Pergamon

Tetrahedron 55 (1999) 7707–7724

TETRAHEDRON

Conformationally Locked Nucleosides. Synthesis And Stereochemical Assignments of 2'-*C*,4'-*C*-Bridged Bicyclonucleosides[1,2]

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Received 10 February 1999; accepted 27 April 1999

Abstract: 1-α-*O*-Methyl-3-*O*,5-*O*-TIPDS-arabinose was converted, in multiple steps, to 2,6-dioxa-bicyclo[3,2,1]octane derivatives, which were condensed with silylated nucleoside bases to give the desired 2',4'-bridged bicyclonucleosides. In this article, synthesis and stereochemical assignments of the bicyclonucleosides are described.

Keywords: carbohydrates, nucleosides, stereochemistry, X-ray crystallography

INTRODUCTION

Recently, conformationally locked nucleosides have drawn considerable attention since these nucleosides adopt certain desired, restricted, geometrical shapes and are potentially useful as small molecule inhibitors[3-8] of certain enzymes as well as building blocks of oligonucleotides.[9-17] It was reported that a conformationally locked nucleoside (**a**) having the Northern bicyclo[3,1,0]hexane as the sugar moiety demonstrated potent activities against HSV, HCMV and EBV.[3-4] A conformationally locked, carbocyclic AZT 5'-triphosphate (**b**) was reported to be an equipotent inhibitor of HIV reverse transcriptase.[5] However, the Southern isomers, **c** and **d**, showed few activities. Other conformationally restricted bicyclonucleosides which were designed as enzyme inhibitors were also reported.[6-8] However, their biological activities were either not significant or not reported. Nevertheless, conformationally locked nucleosides, especially those having the C3'-endo (the Northern) sugar pucker, are promising candidates for antiviral drug screening and deserve further investigation. In addition, conformationally locked nucleosides can be useful as building blocks of oligonucleotides of biological importance. It was well established that the sugar pucker in the DNA-RNA double helix tends to adopt the 3'-endo conformation while the 2'-endo sugar pucker predominates in the DNA-DNA duplex.[18] It was anticipated that conformationally locked 3'-endo nucleosides would enhance hybridization of oligonucleotides to the complementary RNA. Recently, 2'-*O*,4'-*C*-methylene ribonucleosides (**e**), which have a locked 3'-endo sugar pucker, were synthesized and incorporated into oligonucleotides.[14-17] Thermodynamic melting studies showed that these conformationally locked nucleosides can dramatically enhance hybridization of the modified oligonucleotides to the complementary RNA, with Tm increase by 4-6 degrees per modification. Other conformationally restricted nucleosides that were incorporated into oligonucleotides include 4',6'- and 1',6'-methanocarbocyclic nucleosides,[9,10] 3',5'-ethanonucleosides,[11,12] and 2'-*C*,3'-*O*-linked arabinonucleosides.[13] Recently, we have independently explored conformationally locked nucleosides as small molecule enzyme inhibitors as well as building blocks of antisense oligonucleotides. Our first attempt to synthesize the bicyclothymidine (**e**) from condensation of 3,5-*O*-dibenzoyl-1-methyl-2-*O*,4-*C*-

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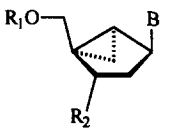
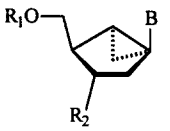
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00394-4

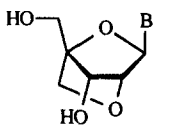
methyleneribofuranose with silylated thymine failed to give the desired product in a practical yield because the ribose ring was opened.[19] However, the synthesis of the bicyclonucleosides (**f**) from the 2,6-dioxabicyclo[3,2,1]octane derivatives[2] was successful and the products were obtained in good yields. In this article, synthesis and stereochemistry of 2'-*C*,4'-*C*-bridged bicyclonucleosides (**f**) are described.



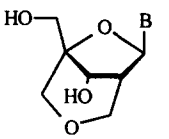
a R_1 = H, R_2 = OH
b R_1 = TP, R_2 = N_3



c R_1 = H, R_2 = OH
d R_1 = TP, R_2 = N_3



e



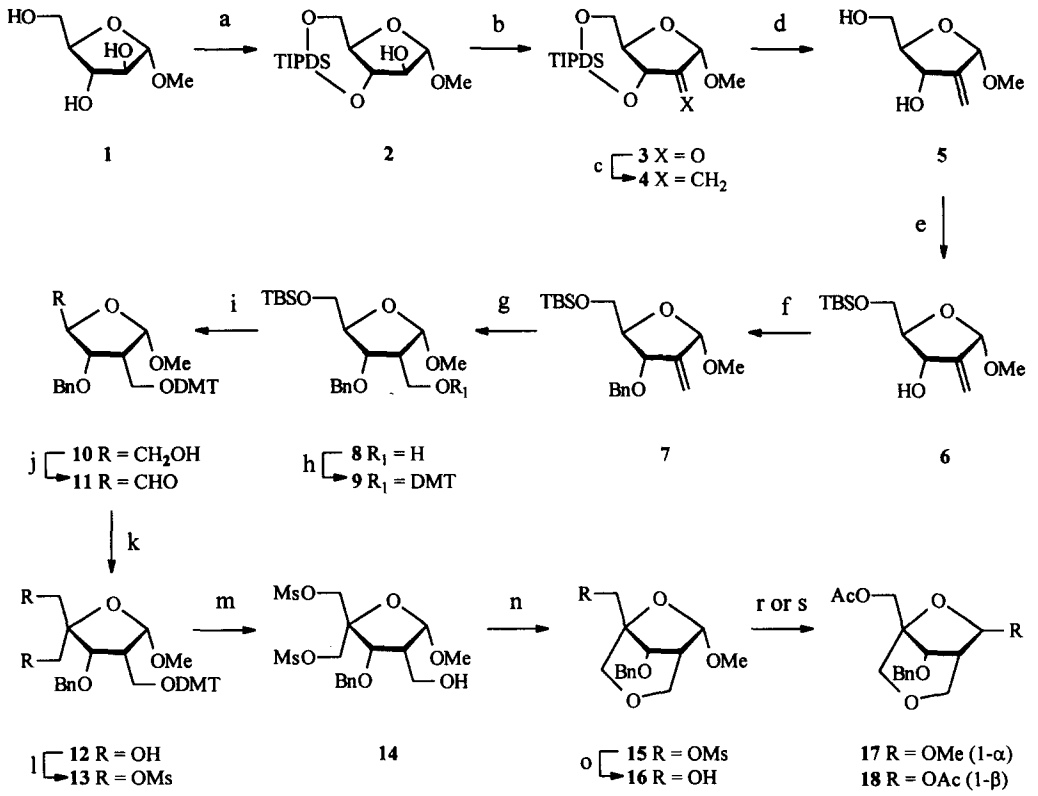
f

RESULTS AND DISCUSSION

Synthesis of the 2,6-dioxabicyclo[3,2,1]octane derivatives[2] is shown in Scheme 1. 1-α-Methylarabinose **1**, prepared according to a published procedure,[21] was protected with 1,1,3,3-tetraisopropyldisiloxanyl (TIPDS) at O3 and O5 to give **2**, which was converted to the ketone **3**. The subsequent Wittig reaction afforded the alkene **4** in very good yield. Previously, di(t-butyl)silyl was used as the protecting group,[2] instead of TIPDS, but the Wittig reaction gave poor yield of the product, probably, because the di(t-butyl)silyl ether was not stable enough at the Wittig reaction condition. After removal of TIPDS, **5** was protected with TBDMS at O5 and with Bn at O3 to give **7**. The hydroboration of **7** was conducted with 9-BBN to give exclusively the 2-deoxy-2-hydroxymethyl derivative **8** in excellent yield. The 2-hydroxymethyl of **8** was protected with DMT and the TBDMS at O5 was removed to give **10**. The 5-hydroxyl of **10** was oxidized to give the aldehyde **11**, which was treated with formaldehyde and sodium hydroxide to yield the 4-hydroxymethyl derivative **12** in excellent yield. The mesylation of **12** and the subsequent removal of DMT yielded **14**. The ring closure of **14** was effected with NaH in THF to give **15**. After removal of the mesyl group, **16** was converted to **17**, in which the methoxy at C1 has the same orientation as in **16** (1-α). Treatment of **16** with acetic anhydride/acetic acid in the presence of sulfuric acid gave **18** almost exclusively, in which the acetoxy at C1 has an inverted orientation (1-β) as compared to the methoxy of **16**. This can be clearly seen from the proton NMR spectra. The H1 of **18** is a single peak, whereas the H1 of **17** is doublet.

The bicyclonucleosides having the 2',4'-bridged sugar moiety were synthesized from condensations of silylated nucleoside bases and the bicyclic sugars as shown Scheme 2 and Scheme 3. At first, trimethylsilyl triflate was chosen as the coupling reagent since it is convenient for work-up and purification of the products. Thus, the condensation of **18** with bis(trimethylsilyl)thymine yielded the coupling product **19** in excellent yield, but it was the α-anomer. Treatment of **19** with BCl_3 removed acetyl and benzyl simultaneously to give the α-bicyclothymidine **20**. The condensation of **18** with 6-chloro-9-trimethylsilylpurine gave a mixture of the α- and β-purine nucleosides, **22** and **21** (ratio, 1:1 to 2:3), which could be separated by chromatography. Treatment of **21** and **22** with ammonia in methanol, followed by hydrogenolysis, gave the adenosine analogs

Scheme 1.



