which time TLC showed complete reaction. After methanol was evaporated, to the residue was added 5 mL of water and 5 mL of 5% HCl, then extracted with $CHCl_3$. Extracts were dried over $MgSO_4$ and solvent was evaporated to provide a crude product that was purified by silica gel chromatography with 20–30% EtOAc/hexane as eluant to give 245 mg (81%) of ethyl 3α-hydroxybicyclo[3,3,0]octane-1β-carboxylate (**8**) as colorless oil. Mass spectrum, m/z 180 ($M-H_2O$)$^+$. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.1 Hz, 3H), 1.19–1.30 (m, 1H), 1.40 (dd, J = 9.1 Hz and 12.7 Hz, 1H), 1.53 (m, 1H), 1.55–1.79 (m, 4H), 1.95–2.05 (m, 2H), 2.21 (m, 1H), 2.53–2.65 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.23 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 14.13, 25.33, 33.49, 38.07, 41.91, 45.49, 46.38, 57.29, 60.50, 73.06, 178.40. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.54; H, 9.26.

Ethyl 3α-(*p*-toluenesulfonyloxy)bicyclo[3,3,0]octane-1β-carboxylate (9): A solution of alcohol **8** (800 mg, 4.0 mmol) in dried pyridine under nitrogen was cooled in an ice-water bath and to the solution was added *p*-toluenesulfonyl chloride (1.140 g, 6.0 mmol). This reaction mixture was stirred for 18 h and then allowed to

warm up gradually to room temperature. The solvent was evaporated and the residue was taken up in chloroform and washed with water. The organic portion was dried over $MgSO_4$ and concentrated and the crude product was purified by silica gel chromatography with 0–20% EtOAc/hexane as eluant to give 1.25 g (88%) of tosylate **9** as a colorless syrup. Mass spectrum, m/z 307 $(M-OEt)^+$. ^1H NMR ($CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 3H), 1.29 (m, 1H), 1.48–1.78 (m, 6H), 2.06 (m, 1H), 2.19 (m, 1H, H-4'β), 2.45 (s, 3H), 2.45–2.60 (m, 2H, H-2'β and H-5'), 4.09 (q, J = 7.1 Hz, 2H), 4.83 (m, 1H, H-3'), 7.35 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.02, 21.54, 25.42, 33.37, 37.59, 38.82, 42.34, 46.22, 56.99, 60.67, 82.51, 127.68, 127.76, 129.73, 144.55, 177.27. Anal. Calcd for $C_{18}H_{24}SO_5$: C, 61.34; H, 6.86. Found: C, 61.14; H, 6.93.

Ethyl 3β-(6-amino-9*H*-purin-9-yl)bicyclo[3,3,0]octane-1β-carboxylate (10): The tosylate **9** (1.10 g, 3.1 mmol) was coupled with adenine using procedure A at 75–80 °C to afford **10** (664 mg) as a white solid in 68% yield. Melting point 122–123 °C. Mass spectrum, m/z 315 (M^+), 136 (base+H), 135 (base). UV (MeOH) λ_{max} 259.5 nm. ^1H NMR ($CDCl_3$): δ 1.23 (t, J = 7.1 Hz, 3H), 1.47 (m, 1H), 1.58–1.87 (m, 3H), 2.00–2.21 (m, 2H), 2.24–2.43 (m, 3H), 2.67 (dd, J = 10.2 Hz and 12.9 Hz, 1H), 2.98 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 5.00 (m, 1H), 6.77 (br, 2H), 7.97 (s, 1H), 8.36 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.96, 26.60, 34.36, 38.79, 39.02, 42.77, 46.60, 54.13, 57.75, 60.77, 119.57, 138.09, 149.92, 152.54, 155.79, 177.19. Anal. Calcd for $C_{16}H_{21}N_5O_2$: C, 60.94; H, 6.71, N, 22.20. Found: C, 60.60; H, 6.74; N, 21.75.

