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Carbohydrate Research 328 (2000) 37–48

CARBOHYDRATE RESEARCH

Synthesis of novel 3′-*C*-methyl-apionucleosides: an asymmetric construction of a quaternary carbon by Claisen rearrangement

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Received 6 October 1999; accepted 8 December 1999

Abstract

The synthesis of 2,3-dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-D-*glycero*-tetrofuranosyl nucleosides was accomplished in high enatiomeric purity (98.5% ee) via [3,3]-sigmatropic Claisen rearrangement of (*E*)(*S*)-5-benzyloxy-1-*tert*-butyldimethylsilanyloxy-4-methyl-pent-3-en-2-ol prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde. The synthesized nucleosides were assayed against human immunodeficiency virus (HIV) and hepatitis B virus in human peripheral blood mononuclear (PBM) and 2.2.15 cells, respectively. 6-Amino-9-[2,3-dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-D-*glycero*-tetrofuranosyl]-2-fluoropurine shows moderate antiviral activity ($EC_{50} = 2.55$ μM) against HIV-1 strains and 6-amino-9-[3-deoxy-3-*C*-(hydroxymethyl)-3-methyl-α-D-*glycero*-tetrofuranosyl]-2-fluoropurine exhibits potent anti-HIV activity ($EC_{50} = 0.073$ μM) with significant cytotoxity ($IC_{50} = 1.0$ μM).

Keywords: Apionucleosides; Claisen rearrangement; Anti-HIV activity

1. Introduction

Emerging drug-resistant virus strains as well as toxicity are major problems in antiviral chemotherapy [1,2]. Therefore, a number of structurally modified nucleosides have been synthesized to overcome these drawbacks. Among the compounds synthesized, 4′-cyanothymidine [3], 4′-azidothymidine [4] and 4′-fluoronucleosides [5] are of particular interest as they represent a new class of compounds and exhibit significant biological activity. Furthermore, more fundamental modifications of pentofuranose moiety, such as isonucleosides and apionucleosides, have been reported to be compatible with antiviral activities [6]. In attempts to find new lead compounds with improved biological activity, we have synthesized a number of apionucleosides with several substituents at the 3′-position. Previously, we reported an efficient synthetic method of 3′-fluoro-substituted apionucleosides using the Claisen rearrangement reaction in a communication [7]. In this paper we focus on the synthesis of 3′-*C*-methyl-substituted apionucleoside analogues.

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0008-6215/00/$ - see front matter
PII: S0008-6215(00)00005-7

It is well known that the Claisen rearrangement has been widely employed in synthetic organic chemistry with a high degree of 1,3-chirality transmission [7]. However, few examples of 4′-*C*-alkyl nucleosides [8] or 4′-*C*-alkyl carbocyclic nucleosides [9] have been reported to date in the literature. The scarcity of examples of 4′-alkyl-substituted nucleosides may be due to the synthetic difficulties for elaborating a necessary quaternary carbon center. The synthesis of the quaternary carbon stereocenter has frequently been a difficult task since a large number of natural products possess the quaternary carbon [10]. The methodology for the elaboration of the quaternary carbon stereocenter has been extensively discussed in the literature [11], such as aldol reactions [12], Michael reactions [13], palladium-catalyzed allylation [14], Heck reactions [15], cycloaddition reactions [16], and sigmatropic rearrangements [17]. Recently, we published a method of the synthesis for 3′-*C*-methyl-4′-thio-apionucleosides [18]. Herein, we wish to report the full account of the synthesis of 3′-*C*-methyl-apionucleosides.