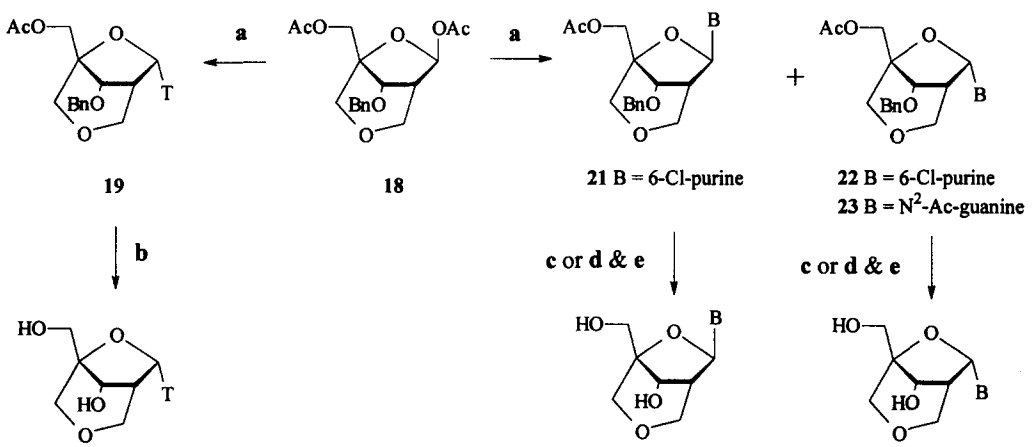
TBS = TBDMS. a) TIPDS-Cl_2, pyridine, r.t., 1.5 h, 88%; b) DMSO, DCC, TFA, pyridine, r.t., 5 h, 89%; c) $Ph_3P{=}CH_2$, ether; -10 °C, 1 h, 91%; d) TBAF, THF, r.t., 1 h, 88%; e) TBDMS-Cl, pyridine, overnight; f) Bn-Br, NaH, THF, r.t., 4 h, 76% (two steps); g) 1. 9-BBN, THF, 40 °C, 14 h; 2. $NaBO_3$, H_2O, 50 °C, 4 h, 93%; h) DMT-Cl, pyridine, r.t., overnight; i) TBAF, THF, r.t., 0.5 h, 94% (two steps); j) DMSO, DCC, TFA, pyridine, r.t., 6 h, 90%; k) CH_2O, NaOH, dioxane, H_2O, r.t., 48 h, 95%; l) Ms-Cl, pyridine, r.t., 15 min; m) AcOH, H_2O, r.t., 2 h, 90% (two steps); n) NaH, THF, 55 °C, 28 h; o) NaOH, H_2O, reflux, 24 h, 98% (two steps); r) for **17**, Ac_2O, pyridine, r.t., 99%; s) for **18**, Ac_2O, AcOH, H_2SO_4, r.t., 2 h, 93%.

24 and **25**, respectively. The hydrogenolysis required a large amount of catalyst and prolonged reaction time because of the increased steric hindrance on the sugar moiety. Treatment of **21** and **22** with mercaptoethanol in the presence of sodium methoxide, followed by hydrogenolysis, gave inosine analogs **26** and **27**, respectively. The condensation of **18** with the silylated N^2-acetylguanine was complicated, giving the α-guanosine derivative **23** as the major product (30%), a small amount of the β-isomer and N^7-coupled products. Treatment of **23** with ammonia in methanol, followed by hydrogenolysis, gave the α-bicycloguanosine **28**.

As described above, the condensation reactions gave either the α-nucleoside, exclusively, or a mixture of the α- and β-nucleosides, without preference for the β-anomers. In order to increase the ratio of β-nucleosides, different condensation conditions were investigated. It seems that temperature had little effect on the ratio of α- and β-anomers. However, the coupling reagent and the functional group at C1 of the sugar did have significant effects on the ratio of α- and β-nucleosides. The condensation of **17** with bis- or tri(trimethylsilyl)

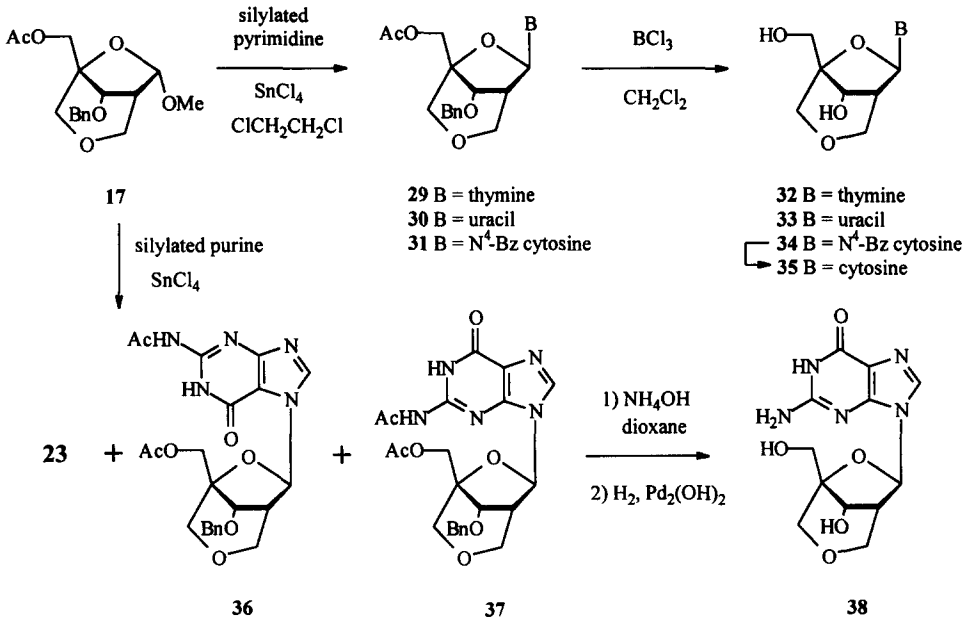
pyrimidines in the presence of tin (IV) chloride gave the β-nucleosides as major products in good yields. Thus, the reaction of **17** with silylated thymine gave the thymidine derivative **29**, with β:α ratio of ~4:1. The condensation of **17** with the silylated uracil and N^4-benzoylcytosine gave the corresponding nucleosides **30** and **31**, respectively, with β:α ratio of ~9:1 in both reactions. Treatment of **29-31** with boron trichloride afforded the pyrimidine bicyclonucleosides **32-34**, respectively. The benzoyl group of **34** was removed by treatment with ammonia to give **35**. An alternative route (not shown) to prepare **35** started from **33**, which was acetylated at O3' and O5', followed by the reaction with triazole and the subsequent treatment with ammonia. In this way, **35** was obtained in moderate yield. The condensation of **17** with the silylated purines with tin (IV) chloride as the coupling reagent was also investigated. Unlike the reactions with pyrimidines, the condensation of the silylated 6-chloropurine with **17** yielded not only the α- and β-nucleosides **22** and **21**, but also an N^7-coupling product. Similarly, the condensation of the silylated N^2-acetylguanine with **17** yielded a mixture of three products, the N^7-coupled β-nucleoside **36** (42%), the desired β-nucleoside **37** (10%) and the α-nucleoside **23** (6%). However, when heated with the silylated N^2-acetylguanine in the presence of trimethylsilyl triflate, the N^7-coupled product **36** was partially converted to the α- and β-bicyclonucleosides **23** (~22%) and **37** (~25%). The separated **37** was subjected to the same treatments as **23** to give the β-bicycloguanosine **38**. It seems that the condensation reactions of **17** with silylated purines had a tendency to produce N^7-coupled bicyclonucleosides when tin (IV) chloride was used as the coupling reagent. Further investigations on preparation of the desired purine β-bicyclonucleosides are underway.

Scheme 2.



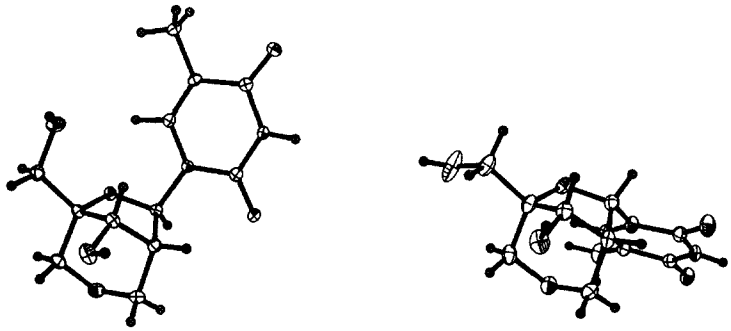
a) TMSOTf, $ClCH_2CH_2Cl$, reflux; 1-2 h, 83% for **19**, 75% for **21** and **22**, 30% for **23**; b) BCl_3, CH_2Cl_2, 15-20 °C, overnight, 93%; c) for **24**, **25**, and **28**, NH_3, MeOH, 100 °C, 6 h-overnight; d) for **26** and **27**, $HSCH_2CH_2OH$, NaOMe, reflux, 24 h; e) 20% $Pd(OH)_2$, MeOH, 3-4 days, 59% for **24** (2 steps), 65% for **25** (2 steps), 61% for **26** (2 steps), 47% for **27** (2 steps), 66% for **28** (2 steps).

Scheme 3.