3β-(6-Amino-9*H*-purin-9-yl)-1β-(hydroxymethyl)bicyclo[3,3,0]octane (11): Reduction of ester **10** (2.10 g, 5.9 mmol) using procedure B afforded the dideoxyadenosine analogue **11** (1.22 g) as a white solid in 64.9% yield. Melting point 179–182 °C. Mass spectrum, m/z 273 (M^+), 136 (base + H), 135 (base). UV (MeOH) λ_{max} 260 nm (ε 14,000). ^1H NMR ((DMSO-d_6): δ 1.22–1.54 (m, 3H, H-6' and H-7'), 1.63 (m, 1H, H-8'α), 1.78 (m, 1H, H-8'β), 1.84–2.00 (m, 3H, H-2'α, H-4'α and H-7'), 2.14 (pseudo t, 1H, H-2'β), 2.19–2.35 (m, 2H, H-4'β and H-5'), 3.32 (2H, overlap with H_2O, CH_2OH), 4.74 (t, J = 5.2 Hz, 1H, exchanges with D_2O, OH), 4.85 (m, 1H, H-3'), 7.16 (br, 2H, exchange with D_2O, NH_2), 8.13 (s, 1H), 8.21 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 25.77, 34.37, 37.05, 38.10, 41.98, 42.99, 53.75, 53.84, 68.02, 119.13, 139.16, 149.52, 152.09, 155.92. Anal. Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01, N, 25.62. Found: C, 61.25; H, 6.85, N, 25.16.

Ethyl 3β-(2-amino-6-chloro-9*H*-purin-9-yl)bicyclo[3,3,0]octane-1β-carboxylate (12): The tosylate **9** (650 mg, 1.8 mmol) was coupled with 2-amino-6-chloropurine using procedure A at 70–75 °C to afford **12** (224 mg) as white needles in 35% yield. Melting point 123–125 °C. Mass spectrum, m/z 349 (M^+), 169 (base). UV (MeOH) λ_{max} 247, 308 nm. ^1H NMR ($CDCl_3$): δ 1.24 (t, J = 7.1 Hz, 3H), 1.45 (m, 1H), 1.61–1.84 (m, 4H), 2.05–2.14 (m, 2H), 2.22–2.38 (m, 2H), 2.63 (dd, J = 10.2 Hz and 13.0 Hz, 1H), 2.96 (m, 1H), 4.15 (q, J =

7.1 Hz, 2H), 4.83 (m, 1H), 5.12 (br, 2H), 7.87 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.14, 26.76, 34.55, 38.60, 39.24, 42.53, 46.68, 54.48, 57.91, 61.00, 140.38 (C × 2), 151.23, 153.89, 158.79, 177.21. Anal. Calcd for $C_{16}H_{20}ClN_5O_2$: C, 54.94; H, 5.76; N, 20.02. Found: C, 54.95; H, 5.65; N 20.05.

3β-(2-Amino-6-chloro-9*H*-purin-9-yl)-1β-(hydroxymethyl)bicyclo[3,3,0]octane (13): Reduction of ester **12** (270 mg, 0.77 mmol) using procedure B afforded compound **13** (159 mg) as a glass in 67% yield. Mass spectrum, m/z 307 (M^+), 170 (base + H), 169 (base). UV (MeOH) λ_{max} 247, 308 nm. ^{1}H NMR ($CDCl_3$): δ 1.32–1.82 (m, 6H), 1.95–2.18 (m, 3H), 2.20–2.45 (m, 2H), 2.66 (br, 1H), 3.45–3.70 (m, 2H), 4.80 (m, 1H), 5.24 (br, 2H), 7.86 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 26.05, 34.55, 37.80, 38.94, 41.67, 44.21, 54.24, 55.10, 69.75, 126.00, 140.98, 151.27, 153.62, 158.62. Anal. Calcd for $C_{14}H_{18}ClN_5O$: C, 54.63; H, 5.89; N, 22.75. Found: C, 54.34; H, 6.06; N, 22.23.

3β-(2-Amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)-1β-(hydroxymethyl)bicyclo[3,3,0]octane (14): A suspension of compound **13** (100 mg, 0.32 mmol) in 20 mL of 1 N NaOH was stirred at 90 °C for 1 h at which time dissolution occurred. The reaction mixture was neutralized with 1 N acetic acid and the solvents were evaporated. To the residue was added 3 mL of water and the suspension was filtered. Recrystallization of the solid from EtOH–H_2O several times and then from MeOH afforded 36 mg (39%) of the dideoxyguanosine analogue **14** as a white solid. Melting point 299–302 °C (dec.). UV (MeOH) λ_{max} 253.5 nm (ε 10700). ^{1}H NMR (DMSO-d_6): δ 1.19–1.49 (m, 3H), 1.61 (m, 1H), 1.72–2.03 (m, 5H), 2.04–2.30 (m, 2H), 3.20–3.40 (m, 2H, overlap with H_2O), 4.64 (m, 1H), 4.72 (t, J = 3.2 Hz, 1H, exchange with D_2O), 6.39 (br, 2H), 7.79 (s, 1H), 10.49 (br, 1H, exchanged with D_2O). ^{13}C NMR (DMSO-d_6): δ 25.72, 34.43, 37.09, 38.39, 42.37, 42.98, 52.96, 53.69, 68.00, 116.76, 135.27, 151.07, 153.21, 156.74. Anal. Calcd for $C_{14}H_{19}N_5O_2$: C, 58.12; H, 6.62; N, 24.20. Found: C, 57. 81; H, 6.25; N, 23. 79.

