Pergamon

Tetrahedron 54 (1998) 3113–3124

TETRAHEDRON

Concise and Stereospecific Synthesis of Novel Bicyclic Dideoxynucleosides as Potential Antiviral Agents

Qi Chao,[#] Jianzhong Zhang,[#] Lea Pickering, Tamera S. Jahnke and Vasu Nair*

Department of Chemistry, The University of Iowa, Iowa City, IA 52242

Received 28 July 1997; revised 12 January 1998; accepted 14 January 1998

Abstract: A novel class of dideoxynucleosides containing a bicyclic sugar moiety, structurally related to the natural griseolic acids, was synthesized starting from the stereochemically defined compound, 1,4:3,6-dianhydro-D-glucitol. The key intermediate in the synthesis was a [3.3.0] fused bicyclic glycal. Glycosylation of this compound with nucleobase proceeded both regiospecifically and stereospecifically in the presence of an auxiliary agent, N-iodosuccinamide. Changes in stereochemistry during the synthesis was monitored by optical rotation data and confirmed by both 1D and 2D NMR experiments. The synthetic approach described possesses general usefulness.

Introduction

A number of 2',3'-dideoxyribonucleosides have been discovered to possess significant antiviral activity against HIV and other viruses. It has been suggested that proper conformation of the dideoxynucleosides in terms of ring puckering of the five-membered monocyclic carbohydrate moiety is required for them to exhibit antiviral activity.[1] However, some bicyclic nucleosides which belong to a conformationally different class of nucleosides, such as the fused-ring cytidine analogues **1**[2-3] and **2**[4] and the oxetanylthymidine **3**[5] (Figure 1), were

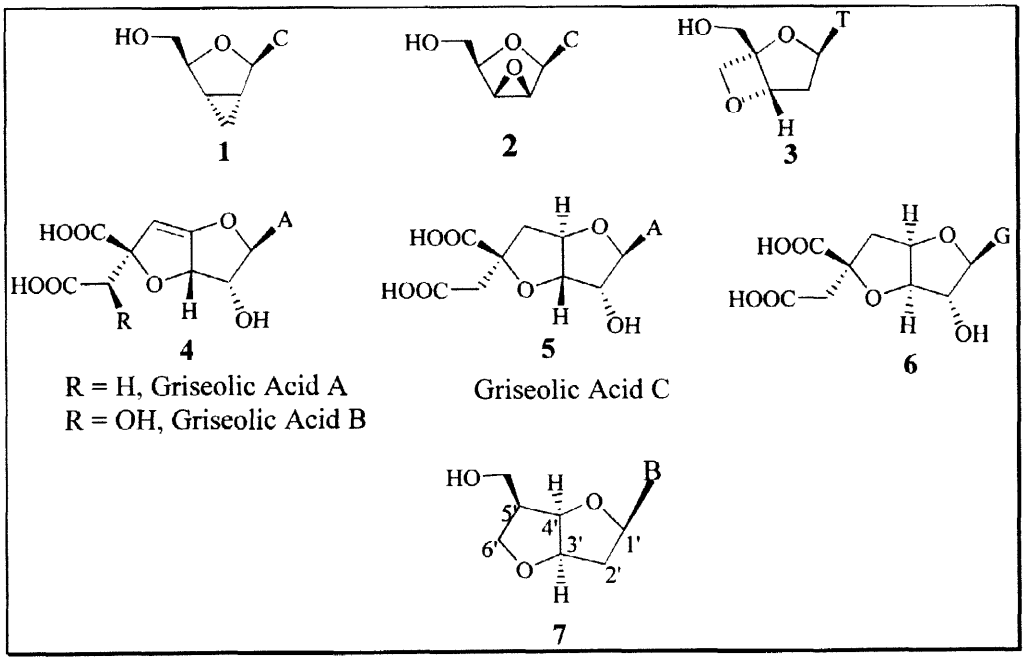


Figure 1

* E-mail address: vasu-nair@uiowa.edu

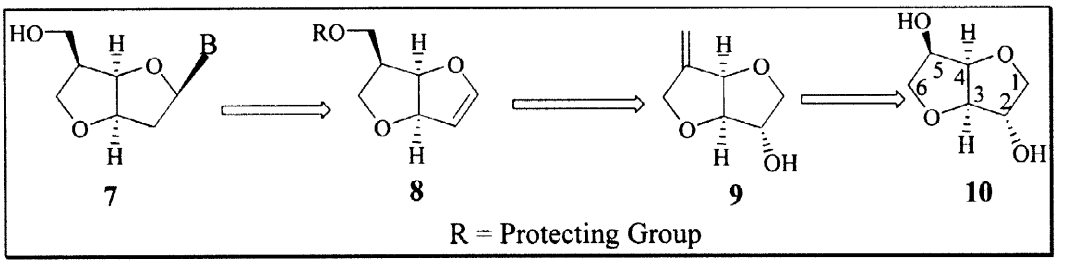
0040-4020/98/$19.00
PII: S0040-4020(98)00061-1

recently found to have moderate to significant antiviral activity against HIV through inhibition of HIV reverse transcriptase. These findings led to additional investigations on the conformational requirements for dideoxynucleosides as inhibitors of HIV-RT,[6] and also triggered further studies on bicyclic nucleosides.[7-10] However, there are few examples of the effect of a second tetrahydrofuranyl ring in a bicyclic dideoxynucleoside structure as it relates to antiviral activity. Bicyclic nucleosides containing a [3.3.0] fused bicyclic carbohydrate moiety may be of biological importance as certain members of the class are known to possess interesting cellular activity. For example, naturally occurring bicyclic nucleosides called griseolic acids A, B and C (**4** and **5**), isolated from the cultured broth of *Streptomyces griseoaurantiacus*, show significant inhibitory activity against 3',5'-cyclic nucleotide phosphodiesterases.[12-13] The synthetic guanosine analogues of griseolic acids such as **6** are even more potent against these enzymes.[13] Some derivatives of griseolic acids have been reported to be potent antihypertensive agents.[14] Bicyclic nucleosides have also received attention recently in studies of the stabilities of antisense oligonucleotides.[15-19] Oligonucleotides containing bicyclic nucleoside units exhibit increased affinity for complementary RNA or DNA and bicyclic nucleosides are also important in the preparation of triple-helix forming oligonucleotides.[15,18]

As a continuation of our efforts in the discovery of antiviral agents with unusual chemical structures, we designed a class of novel bicyclic nucleosides, represented by the general structure **7.** These novel bicyclic nucleosides contain a dideoxydianhydrohexitol, structurally related to the carbohydrate moiety found in natural griseolic acids. As in the normal dideoxynucleosides, the hydroxymethyl group at the 5'-position in **7** has a *cis*-relationship with the nucleobase attached to the 1'-position.