The stereochemical assignments of the 2,6-dioxabicyclo[3,2,1]octane derivative **16** were described in a previous communication.[2] The stereochemistry of the bicyclonucleosides formed from the condensation of the bicyclic sugars with silylated nucleoside bases can be assigned by the same token. As indicated by a stick-ball model, the rigid dioxabicyclo[3,2,1]octane ring system forces the protons (H1' and H2') at C1' and C2' of the α-bicyclonucleosides to become nearly parallel, whereas the H1' and H2' in the β-bicyclonucleosides direct to the opposite sides. For example, the torsion angle of H1'-C1'-C2'-H2' of the α-bicyclothymidine **20** after a geometry optimization (Alchemy) is 37° and, in consistency with this, a coupling constant of 3.9 Hz in proton NMR was observed. The torsion angle of H1'-C1'-C2'-H2' in the β-bicyclothymidine **32** is 96° after a geometry optimization and, as expected, no coupling between the H1' and H2' was observed. In fact, the proton at C1' in all the β-bicyclonucleosides **24**, **26**, **32**, **33**, **35**, and **38** is a single peak. In contrast, in all the α-bicyclonucleosides **20**, **25**, **27**, and **28**, the proton at C1' is a doublet with a coupling constant of ~4.0 Hz. The stereochemical assignments of the bicyclonucleosides were further confirmed by X-ray crystal structures of the bicyclothymidines **20** and **32**. As can be seen from Fig. 1, the ribose ring of the dioxabicyclo[3,2,1]octane sugar moiety in both compounds adopts a typical C3'-endo sugar pucker while the six-membered ring in the sugar moiety adopts the chair form. The thymine base in both compounds has the anti orientation.

In the crystal of the β-bicyclothymidine **32**, the unit cell contained two conformers (I and II), which have slightly different endocyclic torsion angles. The ν_0 of the conformer I is 1.6°, which is smaller than the ν_0 (4.8°) of the comformer II. These data indicate that C4', O4', C1', and C2' of the conformer I are almost on the same plane, whereas C4' or C2' of the conformer II deviates slightly from the plane. The pseudorotation phase angles *P* were calculated according to a widely used equation.[18] The phase angle *P* is 16.5° for the conformer I



32 **20**

Fig. 1. X-ray crystal structures of the α- and β-bicyclothymidines **20** and **32**[22]

and 12.7° for the conformer II, which correspond to the typical C3'-endo sugar pucker (P = -1° to 34° for the C3'-endo sugar pucker).[18] The sugar pucker of the conformer I is a nearly perfect envelope form ^{3}E, whereas that of the conformer II exists between the envelope and twist forms, but closer to ^{3}E. The torsion angles χ of O4'-C1'-N1-C2 in the conformer I and II are -159.7° and -178.8°, respectively, which indicates the thymine base in both conformers has the anti orientation. That the six-membered ring in the dioxabicyclo[3,2,1]octane sugar moiety adopts the chair form was evidenced by the torsion angles of C3'-C2'-C2"-O3" and C3'-C4'-C4"-O3", which are 61.2° and -60.9°, respectively for the conformer I and 61.2° and -63.8°, respectively, for the conformer II. These data imply an almost perfect chair form. The torsion angle γ of O5'-C5'-C4'-C3' is 56.6° in the conformer I and 51.7° in the conformer II. The data suggest that the preferred conformation of O5' is + sc in both conformers.

In the crystal of the α-bicyclothymidine **20**, the cell unit had four conformers, which have the pseudorotation phase angles P of 11.1°, 14.8° 16.4° and 19.3°, respectively. As can be seen from the phase angles P, all four conformers have the C3'-endo sugar pucker. The sugar puckers of three conformers (i, ii, iii) that have the P angles of 14.8°, 16.4° and 19.3° are the envelope or nearly envelop form ^{3}E, whereas the one (iv) that has the P angle of 11.1° exists as an unsymmetrical form $^3T_2$. These data reveal that the "conformationally locked nucleosides" are not completely locked and there is limited flexibility there. The torsion angles of C3'-C2'-C2"-O3" in these four conformers are in the range of 62.1-63.7° and those of C3'-C4'-C4"-O3" are from -60.9° to -62.8°. As those in the β-anomer **32**, these data indicate that the six-membered ring of the dioxabicyclo[3,2,1]octane sugar moiety in all four conformers has the typical chair form. The torsion angles χ of O4'-C1'-N1-C2 in three conformers (i, ii, iii) are nearly identical (168.5°, 169.0°, 169.9°) and the conformer (iv) that exists as $^3T_2$ has the torsion angle χ of 176.4°. The data suggest that the thymine base in all four conformers of **20** adopts the anti orientation.

CONCLUSION

We have synthesized 3-benzyl-2-deoxy-2-*C*,4-*C*-(dimethylether-1,1'-diyl)-1-methylribofuranoside, a 2,6-dioxabicyclo[3,2,1]octane derivative. A number of bicyclonucleosides built on the dioxabicyclo[3,2,1]octane ring system were prepared from condensations of the bicyclic sugar with silylated nucleoside bases. The stereochemical assignments were achieved with the help of NMR and X-ray crystallography. The synthetic approach described is useful for preparation of novel bicyclonucleosides having locked 3'-endo sugar pucker and allows direct introduction of desired nucleoside bases, modified or unmodified. The synthetic route for the bicyclic sugar was efficient and all the reactions had very good to excellent yields. The condensation conditions for selective formation of pyrimidine α- or β-bicyclonucleosides were well established while selective formation of purine β-bicyclonucleosides requires further attention. Oligonucleotides containing these bicyclonucleosides (**f**) demonstrated excellent hybridization to the complementary RNA.[20] Biological evaluation of the bicyclonucleosides as enzyme inhibitors are underway and will be reported in the due time.

Acknowledgement. The authors wish to thank Dr. Joseph Ziller, the X-Ray Crystallography Facility, University of California at Irvine, for obtaining the X-ray crystal structures, Ms. Jace Collins in their department for the proofreading of this article, and Dr. Devron Averett for his encouragement.

EXPERIMENTAL

Proton NMR spectra were recorded on a 300 MHz spectrometer and chemical shifts are reported in δ values (parts per million) with tetramethylsilane (TMS) as the internal standard. For the compounds containing the 2,6-dioxabicyclo[3,2,1]octane ring system, the resonance in proton NMR was assigned according to the numbering system for nucleosides, instead of that for the bicyclo[3,2,1]octanes. Mass spectra and elemental analysis data were obtained from NuMega Resonance Labs, San Diego. Melting points were measured with a capillary melting points apparatus and are uncorrected. Anhydrous solvents containing <0.005% water were purchased from Fluka or Aldrich and used directly without further treatment. Thin layer chromatography plates and silica gel for column chromatography were supplied by ICN.

2-*C*,2-*O*-Didehydro-1-α-methyl-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-ribofuranose (3). α-Methylarabinose **1** was prepared according to a published procedure[21] and separated from its β-anomer (a minor product) through chromatography on silica. To a stirred solution of **1** (19.27 g, 119.9 mmol) in anhydrous pyridine (200 mL) at 0 °C was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (38.4 mL, 119.9 mmol). The resulting solution was stirred at 0 °C for 1 h and then at room temperature for 1.5 h. The solution was cooled to 0 °C and water (20 mL) added. The mixture was stirred for 10 min and diluted with EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with 15% EtOAc in hexanes gave 42.7 g (88%) of **2** as a colorless syrup.

To a stirred solution of **2** (42.6 g, 104.9 mmol) and DCC (43.4 g, 209.8 mmol) in anhydrous DMSO (250 mL) and ether (100 mL) at 0 °C under argon was added a solution of trifluoroacetic acid (4.04 mL, 52.5 mmol)

and pyridine (8.44 mL, 105 mmol) in DMSO (30 mL). The resulting reaction mixture was warmed to room temperature, stirred for 5 h, and then cooled to 0 °C. Oxalic acid (21.3 g, 236 mmol) in methanol (60 mL) was added, followed by addition of water (30 mL). The resulting mixture was stirred at room temperature for 1 h and the precipitate was filtered and washed thoroughly with hexanes. The filtrate was further diluted with hexanes, washed with water five times, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with 2% MeOH in methylene chloride-hexanes (1:2) gave 37.6 g (89%) of **3** as a colorless syrup; ^1H NMR ($CDCl_3$) δ 1.00-1.12 (m, 28H, TIPDS), 3.47 (s, 3H, OCH_3), 4.05-4.19 (m, 3H, H4, H5a, H5b), 4.51 (dd, J = 9.3 Hz, 1.5 Hz, 1H, H3), 4.89 (t, J = 1.5 Hz, 1H, H1).

2-Deoxy-2-methylene-1-α-methyl-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-D-ribofuranose (4). To a stirred suspension of methyltriphenylphosphonium bromide (21.5 g, 60.1 mmol) in anhydrous ether (1380 mL) at room temperature under argon was added a solution of sodium *t*-pentoxide (5.97 g, 54.0 mmol) in anhydrous benzene (50 mL). The resulting light-yellow mixture was stirred at room temperature for 6 h and cooled to -10 °C, then a solution of **3** (12.1 g, 30.1 mmol) in ether (35 mL) was added. The reaction mixture was stirred at -10 °C for 1 h, washed with brine twice, dried (Na_2SO_4), and concentrated. Chromatography on silica with 5% EtOAc in hexanes gave 11.0 g (91%) of **4** as a colorless syrup; ^1H NMR ($CDCl_3$) δ 1.00-1.12 (m, 28H, TIPDS), 3.45 (s, 3H, OCH_3), 3.73 (dt, J = 9.0 Hz, 3.0 Hz, 1H, H4), 4.02, 4.03 (2s, 2H, H5), 4.62 (dt, J = 9.0 Hz, 2.7 Hz, 1H, H3), 5.27 (m, 1H, H1), 5.32-5.36 (m, 2H, H2').