Ethyl 3β-(1,3-dihydro-2,4-dioxo-5-methylpyrimidin-1-yl)bicyclo[3,3,0]octane-1β-carboxylate (15): The tosylate **9** (1.15 g, 3.2 mmol) was coupled with thymine using procedure A at 105 °C. Recrystallization from EtOAc–hexane afforded **15** (228 mg) as a white solid in 29% yield. Melting point 104–106 °C. Mass spectrum, m/z 306 (M^+), 181 (M – base), 127 (base + H), 126 (base). UV (MeOH) λ_{max} 270 nm. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7.1 Hz, 3H), 1.38 (m, 1H), 1.55–2.10 (m, 7H), 1.95 (s, 3H), 2.23–2.37 (m, 2H), 2.80 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 5.07 (m, 1H), 7.18 (s, 1H), 8.79 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 12.60, 14.18, 26.87, 34.38, 37.18, 38.87, 41.09, 46.77, 53.99, 57.36, 61.00, 111.01, 136.13, 151.11, 163.42, 177.62. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.71; H, 7.29; N 8.98.

3β-(1,3-Dihydro-2,4-dioxo-5-methylpyrimidin-1-yl)-1β-(hydroxymethyl)bicyclo[3,3,0]octane (16): Reduction of ester **15** (150 mg, 0.49 mmol) using procedure B afforded the dideoxythymidine analogue **16**. Recrystallization from water afforded 86 mg (67%) of **16** as a white solid. Melting point 75–76 °C. Mass spectrum, m/z 264 (M^+), 127 (base + H), 126 (base). UV (MeOH) λ_{max} 271 nm (ε 9852). ^{1}H NMR ($CDCl_3$): δ 1.30–1.54 (m, 3H), 1.62–2.08 (m, 8H), 1.93 (s, 3H), 2.25 (m, 1H), 3.40–3.65 (m, 2H), 4.99 (m, 1H), 7.17 (s, 1H), 8.76 (br, 1H, exchanges with D_2O). ^{13}C NMR ($CDCl_3$): δ 12.54, 26.05, 34.68, 37.54, 37.58, 40.14, 43.41, 53.29, 54.41, 69.47, 110.6, 136.6, 151.1, 163.6. Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.22; H, 7.97; N, 10.42.

Ethyl 3β-(1,3-dihydro-2,4-dioxopyrimidin-1-yl)bicyclo[3,3,0]octane-1β-carboxylate (17): The tosylate **9** (1.53 g, 4.3 mmol) was coupled with uracil using procedure A at 105 °C. Purification by preparative TLC (silica gel) with 3% MeOH/$CHCl_3$ afforded **17** (332 mg) as a syrup in 26% yield. Mass spectrum, m/z 292 (M^+), 181 (M – base). UV (MeOH) λ_{max} 265 nm. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 3H), 1.40 (m, 1H), 1.56–2.10 (m, 7H), 2.23–2.36 (m, 2H), 2.79 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 5.07 (m, 1H), 5.76 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 9.41 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 14.14, 26.76, 34.25, 37.23, 38.76, 41.18, 46.85, 54.41, 57.42, 60.99, 102.54, 140.38, 151.19, 163.11, 177.47. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.33; H, 6.92; N, 9.29.