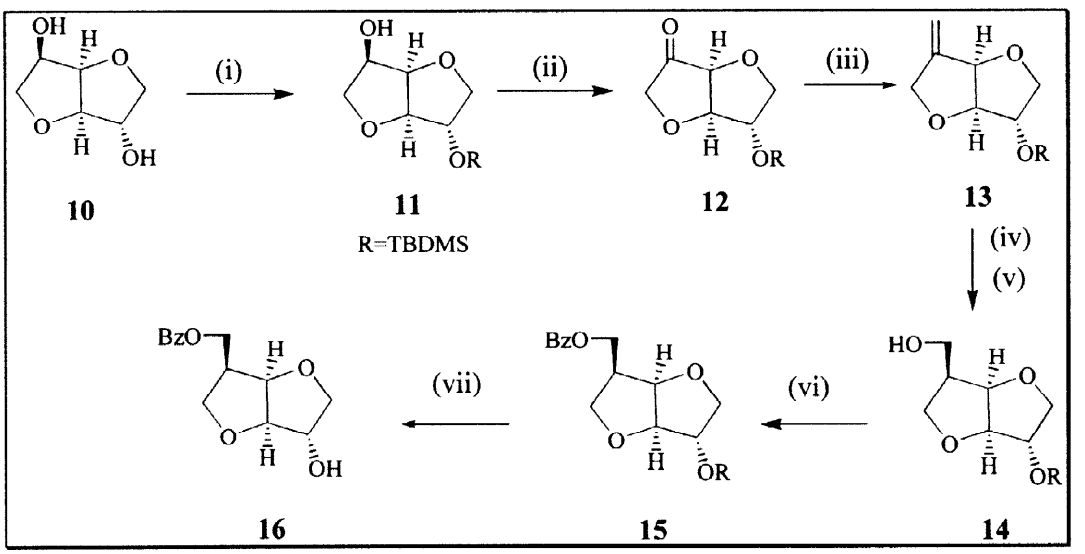
Results and Discussion

Several synthetic strategies could be employed for the total synthesis of these novel bicyclic nucleosides. However, total construction of the bicyclic carbohydrate moiety was not considered, as this would involve many synthetic steps.[13-14] The search for a proper starting material among commercially available compounds revealed that isosorbide **10**, a bicyclic carbohydrate that contains the structural frame of the sugar moiety of the nucleosides to be synthesized, would be the best candidate (Scheme 1). Condensation of an appropriate nucleobase to the desired position (i.e. position-1 in **10**), would then be realized by reaction of the base with a glycal such as **8** in the presence of an appropriate auxiliary agent.[20-21] The glycal structure of **8** could be prepared by dehydration involving the 1,2-position of **10**. Construction of a hydroxymethyl group at carbon-5 of **10** could be accomplished by initial conversion of the hydroxyl group at that position to a methylene group (see structure **9**) through oxidation of the hydroxyl group followed by an olefination reaction, and conversion of the resulting exocyclic methylene group to a hydroxylmethyl group through hydroboration and oxidation.



Scheme 1

Isosorbide is an important precursor in this asymmetric synthesis as it contains two hydroxyl groups at positions 2 and 5 with different reactivities.[22] The hydroxyl group at carbon-5 is more reactive than that at carbon-2 as it can form an intramolecular H-bond with the ring oxygen atom of the adjacent ring. Selective preparation of the 2-O-TBDMS protected isosorbide **11** in three steps from **10** (Scheme 2), utilized this reactivity difference.[22] Subsequent oxidation of **11** to ketone **12** was achieved by refluxing **11** with PCC in dichloromethane. A marked change occurred in the optical rotation data (Table 1) and a carbonyl carbon peak, which appeared at 209.8 ppm in the ^{13}C NMR spectrum of **12**, indicated success of the reaction (Table 2).



Reagents: (i) (a) Ac_2O, PbO, (b) TBDMSCl, CH_2Cl_2, imidazole, (c) KOH, EtOH[22]; (ii) PDC, CH_2Cl_2, mol. sieves or PCC, CH_2Cl_2, reflux or; (iii) $TiCl_4$, CH_2Br_2, Zn, THF or Ph_3PCH_3I, t-BuOK, PhH, reflux; (iv) $BH_3.SMe_2$, THF, 0 °C- r.t.; (v) H_2O_2, NaOH, r.t.; (vi) BzCl, pyr., -10 °C, r.t.; (vii) TBAF, THF, r.t.

Scheme 2

Conversion of the ketone **12** to the alkene **13** was accomplished by the Wittig reaction of **12** with Ph_3PCH_3I in the presence of an appropriate organic base such as t-BuOK. The use of n-BuLi as base resulted in rapid formation of the enolate of **12** which quenched the reaction. Formation of the alkene was evident from the ^{13}C NMR spectrum which showed two peaks at 109.8 and 147.6 ppm.