3-*O*-Benzyl-5-*O*-(*t*-butyldimethylsilyl)-2-deoxy-2-methylene-1-α-methyl-D-ribofuranose (7). To a stirred solution of **4** (35.0 g, 87.1 mmol) in THF (200 mL) was added 1.0 M TBAF in THF (180 mL). The resulting solution stood at room temperature for 1 h. THF was evaporated and the residue chromatographed on silica with 10% EtOH in methylene chloride to give 14.6 g (88%) of **5** as a syrup.

A solution of **5** (13.7 g, 85.5 mmol) and TBDMS-Cl (13.5 g, 89.6 mmol) in anhydrous pyridine (130 mL) stood at room temperature for 15 h. After cooling to 0 °C and addition of water (2 mL), the resulting mixture was stirred at room temperature for 1 h, concentrated to half the volume, diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated to dryness. The thoroughly dried crude **6** in THF (70 mL) was added to a stirred mixture of NaH (60% in mineral oil, 5.6 g, 140 mmol) in THF (350 mL) at 0 °C. After stirring at room temperature for 40 min, benzyl bromide (10.75 mL, 90.5 mmol) was added. The reaction mixture was stirred for 4 h and cooled to 0 °C, followed by slow addition of water (2 mL) and then 10% AcOH in water until pH 7. The mixture was diluted with EtOAc, washed with brine, then with dilute sodium bicarbonate, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with 0-10% EtOAc in hexanes gave 23.8 g (76%) of **7** as a colorless liquid; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.85 (s, 9H, t-Bu), 3.41 (s, 3H, OCH_3), 3.60-3.72 (m, 2H, H5a, H5b), 4.20 (dd, J = 8.7 Hz, 4.5 Hz, 1H, H3), 4.57, 4.66 (AB, J = 12.0 Hz, 2H, Bn), 5.22 (t, J = 1.2 Hz, 1H, H1), 5.38 (t, J = 1.5 Hz, 1H, H2a'), 5.43 (m, J = 1.2 Hz, 1H, H2b'), 7.23-7.37 (m, 5H, Bn); Anal. Calcd. for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85. Found: C, 65.92; H, 9.22.

3-*O*-Benzyl-5-*O*-(*t*-butyldimethylsilyl)-2-deoxy-2-hydroxymethyl-1-α-methyl-D-ribofuranose (8). To a stirred solution of **7** (5.28 g, 14.50 mmol) under argon was added 9-BBN (0.5 M in THF, 87 mL). The resulting solution was stirred at ambient temperature for 1 h, then at 40 °C overnight, cooled to room temperature, and transferred to a flask containing sodium perborate tetrahydrate (13.39 g, 87 mmol) in water (85 mL) and ethanol (85 mL). The resulting mixture was vigorously stirred at 50 °C for 4 h, cooled to 0 °C, neutralized with AcOH to pH 8, and concentrated to a small volume. The remaining volume was diluted with water (20 mL) and extracted with methylene chloride three times. The combined organic layer was washed with brine twice, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with EtOAc-hexanes (1:2) gave 5.17 g (93%) of **8** as a colorless syrup; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6H, $SiCH_3$), 0.87 (s, 9H, t-butyl), 2.34-2.43 (m, 1H, H2), 3.39 (s, 3H, OCH_3), 3.48 (dd, J = 10.5 Hz, 6.0 Hz, 1H, H5a), 3.60 (dd, J = 10.5 Hz, 3.6 Hz, 1H, H5b), 3.88 (d, J = 7.2 Hz, 2H, H2'), 3.98 (dd, J = 7.2 Hz, 2.7 Hz, 1H, H3), 4.17 (m, 1H, H4), 4.44, 4.66 (AB, J = 12.3 Hz, 2H, Bn), 4.95 (d, J = 5.4 Hz, 1H, H1), 7.23-7.36 (m, 5H, Bn); Anal. Calcd. for $C_{20}H_{34}O_5Si$: C, 62.79; H, 8.96. Found: C, 62.92; H, 9.21.

3-*O*-Benzyl-2-deoxy-2-(4,4'-dimethoxytrityloxymethyl)-1-α-methyl-D-ribofuranose 10. A solution of **8** (6.60 g, 17.28 mmol) and DMT-Cl (7.03 g, 20.74 mmol) in anhydrous pyridine (50 mL) stood at room temperature overnight and the reaction was quenched by adding water (8 mL). The resulting solution stood for 10 min and was diluted with EtOAc, washed with brine three times, dried (Na_2SO_4), and concentrated to give the crude **9**, which was dissolved in THF (52 mL). TBAF (1.0 M in THF, 26 mL) was added and the resulting solution stood at room temperature for 30 min. THF was evaporated and the residue chromatographed on silica with EtOAc-hexane (1:1) to give 9.28 g (94%) of **10** as a white foam; ^1H NMR ($CDCl_3$) δ 2.33-2.42 (m, 1H, H2), 3.26-3.63 (m, 7H, H5a, H5b, H2a', H2b', OCH_3), 3.79 (d, J = 1.2 Hz, 6H, DMT), 3.91 (dd, J = 7.5 Hz, 2.4 Hz, 1H, H3), 4.13 (m, 1H, H4), 4.41, 4.50 (AB, J = 12.9 Hz, 2H, Bn), 5.05 (d, J = 5.1 Hz, 1H, H1), 6.78-6.85 (m, 4H, DMT), 7.14-7.47 (m, 14H, Bn, DMT); Anal. Calcd. for $C_{35}H_{38}O_7$: C, 73.66; H, 6.71. Found: C, 73.57; H, 6.76.

3-*O*-Benzyl-2-deoxy-2-(4,4'-dimethoxytrityloxymethyl)-4-*C*-hydroxymethyl-1-α-methyl-D-ribofuranose (12). To a stirred solution of **10** (9.18 g, 16.16 mmol) and DCC (10.0 g, 48.49 mmol) in anhydrous DMSO (60 mL) at 10 °C was added a solution of trifluoroacetic acid (0.622 mL, 8.08 mmol) and pyridine (1.95 mL, 24.24 mmol) in DMSO (15 mL). The resulting reaction mixture was stirred at 10 °C for 1 h, at room temperature for 6 h, and then cooled to 0 °C. After addition of water (8 mL), the mixture was stirred overnight and diluted with EtOAC. The precipitate was filtered and thoroughly washed with EtOAc. The combined filtrate was washed with brine five times, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with EtOAc-hexanes (1:1) gave 8.26 g (90%) of **11** as a white foam.

To a stirred solution of **11** (8.0 g, 14.08 mmol) and formaldehyde (37% in water, 85 mL) in dioxane (420 mL) at 0 °C was added dropwise an aqueous NaOH solution (2.0 M, 210 mL) during 15 min. The resulting cloudy solution was stirred at room temperature for 2 days to become a clear solution. After cooling to 0 °C, the solution was neutralized with 10% acetic acid to pH 8, concentrated to a small volume, diluted with water (100 mL), and extracted with methylene chloride three times. The combined organic layer was washed with

brine, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with 4-5% ethanol in methylene chloride gave 8.11 g (94%) of **12** as a white foam; ^1H NMR ($CDCl_3$) δ 2.46-2.57 (m, 1H, H2), 3.23-3.73 (m, 9H, H5, H4', H2', OCH_3), 3.79 (d, J = 1.8 Hz, 6H, DMT), 4.14 (d, J = 6.9 Hz, 1H, H3), 4.43, 4.47 (AB, J = 12 Hz, 2H, Bn), 4.97 (d, J = 4.8 Hz, 1H, H1), 6.77-6.85 (m, 4H, DMT), 7.11-7.46 (m, 14H, Bn, DMT).

3-*O*-Benzyl-2-deoxy-2-hydroxymethyl-5-*O*-mesyl-4-mesyloxymethyl-1-α-methyl-D-ribofuranose (14). To a stirred solution of **12** (7.80 g, 13.0 mmol) in anhydrous pyridine (60 mL) at 0 °C under argon was added dropwise methanesulfonyl chloride (3.03 mL, 39 mmol). The resulting reaction mixture was stirred at room temperature for 45 min, cooled to 0 °C, and diluted by adding water (5 mL). The resulting mixture was stirred at room temperature for 15 min, diluted with EtOAc, washed with brine three times, dried (Na_2SO_4), and concentrated to give the crude **13** as a white foam, which was dissolved in AcOH-Water (80:20, 400 mL). The resulting solution stood at room temperature for 2 h and was diluted with water (200 mL), and concentrated to about a quarter of the volume. Water (100 mL) was added and the mixture concentrated to dryness. Chromatography on silica with EtOAc-hexanes (3:1 to 1:0) gave 5.32 g (90%) of **14** as a semi-solid; ^1H NMR ($CDCl_3$) δ 2.43-2.54 (m, 1H, H2), 3.01 (s, 3H, OMs), 3.03 (s, 3H, OMs), 3.41 (s, 3H, OCH_3), 3.81 (d, J = 4.8 Hz, 2H, H2'), 4.01, 4.04 (AB, J = 10.5 Hz, 2H, H4'), 4.21 (d, J = 7.5 Hz, 1H, H3), 4.30, 4.50 (AB, J = 1.8 Hz, 2H, H5), 4.56, 4.63 (AB, J = 12.0 Hz, 2H, Bn), 4.99 (d, J = 5.1 Hz, 1H, H1), 7.30-7.42 (m, 5H, Bn); Anal. Calcd. for $C_{17}H_{27}O_{10}S_2$: C, 44.82; H, 5.97. Found: C, 44.68; H, 6.00.