3β-(4-Amino-2-oxo-1*H*-pyrimidin-1-yl)-1β-(hydroxymethyl)bicyclo[3,3,0]octane (18): To a solution of 1,2,4-triazole (552 mg, 8 mmol) in 5 mL of pyridine under nitrogen was added dropwise phosphorus oxychloride (281 mg, 1.8 mmol). After five minutes, a solution of **17** (260 mg, 0.9 mmol) in 10 mL of dried pyridine was added to the above reaction mixture. The reaction mixture was stirred at room temperature for 6 h, at which time TLC showed completed reaction. After pyridine was evaporated, the residue was treated with 20 mL of 5% $NaHCO_3$ and extracted with $CHCl_3$. Extracts were combined, dried over $MgSO_4$ and evaporated to give a triazole derivative, which was purified by preparative TLC and used in next reaction without further purification. A solution of the triazole intermediate in 10 mL of 1,4-dioxane and 1.6 mL of ammonium hydroxide was stirred at room temperature for 24 h, at which time TLC showed that the reaction was complete. After removal of solvents, the residue was dissolved in 10 mL of dried THF and then cooled down to 0 °C. To the above solution was added dropwise 4 mL of 1.0 M DIBAL-H in THF. After stirring at 0 °C for 2 h and at room temperature for 6 h, 10 mL of 10% NH_4Cl was added with further stirring for 15 min. After removal of solvents, the residue was purified by preparative TLC (silica gel) with 25% MeOH/$CHCl_3$ followed by reversed-phase HPLC on Amberlite XAD-4 column with 0–15% EtOH/H_2O to afford 45 mg (20%) of **18** as white solid (lyophilized powder). Melting point 119–121 °C. UV (MeOH) λ_{max} 275.9 nm (ε 8400). ^{1}H NMR (DMSO-d_6): δ 1.15–1.45 (m, 3H), 1.55–1.93 (m, 7H), 2.12 (dd, J = 8.2 Hz and 16.0 Hz, 1H), 3.22 (dd, J

= 5.3 Hz and 10.3 Hz, 1H), 3.28 (dd, 1H, overlap with H_2O), 4.69 (t, J = 5.3 Hz, 1H, exchanges with D_2O), 4.89 (m, 1H), 5.67 (d, J = 7.3 Hz, 1H), 6.97 (br, 2H, exchange with D_2O), 7.63 (d, J = 7.3 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 25.79, 34.54, 37.16, 37.20, 40.90, 42.70, 53.18, 54.01, 68.08, 93.45, 142.01, 155.87, 165.05. Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.23; H, 7.44; N, 16.66.

Methyl 6α-hydroxybicyclo[3,3,0]oct-2-en-4β-carboxylate (21): To a solution of hydroxyacid **20**[17] (4.13 g, 24.6 mmol) in 60 mL of methanol was added a solution of diazomethane in diethyl ether, which was prepared from *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (10 g), diethyl ether (100 mL), and 40% aqueous potassium hydroxide (40 mL). The reaction mixture was stirred at room temperature for 20 min, at which time TLC revealed a completed reaction. After the solvents were evaporated, the crude product was purified by silica gel chromatography with hexane-EtOAc (8:2, 7:3) as eluant to yield 3.63 g (81%) of **21** as a syrup. Mass spectrum, m/z 182 (M^+). ^1H NMR ($CDCl_3$): δ 1.39–1.50 (m, 2H), 1.63-1.82 (m, 2H), 2.09 (br, 1H), 2.99 (m, 1H), 3.25 (m, 1H), 3.70 (s, 3H), 3.89 (m, 1H), 4.30 (m, 1H), 5.72 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 27.55, 31.91, 48.60, 48.96, 50.27, 51.99, 74.03, 127.98, 136.86, 175.50. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 6.87; H, 7.99.

Methyl 8α-(*p*-toluenesulfonyloxy)bicyclo[3,3,0]octan-2β-carboxylate (23): A suspension of **21** (2.40 g, 13.2 mmol) and 5% palladium on activated carbon (200 mg) in 30 mL of ethanol was hydrogenated at 40 psi of hydrogen overnight. The reaction mixture was filtered with Celite, the filter cake was washed with ethanol, and the filtrate was evaporated. The crude product was purified by silica gel chromatography with 2% MeOH/$CHCl_3$ as eluant to afford 2.39 g (98%) of methyl 8α-hydroxybicyclo [3,3,0]octan-2β-carboxylate (**22**) as a colorless oil. Mass spectrum, m/z 184 (M^+). ^1H NMR ($CDCl_3$): δ 1.22 (m, 1H), 1.35 (m, 1H), 1.56–1.85 (m, 4H), 1.98-2.07 (m, 2H), 2.46-2.60 (m, 1H, exchanges with D_2O), 2.67 (m, 1H), 2.90 (m, 1H), 3.70 (s, 3H), 4.22 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 28.48, 31.34, 32.55, 34.22, 42.47, 44.61, 51.00, 51.86, 73.77, 176.90.