In order to convert the exocyclic methylene group in **13** to a hydroxymethyl group, compound **13** was allowed to react with BH_3 followed by *in situ* oxidation with H_2O_2 in the presence of NaOH. Only one product, **14,** was isolated in the reaction. As expected, a dramatic change in optical rotation was observed in going from **13** to **14**. However, establishment of the absolute stereochemistry of the hydroxymethyl group at carbon-5 of **14** was not performed until **14** was transformed to **16** by benzoylation of the primary hydroxyl group (to give **15**) followed by deprotection of the silyl protecting group of the secondary alcohol group with TBAF. The absolute stereochemistry was determined by extensive 1D and 2D ^1H NMR experiments. Assignment of each proton peak in the ^1H NMR spectrum was based on 2D COSY and homonuclear decoupling NMR experiments (see Table 2). The (*R*)-configuration of the $HOCH_2$ group at carbon-5 in **16** was confirmed by the observation of a strong NOE displayed by H-3 and H-4 when H-5 was irradiated (Figure 2). The stereospecificity of the

Table 2. Selected NMR Data (δ, ppm)

Compound	Carbon Atom Position						
	1	2	3	4	5	6	5'
11	76.5	77.7	88.9	81.9	73.6	72.5	
12	75.8	77.4	87.9	78.8	209.8	70.0	
13	74.8	77.3	89.4	83.1	147.6	70.9	109.8
14	75.9	76.8	89.8	84.3	46.4	69.3	60.0
15	76.1	77.1	90.0	82.3	44.9	70.3	62.2
16	75.6	76.5	89.4	82.3	44.9	70.5	62.2
8	150.7	100.0	85.4	83.9	45.1	66.2	61.9
	Proton Position						
	1	2	3	4	5	6	5'
16	3.99 (m)	4.44 (m)	4.62 (d)	4.93 (t)	2.84 (m)	3.67(t) 4.19(t)	4.53(dd) 4.71(dd)

hydroboration reaction could be explained by the special structural feature of the bicyclic ring system. It has been determined by X-ray techniques that the bicyclic ring system of isosorbide is concave.[11] The top face is thus highly crowded. Therefore, approach of borane to the double bond occurred from the α- or bottom face which resulted in the desired stereochemistry for the hydroxymethyl group.

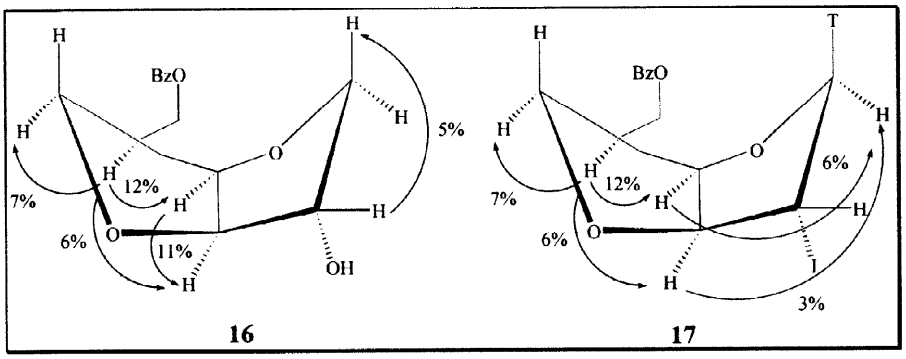
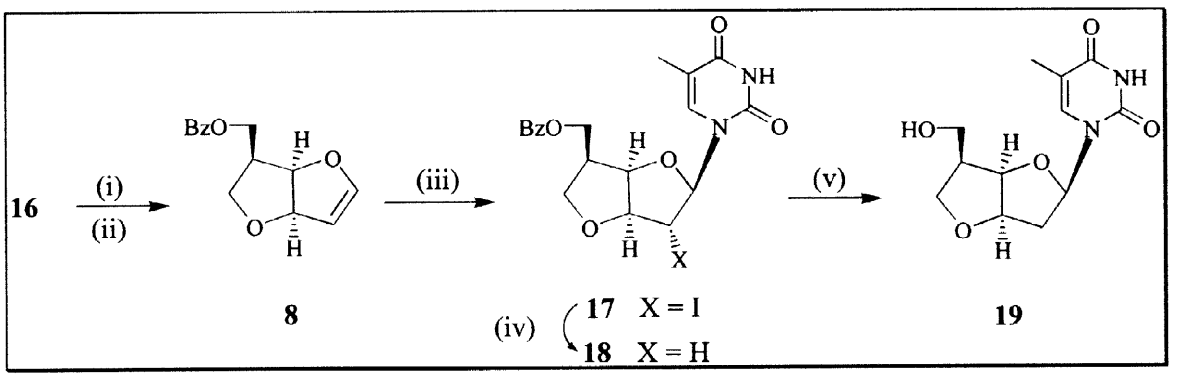


Figure 2

Conversion of **16** to glycal **8**[11] was accomplished by transformation of **16** to its triflate derivative followed by *in situ* elimination of the triflate with DBU (Scheme 3). Success of the elimination reaction was confirmed by both the change in optical rotation in going from **16** to **8** and the NMR experimental results.[11] Two carbon peaks appeared at 100.0 ppm and 150.7 ppm indicating the formation of an alkenyl group. A doublet at 6.60 ppm and a doublet of doublets at 5.45 ppm in its ^{1}H NMR spectrum was also indicative that the double bond was formed between C-1 and C-2.



Reagents: (i) $(CF_3OSO_2)_2O$, DMAP, Et_3N, CH_2Cl_2, -15 °C[11]; (ii) DBU, PhH, r.t.; (iii) silylated thymine, NIS, CH_2Cl_2, r.t.; (iv) n-Bu_3SnH, AIBN, PhH, 65 °C; (v) NaOMe, MeOH, r.t.

Scheme 3

Condensation of glycal **8** with each nucleobase was initiated by N-iodosuccinamide (NIS) (Scheme 3).[21] In the presence of NIS, reaction of the silylated nucleobase, such as thymine, with **8** proceeded rapidly and resulted in only one product **17** in good yields. The stereochemistry of the glycosidic bond was established by extensive 1D and 2D NMR experiments. For example, the β-configuration of the glycosidic bond in **17** was confirmed by the strong NOE observed for H-1 when H-3 or H-4 was irradiated (see Figure 2). The regiospecificity and stereospecificity of the glycosylation reaction could be explained by both the concave topology of the glycal and the mechanistic function of NIS (Figure 3). Attack of NIS on **8** occurred from the

bottom face resulting in cation **21** which is trapped by nucleophile, the silylated nucleobase, to afford nucleoside **17**. Attack by NIS on **8** from the top face is not favored because of steric hindrance (see **22**).