***(1S,3S,4R,8S)*-8-Benzyloxy-1-hydroxymethyl-3-methoxy-2,6-dioxabicyclo[3,2,1]octane (16).** To a stirred mixture of NaH (60% in mineral oil, 1.83 g, 22.90 mmol) in anhydrous THF (200 mL) was added a solution of **14** (5.20 g, 11.45 mmol) in THF (30 mL). The resulting reaction mixture was stirred at 55 °C for 42 h and the reaction quenched by adding water at 0 °C. THF was evaporated and an aqueous NaOH (0.5 M, 250 mL) added. The resulting mixture was heated at reflux for 24 h, cooled to 0 °C, neutralized with dilute hydrochloric acid to pH 8, extracted with methylene chloride four times. The combined organic layer was dried (Na_2SO_4) and concentrated to dryness. Chromatography on silica with EtOAc-hexanes (2:1 to 1:0) gave 3.16 g (98%) of **16** as a colorless syrup; ^1H NMR ($CDCl_3$) δ 2.32 (m, 1H, H2), 3.41 (d, J = 11.4 Hz, 1H, H4a'), 3.46-3.60 (m, 2H, 5H, H5, OCH_3), 3.91 (d, J =11.1 Hz, 1H, H4b'), 3.92 (dd, J = 10.8 Hz, 2.4 Hz, 1H, H2a'), 4.01 (d, J = 5.4 Hz, 1H, H3), 4.04 (d, J = 10.5 Hz, 1H, H2b'), 4.58, 4.64 (AB, J = 12.0 Hz, Bn), 5.07 (d, J = 3.9 Hz, 1H, H1), 7.28-7.40 (m, 5H, Bn).

***(1R,3S,4R,8S)*-1-Acetoxymethyl-8-benzyloxy-3-methoxy-2,6-dioxabicyclo[3,2,1]octane (17).** A solution of **16** (1.60 g, 5.71 mmol), acetic anhydride (1.08 mL, 11.42 mmol), and DMAP (2.09 g, 17.13 mmol) in anhydrous methylene chloride (10 mL) was stirred at room temperature for 2 h, cooled to 0 °C, and diluted with methanol (4 mL). The mixture was stirred at room temperature for 15 min, diluted with methylene chloride, washed with brine and then with 10% $NaHCO_3$, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with ethyl acetate-hexanes (1:1) gave 1.82 g (99%) of **17** as a colorless syrup; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H, OAc), 2.33 (m, 1H, H2), 3.50 (d, J = 10.8 Hz, 1H, H4a'), 3.57 (s, 3H, OCH_3),

3.86-4.04 (m, 5H, H2a', H2b', H3, H4b', H5a), 4.14 (d, J = 12.0 Hz, 1H, H5b), 4.50, 4.64 (AB, J = 12.0 Hz, 1H, Bn), 5.09 (d, J = 3.9 Hz,1H, H1), 7.29-7.42 (m, 5H, Bn); Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.41; H, 6.94.

(*1R,3S,4R,8S*)-3-Acetoxy-1-acetoxymethyl-8-benzyloxy-2,6-dioxabicyclo[3,2,1]octane (18). To a stirred solution of **16** (600 mg, 2.14 mmol) in a mixture of acetic acid (6.0 mL) and acetic anhydride (0.6 mL) at 0 °C was added dropwise concentrated sulfuric acid (57 μL, 1.07 mmol). The resulting reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. After cooling to 0 °C, the solution was diluted with EtOAc, washed with brine three times and then with 10% sodium bicarbonate, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with EtOAc-hexanes (2:3) gave 696 mg (93%) of **18** (β-anomer) and 31 mg (3%) of the α-anomer, both as a colorless syrup. The β-anomer **18** was solidified after standing at room temperature for days; m.p. 55-58 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.36-2.39 (m, 1H, H2), 3.49 (d, J = 10.8 Hz, H4a'), 3.73 (d, J = 11.1 Hz, 2.7 Hz, 1H, H2a'), 3.89 (d, J = 11.1 Hz, 1H, H4b'), 4.01 (d, J = 11.1 Hz, 1H, H2b'), 4.03 (d, J = 9.3 Hz, 1H, H5a), 4.14 (d, J = 5.1 Hz, 1H, H3), 4.55 (d, J = 9.6 Hz, 1H, H5b), 4.55, 4.64 (AB, J = 11.7 Hz, 2H, Bn), 6.39 (s, 1H, H1), 7.29-7.42 (m, 5H, Bn); Anal. Calcd. for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.74; H, 6.46.

(*1R,3S,4R,8S*)-1-Acetoxymethyl-8-benzyloxy-3-(thymin-1-yl)-2,6-dioxabicyclo[3,2,1]octane (19). A mixture of thymine (189 mg, 1.5 mmol) and anhydrous ammonium sulfate (15 mg) in HMDS (6 mL) was heated at reflux overnight. After removal of HMDS, the residue was co-evaporated with anhydrous *m*-xylene, dried under vacuum for 30 min, and dissolved in a solution of **18** (306 mg, 0.87 mmol) in 1,2-dichloroethane (5 mL). To this stirred solution under argon was added dropwise trimethylsilyl triflate (0.38 mL) in 1,2-dichloroethane (2 mL). The resulting solution was heated under reflux for 2 h, cooled to 0 °C, diluted with chloroform, and neutralized with 10 % $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer extracted with chloroform twice. The combined organic layer was dried (Na_2SO_4) and concentrated to dryness. Crystallization from EtOAc-CH_2Cl_2 gave **19** (303 mg, 83%) as a colorless solid; m.p. 198-200 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (d, J = 1.2 Hz, 1H, $ArCH_3$), 2.04 (s, 3H, OAc), 2.93 (m, 1H, H2'), 3.50 (dd, J = 11.8 Hz, 2.1 Hz, 1H, H2a"), 3.59 (d, J = 11.4 Hz, 1H, H4a"), 4.016 (d, J = 11.7 Hz, 1H, H4b"), 4.022 (d, J = 12.6 Hz, 1H, H5a'), 4.09 (d, J = 12.0 Hz, 1H, H2b"), 4.11 (d, J = 4.5 Hz, 1H, H3'), 4.27 (d, J = 12.6 Hz, 1H, H5b'), 4.53, 4.70 (AB, J = 11.7 Hz, 2H, Bn), 5.88 (d, J = 3.6 Hz,1H, H1'), 7.30-7.42 (m, 5H, Bn), 7.74 (d, J = 1.5 Hz, 1H, H6), 8.79 (s, 1H, NH); Anal. Calcd. for $C_{21}H_{24}N_2O_7$: C, 60.57; H, 5.81; N, 6.73. Found: C, 60.55; H, 5.84; N, 6.69.

(*1S,3S,4R,8S*)-8-Hydroxy-1-hydroxymethyl-3-(thymin-1-yl)-2,6-dioxabicyclo[3,2,1]octane (20). To a solution of **19** in anhydrous methylene chloride (3 mL) at 10 °C was added boron trichloride (1.0 M in CH_2Cl_2, 6 mL). The resulting reaction mixture was stirred at 15 °C to room temperature overnight and cooled to 0 °C. Methanol (1.5 mL) was added dropwise and the resulting mixture stirred at 0 °C for 15 min, followed by addition of triethylamine (2 mL). The solvent was evaporated and the precipitate thoroughly extracted with warm acetone. The acetone solution was dried (Na_2SO_4) and concentrated to dryness. Chromatography on

silica with 10% methanol in chloroform gave 99 mg of **20** as a white foam. Crystallization from acetone gave 95 mg (93%) of **20** as a colorless solid; m.p. 225-226 °C; ^{1}H NMR (DMSO-d_6) δ 1.76 (d, J = 0.9 Hz, 1H, $ArCH_3$), 2.45 (m, 1H, H2'), 3.25 (dd, J = 11.4 Hz, 2.1 Hz, 1H, H2a"), 3.32-3.52 (m, 2H, H5'), 3.53 (d, J = 11.4 Hz, 1H, H4a"), 3.72 (d, J = 11.1 Hz, 1H, H4b"), 3.93 (d, J = 11.1 Hz, 1H, H2b"), 4.16 (m, 1H, H3'), 4.84 (t, J = 6.0 Hz, 1H, OH), 5.74 (d, J = 4.2 Hz,1H, H1'), 5.84 (d, J = 3.9 Hz, 1H, OH), 7.76 (d, J = 1.2 Hz, 1H, H6), 11.32 (s, 1H, NH); MS m/z 285 (MH^+); Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.85; H, 5.68; N, 9.75.