To a solution of **22** (950 mg, 5.16 mmol) in 10 mL of anhydrous pyridine under nitrogen was added *p*-toluenesulfonyl chloride (1.18 g, 6.2 mmol). The reaction mixture was stirred at room temperature for 30 h. After the solvent was evaporated, the residue was treated with 20 mL of 5% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, and evaporated. The crude product was purified by silica gel chromatography with hexane-EtOAc (8:1, 6:1) as eluant to provide 1.49 g (85%) of **23** as syrup. Mass spectrum, m/z 306 (M - MeOH)$^+$. ^1H NMR ($CDCl_3$): δ 1.26–1.40 (m, 2H), 1.66–1.90 (m, 4H), 1.90–2.04 (m, 2H), 2.45 (s, 3H), 2.55 (m, 1H, H-5'), 2.87 (m, 2H, H-1' and H-8'β), 3.62 (s, 3H, CO_2CH_3), 4.81 (m, 1H, H-2'), 7.33 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.57, 28.5, 32.72, 32.77, 33.91, 42.32, 44.91, 49.98, 51.65, 83.89, 127.72, 129.70, 134.05, 144.53, 175.71. Anal. Calcd for $C_{17}H_{22}SO_5$: C, 60.33; H, 6.55. Found: C, 60.58; H, 6.64.

Methyl 8β-(6-amino-9*H*-purin-9-yl)bicyclo[3,3,0]octan-2β-carboxylate (24): The tosylate **23** (530 mg, 1.57 mmol) was coupled with adenine using procedure A at 80 °C to afford **24** (243 mg) as a white solid in 52% yield. Melting point 131–132 °C. Mass spectrum, m/z 301 (M^+). UV (MeOH) λ_{max} 259.5 nm. ^1H NMR ($CDCl_3$): δ 1.46 (m, 1H), 1.85–2.19 (m, 6H), 2.26 (m, 1H), 2.78 (m, 1H), 2.95 (m, 1H), 3.12 (m, 1H), 3.55 (s, 3H), 4.68 (m, 1H), 6.07 (br, 2H), 7.89 (s, 1H), 8.35 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 30.85, 30.89, 32.81, 33.87, 42.54, 49.68, 51.77, 53.12, 61.27, 119.94, 138.63, 150.22, 152.73, 155.65, 175.16. Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.35; N, 23.24. Found: C, 59.68; H, 6.26; N, 23.15.

2β-(6-Amino-9*H*-purin-9-yl)-8β-(hydroxymethyl)bicyclo[3,3,0]octane (25): Reduction of ester **24** (150 mg, 0.5 mmol) using procedure B afforded the dideoxyadenosine analogue **25** (106 mg) as a white solid in 78% yield. Melting point 192–193 °C. Mass spectrum, m/z 273 (M^+). UV (MeOH) λ_{max} 259.8 nm (ε 13100). ^1H NMR (DMSO-d_6): δ 1.27–1.42 (m, 3H), 1.72–2.12 (m, 6H), 2.54 (m, 1H, overlap with the H_2O, H-1'), 2.73 (m, 1H, H-5'), 3.23 (m, 2H, CH_2OH), 4.53–4.62 (m, 2H, 1H exchange with D_2O, H-2' and OH), 7.18 (br, 2H, exchange with D_2O), 8.12 (s, 1H), 8.18 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 29.09, 30.75, 32.09, 32.41, 41.80, 48.10, 52.45, 61.14, 63.78, 119.10, 139.30, 149.40, 152.10, 156.00. Anal. Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.28; H, 6.99; N, 25.42.

Methyl 8β-(1,3-Dihydro-2,4-dioxo-5-methylpyrimidin-1-yl)bicyclo-[3,3,0]octan-2β-carboxylate (26): The tosylate **23** (1.15 g, 3.26 mmol) was coupled with thymine using procedure A at 105 °C to afford **26** (288 mg) as a white solid, which recrystalized from EtOAc–hexane in 52% yield. Melting point 194–196 °C. Mass spectrum, m/z 292 (M^+). UV (MeOH) λ_{max} 271 nm. ^1H NMR ($CDCl_3$): δ 1.26–1.45 (m, 2H), 1.72–1.99 (m, 3H), 1.94 (s, 3H), 2.01–2.10 (m, 3H), 2.67–2.81 (m, 3H), 3.62 (s, 3H), 4.69 (m, 1H), 7.06 (s, 1H), 9.06 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 12.57, 30.62, 30.73, 32.84, 33.07, 42.58, 49.13, 51.54, 51.79, 61.56, 110.95, 136.57, 151.42, 163.56, 175.31. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.49; H, 7.10; N, 9.30.