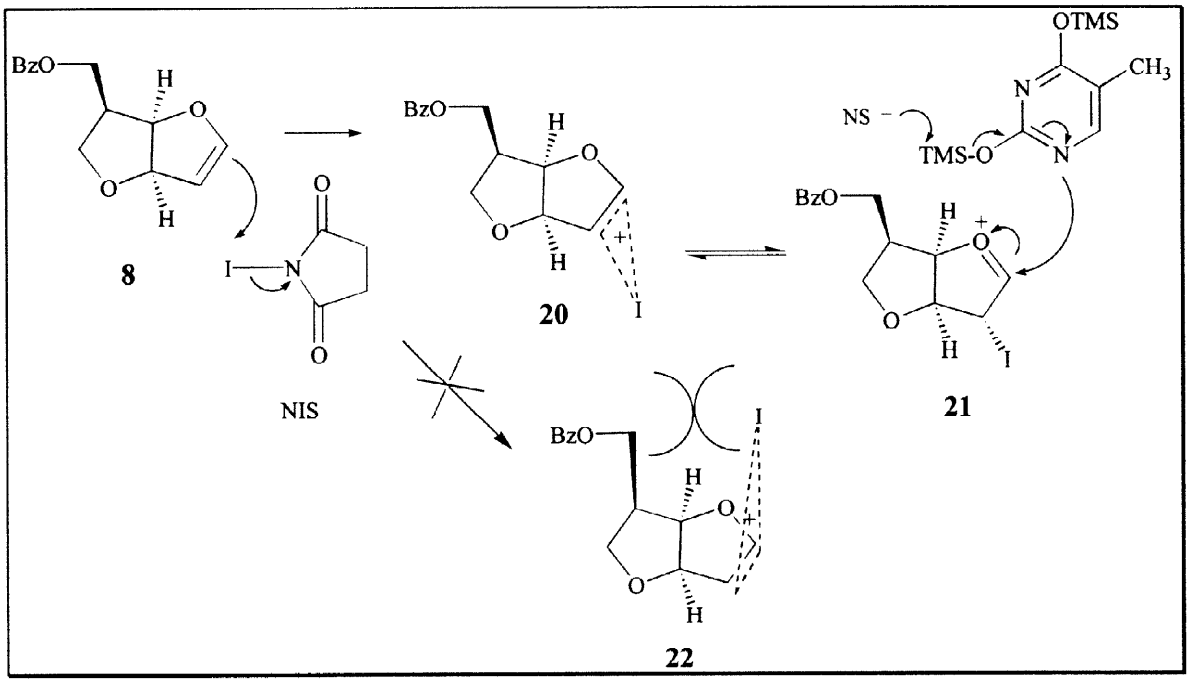
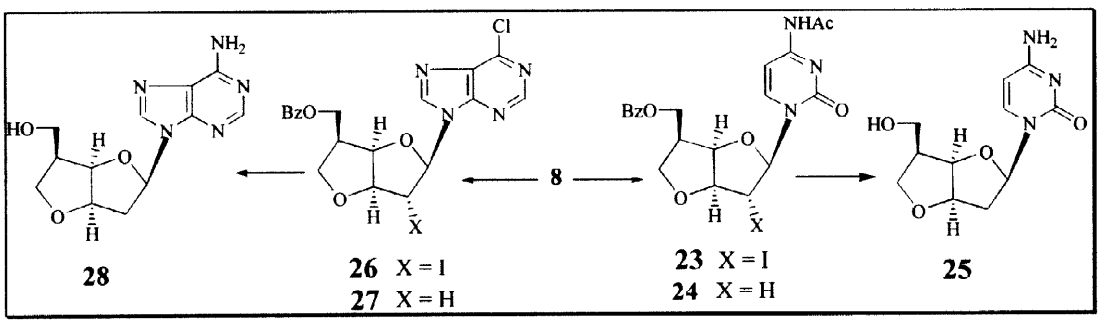


Figure 3

Radical reductive deiodination of **17** with n-Bu_3SnH in the presence of an initiator (AIBN), followed by deprotection of the 5'-hydroxymethyl group afforded the target compound **19**, a bicyclic analogue of thymidine (see Scheme 3). The bicyclic analogues of cytidine **25** and adenosine **28** were similarly synthesized (Scheme 4).



Scheme 4

In summary, a concise and stereospecific approach toward the synthesis of a novel class of bicyclic nucleosides of potential antiviral interest has been developed. The methodology developed has generality and can be used for the synthesis of a variety of related new nucleosides. Antiviral evaluation of these novel bicyclic nucleosides is in progress and those results 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. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument at 300 and 75 MHz, respectively. Chemical shifts are referenced to an internal TMS standard for ^{1}H NMR spectra and to solvent ($CDCl_3$ or DMSO-d_6) for ^{13}C NMR spectra. Column chromatographic separations were carried out using 63-200 or 230-400 mesh silica gel. Elemental analyses were performed by Supersun Technology Analytical Laboratory, Stony Brook, NY, and Desert Analytics, Tucson, AZ.

1,4:3,6-Dianhydro-2-O-(tert-butyldimethylsilyl)-5-deoxy-5(*R*)-hydroxymethyl-D-glucitol (14). To a solution of 1,4:3,6-dianhydro-2-O-(tert-butyldimethylsilyl)-D-glucitol **11** (4.71 g, 12.24 mmol) in 60 mL of dry CH_2Cl_2 was added pyridinium chlorochromate (PCC, 7.92 g, 36.72 mmol) under N_2 protection. The reaction mixture was refluxed for 3 h then cooled to room temperature. The suspension was chromatographed on silica gel with 0-20% EtOAc/hexanes as eluant to afford 3.89 g (10.16 mmol, 83% yield) of ketone **12** as a yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.12(s, 3H), 0.90(s, 9H), 3.89(m, 1H), 3.93(d, J=5.7 Hz, 1H), 4.01(dd, J=9.6 Hz, 3.3 Hz, 1H), 4.30(d, J=3.9 Hz, 2H), 4.44(dd, J=3.3 Hz, 1.5 Hz, 1H), 4.62(d, J=3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -4.9, -4.8, 18.0, 25.7, 70.0, 75.8, 77.4, 78.8, 87.9, 209.9.