***(1R,3R,4R,8S)*-1-Acetoxymethyl-8-benzyloxy-3-(6-chloropurin-9-yl)-2,6-dioxabicyclo[3,2,1]octane (21) and *(1R,3S,4R,8S)*-1-acetoxymethyl-8-benzyloxy-3-(6-chloropurin-9-yl)-2,6-dioxabicyclo[3,2,1]-octane (22).** A mixture of 6-chloropurine (246 mg, 1.6 mmol) and HMDS (8.0 mL) was refluxed under argon for 2 h. HMDS was evaporated and the residue dried under vacuum for 30 min and then dissolved in a solution of **18** (302 mg, 0.83 mmol) in anhydrous 1,2-dichloroethane (5.0 mL), followed by addition of trimethylsilyl triflate (0.38 mL, 2.25 mmol) in 1,2-dichloroethane (2.0 mL). The resulting solution was heated at reflux under argon for 45 min. The work up was the same as that described for **19**. Chromatography on silica with EtOAc-hexanes (1:1) gave **22** (122 mg, α-anomer) and **21** (157 mg, β-anomer), both as a colorless solid. Total yield was 75%. **22**: ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, OAc), 2.89 (m, 1H, H2'), 3.23 (dd, J = 12.0 Hz, 2.4 Hz, 1H, H2a"), 3.72 (d, J = 11.7 Hz, H4a"), 4.09 (d, J = 12.3 Hz, 2H, H4", H5a'), 4.13 (d, J = 13.2 Hz, 1H, H2b"), 4.24 (d, J = 4.8 Hz, H3'), 4.29 (d, J = 12.3 Hz, 1H, H5b'), 4.60, 4.74 (AB, J = 11.7 Hz, 2H, Bn), 6.50 (d, J = 4.2 Hz, 1H, H1'), 7.32-7.44 (m, 5H, Bn), 8.69 (s, 1H, H8), 8.78 (s, 1H, H2). **21**: m.p. 124-125 °C (EtOAc-hexanes); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, OAc), 2.90 (m, 1H, H2'), 3.55 (d, J = 11.1 Hz, H4a"), 3.95-4.03 (m, 2H, H2a", H4b"), 4.18-4.24 (m, 3H, H5', H2b"), 4.32 (d, J = 4.8 Hz, H3'), 4.47, 4.63 (AB, J = 11.7 Hz, 2H, Bn), 6.52 (s, 1H, H1'), 7.24-7.35 (m, 5H, Bn), 8.40 (s, 1H, H8), 8.72 (s, 1H, H2); Anal. Calcd. for $C_{21}H_{21}N_4O_5Cl$: C, 56.70; H, 4.76; N, 12.59. Found: C, 56.36; H, 4.56; N, 12.37.

***(1R,3S,4R,8S)*-1-Acetoxymethyl-3-(N^2-acetylguanin-9-yl)-8-benzyloxy-2,6-dioxabicyclo[3,2,1]octane (23).** A mixture of N^2-acetyl guanine (193 mg, 1.0 mmol) and ammonium sulfate (20 mg) in pyridine (1.0 mL) and HMDS (5.0 mL) was refluxed under argon for 3 h. The resulting clear solution was concentrated and co-evaporated with xylene (10 mL, sodium dried). The residue was dried under vacuum at 50 °C for 1 h and dissolved in a solution of **18** (175 mg, 0.5 mmol) in anhydrous 1,2-dichloroethane (5.0 mL), followed by addition of trimethylsilyl triflate (0.27 mL, 1.5 mmol) in 1,2-dichloroethane (1.0 mL). The resulting solution was stirred at room temperature under argon for 30 min, then heated at 70-75 °C for 2 h, cooled to 0 °C, and neutralized with 10% sodium bicarbonate (10 mL). The resulting mixture was stirred for 15 min and the organic layer separated. The aqueous layer was extracted with chloroform twice. The combined organic layer was dried (Na_2SO_4) and concentrated to dryness. Chromatography on silica with 10% ethanol in $CHCl_3$-EtOAc (1:1) gave **23** (72 mg, 30%) as a colorless solid; m.p. 249 °C (decom., EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, OAc), 2.29 (s, 3H, NAc), 2.75 (m, 1H, H2'), 3.29 (dd, J = 11.7 Hz, 1.8 Hz, 1H, H2a"), 3.66 (d, J = 11.4 Hz, 1H, H4a"), 4.03 (d, J = 11.4 Hz, 1H, H4b"), 4.05 (d, J = 11.7 Hz, 1H, H2b"), 4.70 (d, J = 12.3 Hz,

1H, H5a'), 4.13 (d, J = 4.8 Hz, H3'), 4.23 (d, J = 12.3 Hz, 1H, H5b'), 4.53, 4.67 (AB, J = 11.7 Hz, 2H, Bn), 6.17 (d, J = 4.2 Hz, 1H, H1'), 7.28-7.40 (m, 5H, Bn), 8.32 (s, 1H, H8), 9.80 (s, 1H, NH), 12.12 (s, 1H, NH).

(*1S,3R,4R,8S*)-3-(Adenin-9-yl)-8-hydroxy-1-hydroxymethyl-2,6-dioxabicyclo[3,2,1]octane (24). A solution of **21** (100 mg, 0.225 mmol) in a mixture of dioxane (20 mL) and 30% aqueous ammonium hydroxide (20 mL) was heated in a steel bomb at 100 °C for 16 h. Solvents were evaporated and the residue was dissolved in methanol, followed by addition of 20% palladium hydroxide on charcoal (~50% water, 3 x 250 mg, added each day). The hydrogenolysis was conducted at room temperature under 55 psi hydrogen for 4 days. The catalyst was filtered and washed with methanol. The combined methanol solution was concentrated and the residue chromatographed on silica with 20% methanol in methylene chloride to give **24** (39 mg, 59%) as a colorless solid, which was crystallized from methanol; m.p. 250 °C (decom.); ^{1}H NMR (DMSO-d_6 + D_2O): δ 2.53 (m, 1H, H2'), 3.33 (d, J = 11.1 Hz, 1H, H2a"), 3.40 (d, J = 12.3 Hz, 1H, H5a'), 3.50 (d, J = 12.6 Hz, 1H, H5b'), 3.69-3.76 (m, 2H, H2b", H4a"), 4.05 (d, J = 10.2 Hz, H4b"), 4.45 (d, J = 5.1 Hz, 1H, H3'), 6.26 (s, 1H, H1'), 7.28 (m, 2H, NH_2), 8.12 (s, 1H, H8), 8.33 (s, 1H, H2); MS: 294 (MH^+); Anal. Calcd. for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N, 23.88. Found: C, 49.01; H, 4.97; N, 23.92.

(*1S,3S,4R,8S*)-3-(Adenin-9-yl)-8-hydroxy-1-hydroxymethyl-2,6-dioxabicyclo[3,2,1]octane (25). The same procedure as described for **24** gave **25** (43 mg, 65%) as a colorless solid from **22** (100 mg). ^{1}H NMR (CD_3OD) of **25**: δ 2.71 (m, 1H, H2'), 3.13 (dd, J = 11.7 Hz, 2.4 Hz, 1H, H2a"), 3.57 (d, J = 12.6 Hz, 1H, H5a'), 3.64 (d, J = 11.1 Hz, H4a"), 3.68 (d, J = 12.3 Hz, 1H, H5b'), 3.96 (d, J = 11.1 Hz, 1H, H4b"), 4.14 (d, J = 11.7 Hz, 1H, H2b"), 6.39 (d, J = 4.2 Hz, 1H, H1'), 8.04 (s, 1H, H8), 8.44 (s, 1H, H2); MS m/z 294 (MH^+).

(*1S,3R,4R,8S*)-8-Hydroxy-1-hydroxymethyl-3-(hypoxanthin-9-yl)-2,6-dioxabicyclo[3,2,1]octane (26). To a solution of **21** (150 mg, 0.34 mmol) and mercaptoethanol (0.19 mL, 2.7 mmol) in methanol (20 mL) was added sodium methoxide (0.37 mL of 5.4 M in methanol, 2.0 mmol). The resulting solution was heated under reflux for 6 h, cooled to room temperature, neutralized with 10% AcOH to pH 7. Methanol was evaporated and the residue diluted with 1.0 M $NaHCO_3$ (15 mL), followed by extraction with 10% methanol in chloroform until the aqueous phase did not contain the product. The combined organic layer was dried (Na_2SO_4) and concentrated to dryness. Chromatography on silica with 10-15% methanol in chloroform gave 109 mg (84%) of the inosine derivative (not shown) as a colorless solid, 100 mg (0.26 mmol) of which was dissolved in methanol, followed by addition of 20% palladium hydroxide on charcoal (50% water, 600 mg). The hydrogenolysis was conducted at room temperature under 50 psi hydrogen for 3 days. The catalyst was filtered and washed with methanol. The combined methanol solution was concentrated and the residue chromatographed on silica with 20-25% methanol in methylene chloride to give 61 mg (61%) of **26** as a colorless solid, which was crystallized from methanol-ethyl acetate; m.p. 228 °C (decom.); ^{1}H NMR (DMSO-d_6): δ 2.52 (m, 1H, H2'), 3.30-3.55 (m, 3H, H5', H4a"), 3.69 (dd, J = 11.1 Hz, 2.7 Hz, 1H, H2a"), 3.73 (d, J = 10.8 Hz, H4b"), 4.05 (d, J = 10.8 Hz, 1H, H2b"), 4.40 (m, 1H, H2b"), 5.03 (t, J = 6.0 Hz, 1H, OH), 5.74 (d, J = 4.2 Hz, 1H, OH), 6.24 (s, 1H, H1'), 8.06 (s, 1H, H8), 8.30 (s, 1H, H2), 12.40 (s, 1H, NH); MS m/z 295 (MH^+).