2β-(1,3-Dihydro-2,4-dioxo-5-methylpyrimidin-1-yl)-8β-(hydroxymethyl)bicyclo[3,3,0]-octane (27): Reduction of ester **26** (150 mg, 0.49 mmol) using procedure B afforded the dideoxythymidine analogue **27** (86 mg) as a white solid in 67% yield. Melting point 178–180 °C. Mass spectrum, m/z 264 (M^+). UV (MeOH) λ max 272.1 nm (ε 9700). ^1H NMR ($CDCl_3$): δ 1.24–1.53 (m, 3H), 1.63 (m, 1H), 1.79–2.67 (m, 9H), 2.40–2.68 (m, 2H), 3.42 (m, 1H), 3.64 (m, 1H), 4.66 (m, 1H), 7.06 (s, 1H), 8.72 (br, 1H, exchanges with D_2O). ^{13}C NMR ($CDCl_3$): δ 12.64, 29.97, 31.24, 32.10, 32.60, 43.03, 48.88, 53.39, 62.63, 65.83, 110.65, 137.00, 151.91, 163.85. Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.24; H, 7.68; N, 10.36.

Methyl 8β-(1,3-dihydro-2,4-dioxopyrimidin-1-yl)bicyclo[3,3,0]octan-2β-carboxylate (28): The tosylate **23** (1.10 g, 3.25 mmol) was coupled with uracil (549 mg, 4.9 mmol) using procedure A at 100 °C. to afford **28** (243 mg) as a white solid in 27% yield. Melting point 111–113 °C. Mass spectrum, m/z 278 (M^+). UV (MeOH) λ_{max} 267.4 nm. ^{1}H NMR ($CDCl_3$): δ 1.35-1.42 (m, 2H), 1.77-2.15 (m, 6H), 2.70–2.80 (m, 3H), 3.63 (s, 3H), 4.69 (m, 1H), 5.75 (dd, J = 8.0 Hz and 2.3 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 8.66 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 30.56, 30.92, 32.63, 33.15, 42.55, 49.22, 51.63, 51.92, 61.89, 102.47, 140.79, 151.19, 162.78, 175.17. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.69; H, 6.69; N, 9.95.

8β-(4-Amino-2-oxo-1*H*-pyrimidin-1-yl)-2β-(hydroxymethyl)bicyclo-[3,3,0]octane (29): To a solution of 1,2,4-triazole (380 mg, 5.5 mmol) in 5 mL of pyridine under nitrogen was added dropwise neat phosphorus oxychloride (281 mg, 1.8 mmol). After five minutes, a solution of **28** (170 mg, 0.6 mmol) in 5 mL of dried pyridine was added to above reaction mixture. The reaction mixture was stirred at room temperature for 6 h, at which time TLC showed a completed reaction. After pyridine was evaporated, 20 mL of 5% $NaHCO_3$ was added to the residue and the solution was extracted with $CHCl_3$. The extracts were combined, dried over $MgSO_4$ and evaporated to give a triazole derivative which was purified by preparative TLC and used in the next reaction without further purification. A solution of the triazole intermediate in 10 mL of 1,4-dioxane and 1.6 mL of ammonium hydroxide was stirred at room temperature for 24 h. After removal of solvents the residue was dissolved in 10 mL of dried THF and then cooled down to 0 °C. To the above solution was added dropwise, 4 mL of 1.0 M DIBAL-H in THF. After stirring at 0 °C for 2 h and at room temperature for 12 h, the reaction mixture was treated with 10 mL of 10% NH_4Cl and then stirred for 15 min. After removal of solvents, the residue was purified by preparative TLC (silica gel) with 25% MeOH/$CHCl_3$ and by reversed-phase HPLC on Amberlite XAD-4 column with 0–15% EtOH/H_2O to afford 34 mg (22%) of **29** as a white solid (lyophilized powder). Melting point 95–98 °C. Mass spectrum, m/z 249 (M^+). UV (MeOH) λ_{max} 277.3 nm (ε 9300). ^{1}H NMR (DMSO-d_6): δ 1.21–1.38 (m, 3H), 1.64–1.90 (m, 6H), 2.10 (m, 1H), 2.58 (m, 1H), 3.20 (m, 2H), 4.54 (m, 2H, 1H exchange with D_2O), 5.66 (d, J = 7.2 Hz, 1H), 6.92 (br, 2H, exchange with D_2O), 7.55 (d, J = 7.2 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 29.05, 30.70, 31.99, 32.13, 41.74, 47.80, 51.34, 62.06, 63.68, 93.38, 142.76, 156.02, 165.07. Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.37; H, 7.31; N, 16.64.

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