A suspension of tert-BuOK (1.46 g, 13.0 mmol) and Ph_3PCH_3I (5.26 g, 13.0 mmol) in 20 mL of dry benzene was refluxed under N_2 for 1 h. Most of the benzene was then removed to form a yellow slurry which was treated with a solution of **12** (3.80 g, 9.9 mmol) in 20 mL of dry benzene. The reaction mixture was stirred at 60 °C for 2 h before it was quenched with 40 mL of H_2O and extracted with EtOAc. The extract was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was chromatographed on silica gel with 0-20% EtOAc/hexanes as the eluant to afford 2.84 g of **13** (8.71 mmol, 67% yield) as a light brown oil: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.12(s, 3H), 0.91(s, 9H), 3.74(dd, J=9.6 Hz, 3.0 Hz, 1H), 3.81(d, J=9.6 Hz, 1H), 4.20(dt, J=12.6 Hz, 2.1Hz, 1H), 4.35(m, 2H), 4.42(d, 3.9 Hz, 1H), 4.98(d, J=3.6 Hz, 1H), 5.11(t, J=1.2 Hz, 1H), 5.37(t, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -4.8, -4.7, 19.1, 26.8, 70.9, 74.4, 78.0, 83.3, 89.0, 109.9, 133.2.

To a solution of alkene **13** (2.29 g, 9.39 mmol) in 50 mL of dry THF cooled in an ice bath was added, dropwise, a 2.0M solution of $BH_3.SMe_2$/THF (5.2 mL) under N_2. The reaction mixture was warmed to room temperature and stirred for an additional 5 h. To the solution were then added 8 mL of water, 8 mL of 10% NaOH, and 17 mL of 30% H_2O_2 and the reaction mixture was stirred for 24 h and extracted with EtOAc and the extracts were dried over anhydrous Na_2SO_4. The solvent was then removed and the residue was

chromatographed on silica gel with 0-45% EtOAc/hexanes to give 1.77 g of alcohol **14** (6.76 mmol, 72% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.09(s, 3H), 0.89(s, 9H), 2.44(m, 1H), 2.73(s, brd, 1H, D_2O exchangeable), 3.65-3.98(m, 6H), 4.26(m, 1H), 4.35(d, J=3.0 Hz, 1H), 4.80(t, J=3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -4.9, -4.8, 18.0, 25.7, 46.4, 60.0, 69.3, 75.9, 76.8, 84.3, 89.8. Anal. Calcd. for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55; Found: C, 56.60; H, 9.56.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-2-O-(tert-butyldimethylsilyl)-5-deoxy-D-glucitol (15). To a solution of alcohol **14** (1.05 g, 4.01 mmol) in 10 mL of dry pyridine cooled to about -10 °C in an ice-salt bath was added dropwise benzoyl chloride (0.85 g, 6.02 mmol) under N_2. The reaction mixture was allowed to warm up to room temperature and stirred for 5 h. It was then poured onto crushed ice and extracted with $CHCl_3$. The extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with 0-20 % EtOAc/hexanes to afford 1.13 g of **15** (3.09 mmol, 77% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.10(s, 3H), 0.89(s, 9H), 2.71(m, 1H), 3.56(td, J=6.9 Hz, 1.5Hz, 1H), 3.77(d, J=7.8 Hz, 1H), 3.87(dd, J=7.8 Hz, 3.0Hz, 1H), 4.07(t, J=6.6 Hz, 1H), 4.60(dd, J=9.3 Hz, 3.0 Hz, 1H), 4.77(t, J=3.0 Hz, 1H), 7.44(t, J=6.3 Hz, 2H), 7.56(t, J=6.3 Hz, 1H), 8.04(dd, J=6.6 Hz, 1.2Hz, 2H); ^{13}C NMR ($CDCl_3$) δ -4.9, -4.8, 18.0, 25.7, 44.9, 62.2, 70.2, 76.1, 77.1, 82.3, 90.0, 128.3, 129.6, 130.0, 133.0, 166.4. Anal Calcd. for $C_{20}H_{30}O_5Si$: C, 63.46; H, 7.99; Found: C, 63.59; H, 8.08.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-5-deoxy-D-glucitol (16). A solution of **15** (1.09 g, 2.98 mmol) in 5 mL of THF was stirred with 4 mL of 1M TBAF/THF solution at room temperature for 2 h. The mixture was concentrated and the residue was chromatographed on silica gel with 0-5% MeOH/$CHCl_3$ as the eluant to afford **16** (0.74 g, 2.95 mmol, 99% yield) as a colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.34(br, 1H, D_2O exchangeable), 2.73(m, 1H), 3.56(dd, J=12.1 Hz, 6.9 Hz, 1H), 3.89(m, 2H), 4.09(t, J=6.9 Hz, 1H), 4.34(m, 1H), 4.43(dd, J=9.8 Hz, 6.3 Hz, 1H), 4.51(d, J=3.0 Hz, 1H), 4.61(dd, J=9.3 Hz, 5.7 Hz, 1H), 4.83(t, J=3.6 Hz, 1H), 7.44(t, J=6.6 Hz, 2H), 7.56(t, J=6.3 Hz, 1H), 8.02(dd, J=6.3 Hz, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 44.9, 62.2, 70.5, 75.6, 76.5, 82.3, 89.4, 128.4, 129.6, 130.0, 133.0, 166.4. Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.79; H, 6.16.