(*1S,3S,4R,8S*)-8-Hydroxy-1-hydroxymethyl-3-(hypoxanthin-9-yl)-2,6-dioxabicyclo[3,2,1]octane (27). To a solution of **22** (120 mg, 0.27 mmol), mercaptoethanol (0.15 mL, 2.1 mmol) in methanol (16 mL) was added sodium methoxide (1.62 mmol, 0.30 mL of 5.4 M in methanol). The same procedure as that for **26** gave 37 mg (47%) of **27** as a hygroscopic solid; ^{1}H NMR (DMSO-d_6) δ 2.52 (m, 1H, H2'), 3.06 (dd, J = 11.7 Hz, 2.4 Hz, 1H, H2a"), 3.34-3.53 (m, 2H, H5'), 3.56 (d, J = 11.1 Hz, 1H, H4a"), 3.79 (d, J = 11.4 Hz, 1H, H4b"), 3.98 (d, J = 11.4 Hz, 1H, H2b"), 4.31 (d, J = 4.5 Hz, 1H, H3'), 4.89 (br, 1H, OH), 5.99 (br, 1H, OH), 6.28 (d, J = 4.2 Hz, 1H, H1'), 8.03 (s, 1H, H8), 8.27 (s, 1H, H2), 12.30 (br, 1H, NH).

(*1S,3S,4R,8S*)-3-(Guanin-9-yl)-8-hydroxy-1-hydroxymethyl-2,6-dioxabicyclo[3,2,1]octane (28). The same procedure as described for **24** gave **28** (41 mg, 66%) as an off-white solid from **23** (100 mg). ^{1}H NMR (DMSO-d_6 + D_2O) of **28**: δ 2.42 (m, 1H, H2'), 3.15 (dd, J = 11.4 Hz, 2.1 Hz, 1H, H2a"), 3.34 (d, J = 11.4 Hz, 1H, H5a'), 3.47 (d, J = 12.6 Hz, 1H, H5b'), 3.51 (d, J = 12.0 Hz, 1H, H4a"), 3.77 (d, J = 10.8 Hz, 1H, H4b"), 3.98 (d, J = 11.7 Hz, 1H, H2b"), 4.23 (d, J = 4.8 Hz, 1H, H3'), 4.80 (br, 1H, OH), 5.90 (br, 1H, OH), 6.05 (d, J = 4.2 Hz, 1H, H1'), 6.52 (br, 2H, NH_2), 7.93 (s, 1H, H8), 12.30 (br, 1H, NH); MS m/z 310 (MH^+).

(*1R,3R,4R,8S*)-1-Acetoxymethyl-8-benzyloxy-3-(thymin-1-yl)-2,6-dioxabicyclo[3,2,1]octane (29). The reaction followed the procedure described for **19** except that TMSOTf and **18** were replaced by $SnCl_4$ (0.45 mL, 3.84 mmol) and **17** (202 mg, 0.62 mmol), respectively. Chromatography on silica with 5% EtOH in CH_2Cl_2 gave a mixture (233 mg, 89%) of **19** and **29** (ratio of α:β, ~1:4) as a colorless solid. ^{1}H NMR ($CDCl_3$) of **29** (from the spectrum of a mixture of the α- and β-anomers) δ 1.93 (d, J = 0.9 Hz, 1H, $ArCH_3$), 2.05 (s, 3H, OAc), 2.66 (m, 1H, H2'), 3.48 (d, J = 11.1 Hz, H4a"), 3.86-4.12 (m, 5H, H2a", H2b", H3', H4b", H5a'), 4.26 (d, J = 12.6 Hz, H5b'), 4.44, 4.64 (AB, J = 11.4 Hz, 2H, Bn), 6.06 (s, 1H, H1'), 7.26-7.42 (m, 5H, Bn), 7.59 (d, J = 1.2 Hz, 1H, H6), 8.94 (s, 1H, NH).

(*1R,3R,4R,8S*)-1-Acetoxymethyl-8-benzyloxy-3-(uracil-1-yl)-2,6-dioxabicyclo[3,2,1]octane (30). A similar procedure as described for **29** gave, after chromatography on silica with 5% EtOH in methylene chloride, a mixture (267 mg, 87%) of the α- and β-anomers (ratio of α:β, ~1:9) as a colorless solid from **17** (230 mg, 0.71 mmol) and silylated uracil (2.0 mmol). The β-anomer **30** was partially separated by chromatography on silica; m.p. 145-147 °C (EtOAc-hexanes); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H, OAc), 2.67 (m, 1H, H2'), 3.49 (d, J = 11.4 Hz, 1H, H4a"), 3.86-3.97 (m, 3H, H2a", H3', H4b"), 4.08 (d, J = 12.3 Hz, 1H, H5a'), 4.09 (d, J = 10.5 Hz, 1H, H2b"), 4.25 (d, J = 12.3 Hz, 1H, H5b'), 4.44, 4.64 (AB, J = 11.7 Hz, 2H, Bn), 6.05 (s, 1H, H1'), 7.26-7.40 (m, 5H, Bn), 5.69 (d, J = 8.1 Hz, 1H, H5), 7.79 (d, J = 8.4 Hz, 1H, H6), 8.92 (s, 1H, NH); Anal. Calcd. for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.45; H, 5.56; N, 6.91.

(*1R,3R,4R,8S*)-1-Acetoxymethyl-8-benzyloxy-3-(cytosin-1-yl)-2,6-dioxabicyclo[3,2,1]octane (31). A similar procedure as described for **29** gave, after chromatography on silica with 5% ethanol in methylene chloride, 910 mg (90%) of **31** (β-anomer) from the reaction of **17** (645 mg, 2.0 mmol) with silylated N^4-benzoylcytosine (4.0 mmol). **31**: m.p. 173-174 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, OAc), 2.83 (m, 1H, H2'), 3.51 (d, J = 11.1 Hz, H4a"), 3.86 (d, J = 5.4 Hz, 1H, H3'), 3.97 (d, J = 11.1 Hz, 1H, H4b"), 3.99-4.13

(m, 3H, H2a", H2b", H5a'), 4.27 (d, J = 12.3 Hz, 1H, H5b'), 4.38, 4.61 (AB, J = 11.4 Hz, 2H, Bn), 6.15 (s, 1H, H1'), 7.24-7.38 (m, 5H, Bn), 7.50-7.66 (m, 4H, H5, Bz), 7.90 (m, 2H, Bz), 8.28 (d, J = 7.5 Hz, 1H, H6), 8.84 (br, 1H, NH); Anal. Calcd. for $C_{27}H_{27}N_3O_7$: C, 64.15; H, 5.38; N, 8.31. Found: C, 64.10; H, 5.20; N, 8.43.

(*1S,3R,4R,8S*)-8-Hydroxy-1-hydroxymethyl-3-(thymin-1-yl)-2,6-dioxabicyclo[3,2,1]octane (32). To a solution of the mixture of **29** and **19** (~4:1, 200 mg, 0.48 mmol) in anhydrous methylene chloride (4 mL) at 0 °C was added boron trichloride (1.0 M in CH_2CH_2, 8 mL). The resulting reaction mixture was stirred at room temperature for 8 h, at 15 °C overnight, and then cooled to 0 °C. Methanol (5.0 mL) was added dropwise, followed by addition of 1.0 M NaOMe in MeOH until pH 8. The solution was separated and the precipitate extracted with 20% methanol in methylene chloride thoroughly. The combined filtrate was dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica with 10-15% methanol in ethyl acetate gave **32** (78 mg), a mixture of **32** and **20** (24 mg), and **20** (23 mg), all as a colorless solid. Total yield was 91%. Crystallization from methanol-ethyl acetate gave the crystalline **32**; m.p. 217-218 °C; ^{1}H NMR (DMSO-d_6): δ 1.75 (d, J = 1.2 Hz, 1H, $ArCH_3$), 2.24 (m, 1H, H2'), 3.20 (d, J = 10.8 Hz, 1H, H4a"), 3.33-3.58 (m, 3H, H2a", H5'), 3.66 (d, J = 10.8 Hz, H4b"), 3.97 (d, J = 10.5 Hz, 1H, H2b"), 4.14 (m, 1H, H3'), 5.24 (t, J = 5.1 Hz, 1H, OH), 5.67 (d, J = 2.4 Hz, 1H, OH), 5.82 (s, 1H, H1'), 7.95 (d, J = 0.9 Hz, 1H, H6), 11.32 (s, 1H, NH); MS m/z 285 (MH^+); Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.65; H, 5.57; N, 9.73.

(*1S,3R,4R,8S*)-8-Hydroxy-1-hydroxymethyl-3-(uracil-1-yl)-2,6-dioxabicyclo[3,2,1]octane (33). The same procedure as described for **32** gave, after chromatography on silica with 10% methanol in methylene chloride, 110 mg (76%) of **33** as a white solid from **30** (215 mg, 0.53 mmol). **33** was contaminated by a small amount of its α-anomer. The pure **33** was obtained by recrystallization from acetone-ethyl acetate; m.p. 218-219 °C; ^{1}H NMR (acetone-d_6) δ 2.42 (m, 1H, H2'), 3.27 (d, J = 10.8 Hz, 1H, H4a"), 3.58-3.72 (m, 3H, H2a", H5'), 3.83 (d, J = 10.8 Hz, 1H, H4b"), 4.13 (d, J = 10.5 Hz, 1H, HH2b"), 4.37 (t, J = 5.1 Hz, 1H, OH), 4.42 (m, 1H, H3'), 4.88 (d, J = 3.9 Hz, 1H, OH), 5.52 (d, J = 7.8 Hz, 1H, H5), 5.95 (s, 1H, H1'), 8.17 (d, J = 7.8 Hz, 1H, H6), 10.02 (s, 1H, NH); MS m/z 271 (MH^+); Anal. Calcd. for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.60; H, 5.64; N, 10.21.