1,2:1,4:3,6-Trianhydro-5(*R*)-benzoyloxymethyl-5-deoxy-D-glucitol (8). To a solution of alcohol **16** (4.65 g, 17.6 mmol), DMAP (647 mg, 5.3 mmol) and Et_3N (5 mL) in 30 mL of dry CH_2Cl_2 under nitrogen at -15 °C was added dropwise trifluorosulfonic anhydride (5.95 g, 21.1 mmol). After stirring at -15 °C for 3 h, the reaction mixture was poured onto to ice and extracted with $CHCl_3$. The extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. To the residue was added 30 mL of dry toluene and then DBU (5.36 g, 35.2 mmol). The resulting mixture was stirred at ambient temperature for 6 h and then quenched with 30 mL of water and extracted with $CHCl_3$. The extracts were dried over $MgSO_4$ and concentrated. The crude

product was purified by silica gel chromatography with 10-20% EtOAc/hexanes to give 3.445 g (64%) of glycal **8** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.75(m, 1H), 3.36(dd, J=8.7 Hz, 11.2 Hz, 1H), 4.06(dd, J=6.9 Hz, 8.7 Hz, 1H), 4.39(dd, J=7.6 Hz, 11.2 Hz, 1H), 4.59(dd,J=7.1 Hz, 11.2 Hz, 1H), 5.00(t, J=5.9 Hz, 1H), 5.05(t, J=2.7 Hz, 1H), 5.45(dd, J=2.5 Hz, 6.3 Hz, 1H), 6.60(d, J=2.7 Hz, 1H), 7.42-7.47(m, 2H), 7.54-7.59(m, 1H), 8.03-8.06(m, 2H); ^{13}C NMR ($CDCl_3$) δ 45.1, 61.9, 66.2, 83.9, 85.4, 100.1, 128.4, 129.6, 130.0, 133.0, 150.8, 166.4. Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.35; H, 5.72.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-2,5-dideoxy-2(*S*)-iodo-1-β-(1,3-dihydro-5-methyl-2,4-dioxo-pyrimidin-1-yl)-D-glucitol (17). A suspension of thymine (385 mg, 3.0 mmol) and ammonium sulfate (10 mg) in 10 mL of 1,1,1,3,3,3-hexamethyl-disilazane (HMDS) under nitrogen was refluxed for 4 h until dissolution occurred and then the excess of HMDS was evaporated under reduced pressure. To the residue was added a solution of glycal **8** (500 mg, 2.0 mmol) in dry CH_2Cl_2 (10 mL) followed by N-iodosuccinimide (686 mg, 3.0 mmol). The reaction mixture was stirred at ambient temperature for 3 h, quenched with 20 mL of saturated $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was purified by silica gel chromatography (0-20% MeOH/$CHCl_3$) to give 687 mg (68%) of **17** as a white solid: mp 178-180 °C; $[\alpha]_D$ +55.7 °(c 1.0, $CHCl_3$); UV (MeOH) 262 nm; ^{1}H NMR ($CDCl_3$) δ 1.94(d, J=1.0 Hz, 3H, CH_3), 2.93(m, 1H, H-5'), 3.93(m, 1H, H-6'), 4.24-4.31(m, 2H, H-2', H-6'), 4.45-4.60(m, 2H, H-5''), 4.92(m, 1H, H-4'), 4.96(dd, J=1.5 Hz, 3.2 Hz, 1H, H-3'), 6.56(d, J=5.2 Hz, 1H, H-1'), 7.22(d, J=1.0 Hz, 1H, H-6), 7.42-7.47(m, 2H, Bz), 7.55-7.60(m, 1H, Bz). 8.00-8.03(m, 2H, Bz), 9.69(br, 1H, NH);^{13}C NMR ($CDCl_3$) δ 12.7, 23.9, 43.3, 61.3, 70.6, 82.6, 92.2, 94.7, 112.3, 128.4, 129.5, 133.2, 134.5, 150.4, 163.6, 166.4. Anal. Calcd. for $C_{19}H_{19}IN_2O_6$: C,45.80; H, 3.84; N, 5.62. Found: C, 46.13; H, 3.99; N, 5.68.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-2,5-dideoxy-2(*S*)-iodo-1-β-(4-acetamido-2-oxo-1H-pyrimidin-1-yl)-D-glucitol (23). Compound **23** (an oil) was prepared in 68% yield with **8** and silylated N^4-acetylcytosine as described for **17**: $[\alpha]_D$ + 49.7 ° (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.00(m, 1H), 3.96(t, J=9.3 Hz, 1H), 4.27(t, J=8.8 Hz, 1H), 4.41(m, 1H), 4.54(dd, J=7.2 Hz, 11.2 Hz, 1H), 4.63(dd, J=7.8 Hz, 11.2 Hz, 1H), 4.93(m, 1H), 5.11(m, 1H), 6.55(d, J=3.4Hz, 1H), 7.42-7.60(m, 4H), 7.91(d, J=7.7 Hz, 1H), 8.01-8.04(m, 2H), 10.55(br, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.3, 43.2, 61.4, 70.8, 84.4, 91.6, 96.5, 97.4, 128.3, 129.4, 133.1, 143.1,155.0, 163.1, 166.0, 171.4, 178.6. Anal. Calcd. for $C_{20}H_{20}IN_3O_6$: C, 45.73; H, 3.84; N, 8.00. Found: C, 45.38; H, 3.80; N, 7.81.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-2,5-dideoxy-2(*S*)-iodo-1-β-(6-chloro-9H-purin-9-yl)-D-glucitol (26). Compound **26** was prepared in 52% yield as a light yellow solid from **8** and silylated 6-chloropurine as described for **17**: mp 148-150 °C; $[\alpha]_D$ +67.3 ° (c 0.3, $CHCl_3$); UV (MeOH) 267 nm; ^{1}H NMR ($CDCl_3$) δ 3.03(m, 1H), 3.74(t, J=9.0 Hz, 1H), 4.31(d, J=8.9 Hz, 1H), 4.37(d, J=7.2 Hz, 1H), 4.46(dd, J=11.4

Hz, 7.5 Hz, 1H), 4.73(d, J=2.1 Hz, 1H), 5.08(d, J=3.0 Hz, 1H), 5.27(t, J=3.3 Hz, 1H), 7.21(d, J=2.1 Hz, 1H), 7.42(t, J=7.8 Hz, 2H), 7.56(t, J=7.2 Hz, 1H), 7.95(dd, J=6.9 Hz, 1.8 Hz, 2H), 8.74(s, 1H), 8.93(s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.1, 42.4, 61.5, 69.8, 84.6, 91.0, 93.7, 121.9, 128.6, 129.1, 129.4, 133.3, 142.4, 148.0, 152.1, 161.7, 165.4. Anal. Calcd. for $C_{19}H_{16}N_4O_4ClI$: C, 43.33; H, 3.06; N, 10.64; Found: C, 43.23; H, 3.12; N, 10.25.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-2,5-dideoxy-1-β-(1,3-dihydro-5-methyl-2,4-dioxo-pyrimidin-1-yl)-D-glucitol (18). To a solution of iodothymidine derivative **17** (300 mg, 0.6 mmol) in 10 mL of dry toluene under nitrogen was added 2,2'-azobisisobutyronitrile (49 mg, 0.3 mmol) and, with dropwise addition, tributyltin hydride (210 mg, 0.72 mmol). The reaction mixture was stirred at 65 °C for 5 h. After toluene was evaporated, the residue was dissolved in 40 mL of CH_3CN and washed with hexanes. Removal of solvent under reduced pressure and purification of the crude product by silica gel chromatography with 70-100% EtOAc/hexanes gave 195 mg (87%) of the protected thymidine derivative **18** as a glass: $[\alpha]_D$ + 53.4 ° (c 1.0, $CHCl_3$); UV (MeOH) 264 nm; ^{1}H NMR ($CDCl_3$) δ 1.95(d, J=1.2 Hz, 3H), 2.17(dd, J=10.5 Hz, 3.7 Hz, 1H), 2.66(m, 1H), 2.94(m, 1H), 3.90(t, J=9.0 Hz, 1H), 4.22(t, J=8.5 Hz, 1H), 4.47(dd, J=7.5 Hz, 11.2 Hz, 1H), 4.53-4.60(m, 2H), 4.72(dd, J=3.2 Hz, 4.8 Hz, 1H), 6.41(dd, J=4.6 Hz, 8.4 Hz, 1H), 7.41-7.46(m, 3H), 7.54-7.59(m, 1H), 8.00-8.03(m, 2H), 9.16(br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 37.7, 43.8, 62.0, 70.3, 83.6, 84.2, 85.3, 112.1, 128.4, 129.6, 129.8, 133.1, 135.8, 150.8, 163.6, 166.3. Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 60.88; H, 5.46; N, 7.24.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-2,5-dideoxy-1-β-(4-acetamido-2-oxo-1H-pyrimidin-1-yl)-D-glucitol (24). Compound **24** was obtained in 62% yield as a glass from **23** as described for **18** except that the reaction was conducted at a lower temperature (35 °C) and a longer reaction time (18 h): $[\alpha]_D$ + 46.3 ° (c 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.17(dd, J=4.3 Hz, 15.1 Hz, 1H), 2.29(s, 3H), 2.82(m, 1H), 2.97(m, 1H), 3.88(t, J=9.1 Hz, 1H), 4.19(t, J=8.7 Hz, 1H), 4.50(dd, J=7.4 Hz, 11.1 Hz, 1H), 4.62(dd, J=7.4 Hz, 11.1 Hz, 1H), 4.69-4.73(m, 2H), 6.36(dd, J=4.3 Hz, 7.8Hz, 1H), 7.42-7.50(m, 3H), 7.55-7.61(m, 1H), 8.00-8.06(m, 3H), 10.09(br, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 39.19, 43.8, 62.0, 70.1, 83.5, 85.0, 87.5, 97.3, 128.4, 129.5, 129.7, 133.2, 144.3, 155.2, 162.9, 166.2, 171.1. Anal. Calcd. for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 59.78; H, 5.52; N,10.12.

1,4:3,6-Dianhydro-5(*R*)-benzoyloxymethyl-2,5-dideoxy-1-β-(6-chloro-9H-purin-9-yl)-D-glucitol (27). Compound **27** (an oil) was prepared from **26** as described for **18** in a yield of 66%: UV (MeOH) 266 nm; ^{1}H NMR ($CDCl_3$) δ 2.87(m, 2H), 2.92(m, 1H), 3.58(t, J=7.8 Hz, 1H), 4.15(d, J=7.2 Hz, 1H), 4.20(dd, J=6.0 Hz, 2.4 Hz, 1H), 4.41(dd, J=9.3 Hz, 6.0 Hz, 1H), 4.89(m, 2H), 6.89(t, J=4.5 Hz, 1H), 7.40(t, J=6.3 Hz, 2H), 7.52(t, J=6.0 Hz, 1H), 7.93(dd, J=6.0 Hz, 0.9 Hz, 2H), 8.84(s, 1H), 8.89(s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.6, 43.8, 61.7,

70.4, 83.5, 86.5, 86.8, 122.3, 128.3, 129.4, 129.6, 133.1, 143.0, 147.4, 152.6, 162.2, 166.0; Anal. Calcd. for $C_{19}H_{17}N_4O_4Cl$: C, 56.94; H, 4.28; N, 13.98; Found: C, 57.23; H, 4.35; N, 13.70.

1,4:3,6-Dianhydro-2,5-dideoxy-5(*R*)-hydroxymethyl-1-β-(1,3-dihydro-5-methyl-2,4-dioxo-pyrimidin-1-yl)-D-glucitol (19). To a solution of the thymidine derivative **18** (190 mg, 0.51 mmol) in 10 mL of methanol was added sodium methoxide (75 mg) and the reaction mixture was stirred at ambient temperature for 5 h. After the solvent was evaporated, the residue was treated with 20 mL of water and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure and the crude product was purified by silica gel chromatography with 5-10% MeOH/$CHCl_3$. Lyophilization gave 122 mg (92%) of thymidine derivative **19** as white powder: mp < 65 °C; $[\alpha]_D$ + 51.7 ° (c 0.6, MeOH); UV (MeOH) 263 nm (ε 9800); ^{1}H NMR(CD_3OD) δ 1.89(d, J=1.2 Hz, 3H), 2.16(m, 1H), 2.60-2.73(m, 2H), 3.63(dd, J=7.3 Hz, 10.7 Hz, 1H), 3.75-3.85(m, 2H), 4.09(t, J=8.5 Hz, 1H), 4.56(dd, J=3.3 Hz, 4.3 Hz, 1H), 4.65-4.68(m, 1H), 6.30(dd, J=4.3 Hz, 8.4 Hz, 1H), 7.64(d, J=1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.3, 38.3, 48.2, 60.5, 71.7, 85.2, 86.2, 87.1, 112.2, 138.3, 152.6, 166.2. Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.33; H, 6.18; N, 10.03.