(*1S,3R,4R,8S*)-3-(Cytosin-1-yl)-8-hydroxy-1-hydroxymethyl-2,6-dioxabicyclo[3,2,1]octane (35). The same procedure as described for **20** gave, after chromatography on silica with 10% MeOH in methylene chloride, 364 mg (65%) of **34** from **31** (760 mg). 120 mg (0.32 mmol) of **34** was dissolved in a saturated solution of ammonia in methanol and the solution stirred at room temperature for 24 h. Ammonia and methanol were evaporated and the residue was dissolved in water, followed by thorough extraction with chloroform (5 times) and then with toluene (2 times). Water was evaporated and crystallization from methanol gave 62 mg of **35** (45 mg of crystalline solid and 17 mg of non-crystalline solid); m.p. 250 °C (decom.); ^{1}H NMR (CD_3OD) δ 2.33 (m, 1H, H2'), 3.31 (d, J = 11.1 Hz, 1H, H4a"), 3.57 (d, J = 12.3 Hz, 1H, H5a'), 3.65 (d, J = 12.3 Hz, 1H, H5b'), 3.78 (dd, J = 10.5 Hz, 2.7 Hz, H2a"), 3.84 (d, J = 11.1 Hz, 1H, H4b"), 4.14 (d, J = 10.5 Hz, 1H, H2b"), 4.20 (d, J = 5.1 Hz, 1H, H3'), 5.86 (d, J = 7.5 Hz, 1H, H5), 5.96 (s, 1H, H1'), 8.22 (d, J =

7.8 Hz, 1H, H6); MS: m/z 270 (MH^+); Anal. Calcd. for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61. Found: C, 48.93; H, 5.55; N, 15.64.

An alternative method. A mixture of **33** (170 mg, 0.63 mmol), acetic anhydride (2.16 mL, 20.1 mmol), and pyridine (0.29 mL, 3.5 mmol) in anhydrous DMF (2.5 mL) was stirred at room temperature overnight, diluted with methylene chloride, washed with brine and 10% $NaHCO_3$, dried (Na_2SO_4), concentrated to dryness. Chromatography on silica with ethyl acetate-hexanes (2:1) gave 117 mg (77%) of the 3',5'-diacetyl derivative of **33**.

The dried diacetyl derivative of **33** (175 mg, 0.58 mmol) was dissolved in anhydrous pyridine (1.5 mL) and the resulting solution cooled to 0 °C under argon, followed by addition of 4-chlorophenyl dichlorophosphate (0.29 mL, 1.75 mmol). The resulting solution was warmed up to room temperature and transferred to a septum-capped vial containing 1,2,4-triazole (120 mg, 1.75 mmol). The reaction mixture was stirred at room temperature for 3 days, diluted with CH_2Cl_2, washed with brine and 5% $NaHCO_3$, dried (Na_2SO_4), and concentrated to dryness. The residue was dissolved in dioxane (7 mL) and 30% ammonium hydroxide (10 mL). The solution stood at room temperature for 16 h and the solvents were evaporated. The residue was chromatographed on silica with Et_3N-MeOH-$CHCl_3$ (5:30:65) to give 74 mg (55%) of **35** as a slightly yellow solid, which had the identical proton NMR as that from the condensation of **17** with silylated cytosine base.

***(1R,3R,4R,8S)*-1-Acetoxymethyl-3-(N^2-acetylguanin-7-yl)-8-benzyloxy-2,6-dioxabicyclo[3,2,1]-octane (36)**. The silylated base from N^2-acetylguanine (386 mg, 2.0 mmol) was prepared according to the procedure described for **23** and dissolved in a solution of **17** (477 mg, 1.48 mmol) in anhydrous 1,2-dichloroethane (10 mL), followed by addition of tin (IV) chloride (0.75 mL) in 1,2-dichloroethane (2.0 mL). The resulting mixture was heated at reflux for 3 h, then at 70 °C overnight, and cooled to 0 °C. The mixture was neutralized with 2.0 M sodium carbonate, filtered through celite, and thoroughly extracted with chloroform. The combined filtrate was dried (Na_2SO_4) and concentrated to dryness. Chromatography on silica with 5% EtOH in chloroform gave 297 mg (42%) of **36**, 73 mg (10%) of **37**, and 46 mg (6%) of **23**, all as a white solid. **36**: m.p. 176-178 °C (CH_3Cl-EtOAc); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, OAc), 2.40 (s, 3H, NAc), 2.78 (m, 1H, H2'), 3.53 (d, J = 11.4 Hz, 1H, H4a"), 3.99 (d, J = 11.1 Hz, H4b"), 4.03-4.18 (m, 4H, H2a", H2b", H3', H5a'), 4.26 (d, J = 12.6 Hz, 1H, H5b'), 4.39, 4.58 (AB, J = 11.7 Hz, 2H, Bn), 6.62 (s, 1H, H1'), 7.22-7.40 (m, 5H, Bn), 8.21 (s, 1H, H8), 10.60 (s, 1H, NH), 12.34 (s, 1H, NH); Anal. Calcd. for $C_{23}H_{251}N_5O_8$: C, 55.31; H, 5.05; N, 14.02. Found: C, 55.35; H, 4.83; N, 13.80.

***(1R,3R,4R,8S)*-1-Acetoxymethyl-3-(N^2-acetylguanin-9-yl)-8-benzyloxy-2,6-dioxabicyclo[3,2,1]-octane (37)**. The same amount of the silylated N^2-acetylguanine as described for **36** was dissolved in a solution of **36** (370 mg, 0.76 mmol) in anhydrous 1,2-dicloroethane (10 mL) and trimethylsilyl triflate (0.54 mL, 3.0 mmol) in 1,2-dichloroethane (3 mL) added. The resulting solution was heated under reflux overnight. Additional TMSOTf (0.54 mL) was added and the mixture refluxed for additional two days. The same work-up as described for **23** gave, after chromatography on silica with 5% ethanol in chloroform, 104 mg (28%) of the intact **36**, 91 mg (25%) of **37**, and 80 mg (22%) of **23**, all as a white solid. **37**: m.p. 128-131 °C (CH_3Cl-

EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H, OAc), 2.30 (s, 3H, NAc), 2.67 (m, 1H, H2'), 3.50 (d, J = 10.8 Hz, 1H, H4a"), 3.78 (dd, J = 10.8 Hz, 2.7 Hz, 1H, H2a"), 3.99 (d, J = 10.8 Hz, H4b"), 4.12 (d, J = 12.3 Hz, 1H, H5a'), 4.14 (d, J = 10.8 Hz, 1H, H2b"), 4.27 (d, J = 12.3 Hz, 1H, H5b'), 4.33 (d, J = 5.1 Hz, 1H, H3'), 4.49, 4.62 (AB, J = 11.7 Hz, 2H, Bn), 6.25 (s, 1H, H1'), 7.26-7.38 (m, 5H, Bn), 7.83 (s, 1H, H8), 9.0 (s, 1H, NH), 11.95 (s, 1H, NH); MS: m/z 310 (MH^+); Anal. Calcd. for $C_{23}H_{25}N_5O_8$: C, 55.31; H, 5.05; N, 14.02. Found: C, 55.70; H, 5.00; N, 13.95.

***(1S,3R,4R,8S)*-3-(Guanin-9-yl)-8-hydroxy-1-hydroxymethyl-2,6-dioxabicyclo[3,2,1]octane (38).** The same procedure as described for **28** gave, after chromatography, 52 mg (45%) of **38** as a colorless solid from **37** (180 mg). Crystallization from water-ethanol (9:1) gave a crystalline solid; m.p. 258 °C (decom.); ^{1}H NMR (DMSO): δ 2.45 (m, 1H, H2'), 3.31 (d, J = 10.8 Hz, 1H, H4a"), 3.36-3.50 (m, 2H, H5a', H5b'), 3.60 (dd, J = 10.2 Hz, 2.7 Hz, 1H, H2a"), 3.1 (d, J = 11.1 Hz, H4b"), 4.03 (d, J = 10.5 Hz, 1H, H2b"), 4.36 (m, 1H, H3'), 4.95 (t, J = 5.7 Hz, 1H, OH), 5.70 (d, J = 3.9 Hz, 1H, OH), 6.06 (s, 1H, H1'), 6.55 (br, 2H, NH_2), 7.90 (s, 1H, H8), 10.68 (s, 1H, NH); MS m/z 310 (MH^+).

REFERENCES AND NOTES

1. Part of this work was presented as an oral presentation at *the XIII International Round Table, Nucleosides, Nucleotides, And Their Biological Applications*, Montpellier, 1998.
2. A communication letter as a contribution to *the Proceedings* of *the XIII International Round Table* will appear in *Nucleosides Nucleotides* **1999** (in press). In the letter, we named the 2,4-bridged sugar as 3,6-dioxabicyclo[3,2,1]octane. In this article, 2,6-dioxabicyclo[3,2,1]octane that is more appropriate is used.
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22. Tables of the crystal data and structure refinements, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotopic displacement parameters, and torsion angles were deposited at the *Cambridge Crystallographic Data Centre*. The crystal structures of **32** and **20** shown in Fig 1. were randomly selected from two conformers of **32** and four conformers of **20**, respectively.