1,4:3,6-Dianhydro-2,5-dideoxy-5(*R*)-hydroxymethyl-1-β-(4-amino-2-oxo-1H-pyrimidin-1-yl)-D-glucitol (25). Compound **25** was prepared from **24** as described for **19** in a yield of 90% and as a pale white solid: mp 98-100 °C; $[\alpha]_D$ + 41.8 ° (c 0.1, MeOH); UV (MeOH) 270 nm (ε 7300); ^{1}H NMR (CD_3OD) δ 2.06(ddd, J=1.1 Hz, 4.5 Hz, 15.1 Hz, 1H), 2.62-2.72(m, 2H), 3.63(dd, J=7.4 Hz, 10.8 Hz, 1H), 3.75(t, J=8.9 Hz, 1H), 3.84(dd, J=7.3 Hz, 10.8 Hz, 1H), 4.05(t, J=8.5 Hz, 1H), 4.57(m, 1H), 4.65(m, 1H), 5.93(d, J=7.4 Hz, 1H), 6.27(dd, J=4.5 Hz, 8.1 Hz, 1H), 7.80(d, J=7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 37.9, 46.9, 58.3, 70.1, 83.1, 83.5, 85.4, 94.7, 140.9, 155.1, 165.5. Anal. Calcd. for $C_{11}H_{15}N_3O_3.0.75H_2O$: C, 49.53; H, 6.23; N, 15.75; Found: C, 49.47; H, 6.53; N, 15.79.

1,4:3,6-Dianhydro-2,5-dideoxy-5(*R*)-hydroxymethyl-1-β-(6-amino-9H-purin-9-yl)-D-glucitol (28). A solution of **27** (28 mg, 0.072 mmol) dissolved in 3 mL of isopropanol was stirred with 10 mL of ammonium hydroxide at ambient temperature overnight. Extra ammonia and solvent were removed under reduced pressure. The residue was dissolved in acetone and dried over anhydrous Na_2SO_4 and the solvent removed. The residue was chromatographed on preparative thin layer chromatographic plates (silica gel) with 17% MeOH/$CHCl_3$ to afford 11 mg of **28** (0.04 mmol, 56% yield) as a pale white solid: mp 114-116 °C; $[\alpha]_D$ +59.4 °(c 0.01, MeOH); UV (MeOH) 260 nm (ε 14,200); ^{1}H NMR (DMSO-d_6) δ 2.46 (m,1H), 2.55(m, 2H), 3.09(m, 2H), 3.44(m, 1H), 3.74(t, J=6.9 Hz, 1H), 4.59(s, br, 1H, D_2O exchangeable), 4.81(dd, J=3.3 Hz, 1.5 Hz, 2H), 6.38(d, J=5.1 Hz, 1H), 6.86(s, br, 2H, D_2O exchangeable), 8.21(s, 1H), 8.41(s, 1H); ^{13}C NMR (DMSO-d_6) δ 35. 8, 46.8, 58.2, 70.1, 83.0, 86.3, 86.5, 111.2, 143.2, 151.8, 152.5, 160.3. Anal. Calcd. for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26; Found: C, 51.58; H, 5.29; N, 25.26.

Acknowledgments. We thank the National Institutes of Health for support of our research through AI29842.

References and Notes

# First authors with equal contribution. These names are given in alphabetical order.

1. Taylor, E. W.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. *Antiviral Chem. Chemother.* **1990**, *1*, 163-173.
2. Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *30*, 2203-2206.
3. Beard, A. R.; Butler, P. I.; Mann, J.; Partlett, N.K. *Carbohydr. Res.* **1990**, *205*, 87-91.
4. Webb, T. R.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1988**, *31*, 1475-1479.
5. O-Yang, C.; Kurz, W.; Eugui, E. M.; McRoberts, M. J.; Verheyden, J.P.H.; Kurz, L. J.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 41-44.
6. Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi, J. J. Jr. *J. Med. Chem.* **1994**, *37*, 3389-3399.
7. Chao, Q.; Nair, V. *Tetrahedron Lett.* **1995**, *36*, 7375-7378.
8. Chao, Q.; Nair, V. *Tetrahedron* **1997**, *53*, 1957-1970.
9. Bjorsne, M.; Szabo, T.; Samuelsson, B.; Classon, B. *Bioorg. Med. Chem.* **1995**, *3*, 397-402.
10. Xiang, Y.; Schinazi, R. F.; Zhao, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1475-1478.
11. Pickering, L.; Nair, V. *Nucleosides Nucleotides* **1996**, *15*, 1751-1769.
12. Nakagawa, F.; Okazaki, T.; Naito, A.; Iijima, Y.; Yamazaki, M. *J. Antibiotics* **1985**, *38*, 823-829.
13. Tulshian, D. B.; Doll, R.J.; Stansberry, M.F.; McPhail, A.T. *J. Org. Chem.* **1991**, *56*, 6819-6822.
14. Tulshian, D. B.; Czarniecki, M. *J. Am. Chem. Soc.* **1995**, *117*, 7009-7010.
15. Bolli, M.; Leumann, C. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 694-696.
16. Tarkoy, M.; Bolli, M.; Leumann, C. *Helv. Chim. Acta* **1994**, *77*, 716-744.
17. Tarkoy, M.; Bolli, M.; Schweizer, B.; Leumann, C. *Helv. Chim. Acta* **1993**, *74*, 481-510.
18. Altmann, K.-H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331-2334.
19. Altmann, K.-H.; Imwinkelried, R.; Kesselring, R.; Rihs, G. *Tetrahedron Lett.* **1994**, 35, 7625-7628.
20. Wang, J.; Wurster, J. A.; Wilson, L. J.; Liotta, D. *Tetrahedron Lett.* **1993**, 34, 4881-4884.
21. Kim, C. U., Misco, P. F. *Tetrahedron Lett.* **1992**, 33, 5733-5736.
22. Abenhaim, D.; Loupy, A.; Munnier, L.; Tamion, R.; Marsais, F.; Queguiner, G. *Carbohydr. Res.* **1994**, 261, 255-266.