2. Results and discussion

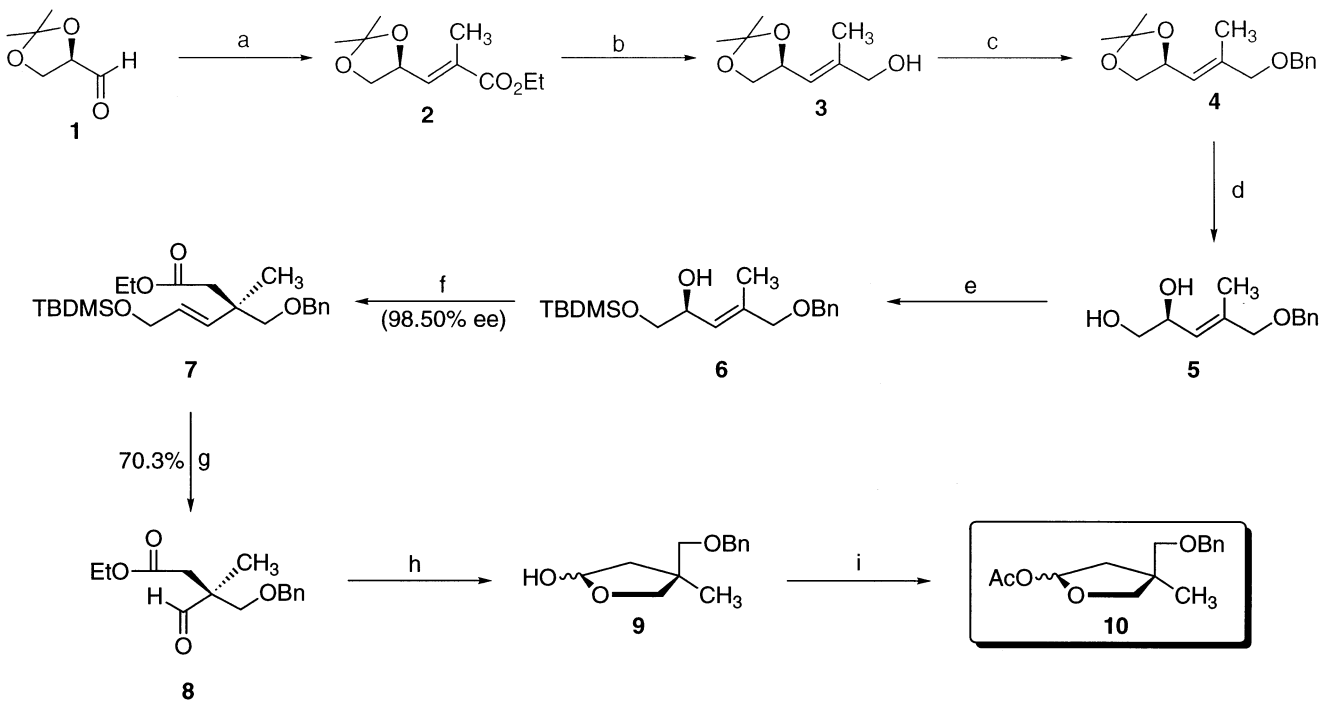
2,3-*O*-Isopropylidene-D-glyceraldehyde (**1**) [19] was prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol and was subjected to the Wittig reaction with ethoxycarbonyl ethylidene(triphenyl)phosphorane in dichloromethane to give the α,β-unsaturated ethyl ester **2** [20]. Compound **2** was reduced by diisobutylaluminum hydride (DIBAL-H) in dichloromethane to give allylic alcohol **3** in 97% yield. The hydroxyl group of compound **3** was protected by treatment with sodium hydride and benzyl bromide to give compound **4**. The isopropylidene group of compound **4** was hydrolyzed to diol **5** using 2 N HCl in 1,4-dioxane. The primary hydroxy group of **5** was selectively protected with a *tert*-butyldimethysilyl group to yield compound **6** in 92% yield under mild reaction conditions. Johnson–Claisen rearrangement of compound **6** with triethyl orthoacetate at 135 °C in the presence of catalytic amounts of propionic acid yielded the γ,δ-unsaturated quaternary carbon ethyl ester **7** in 66% yield. The enantioselectivity (98.5% ee) of the reaction was determined by using a chiral HPLC [18]. The double bond of **7** was then ozonized into aldehyde **8** and subsequently reduced using DIBAL-H in toluene at −78 °C to yield lactol **9** in 47% yield in two steps. The apiose lactol **9** was acetylated in pyridine to yield the key intermediate **10** as a glycosyl donor (Scheme 1). For the preparation of the cytosine derivatives **19** and **20**, compound **10** was condensed with per-*O*-trimethylsilyl-N^4-benzoylcytosine using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst in 1,2-dichloroethane (DCE) to give protected nucleosides **11** and **12** (2:3 = β,α ratio, determined by NMR spectroscopy) as an anomeric mixture, which is readily separated by silica gel column chromatography. Compounds **11** and **12** were separately treated with methanolic ammonia and subsequently debenzylated using catalytic hydrogenolysis to obtain the desired final nucleosides **19** and **20**, respectively (Scheme 2). The stereochemical assignment was determined on the basis of 1D and 2D NOE experiments. Compound **10** was also condensed with corresponding per-*O*-trimethylsilyl-N^4-benzoyl-5-fluorocytosine using TMSOTf as a catalyst in 1,2-dichloroethane to yield the corresponding nucleosides **13** and **14** as an anomeric mixture, which was readily separated by preparative thin-layer chromatography (TLC). To obtain the final nucleosides, compounds **13** and **14** were subjected to the methanolic ammonia and subsequently debenzylated using the same conditions as those used for cytosine nucleosides. In the preparation of thymine and uracil nucleosides, the glycosyl donor **10** was condensed with the corresponding persilylated uracil and thymine using the similar Vorbrüggen reaction conditions [21] to yield protected nucleosides **15**–**18**, respectively. Each nucleoside was debenzylated under the same catalytic hydrogenolysis conditions as the cytosine nucleosides, followed by purification and separation using preparative TLC to obtain compounds **23**–**26**, respectively. The synthesis of adenine and inosine nucleosides was carried out by condensation of compound **10** with silylated 6-chloropurine using TMSOTf

as a catalyst in dichloroethane to give protected 6-chloropurine derivatives **27** and **28** as an anomeric mixture (Scheme 2). In the preparation of adenine derivatives, the anomeric mixture was treated with ammonia in methanol in a steel bomb at 80–90 °C, followed by preparative TLC separation and debenzylation to obtain **31** and **32**. The stereochemical assignment of these nucleosides was also made similarly to the cytosine nucleosides (1D and 2D NOE experiments). The inosine derivatives **33** and **34** were obtained by the treatment of 6-chloropurine analogues with 2-mercaptoethanol and sodium methoxide in methanol by deprotection with dissolving metal (Birch conditions) [22]. For the synthesis of the guanine derivative, compound **10** was condensed with silylated 6-chloro-2-fluoropurine using TMSOTf as the catalyst in dichloroethane to give protected 6-chloro-2-fluoropurine derivatives **29** and **30** as an anomeric mixture. Without separation, this anomeric mixture was subjected to aminolysis to give 2-amino-6-chloro- and 6-chloro-2-fluoropurine analogues, which were converted to guanine derivatives **35** and **36** and 2-fluoroadenine derivatives **37** and **38**, by similar methods for the synthesis of **33** and **34** (Scheme 2).

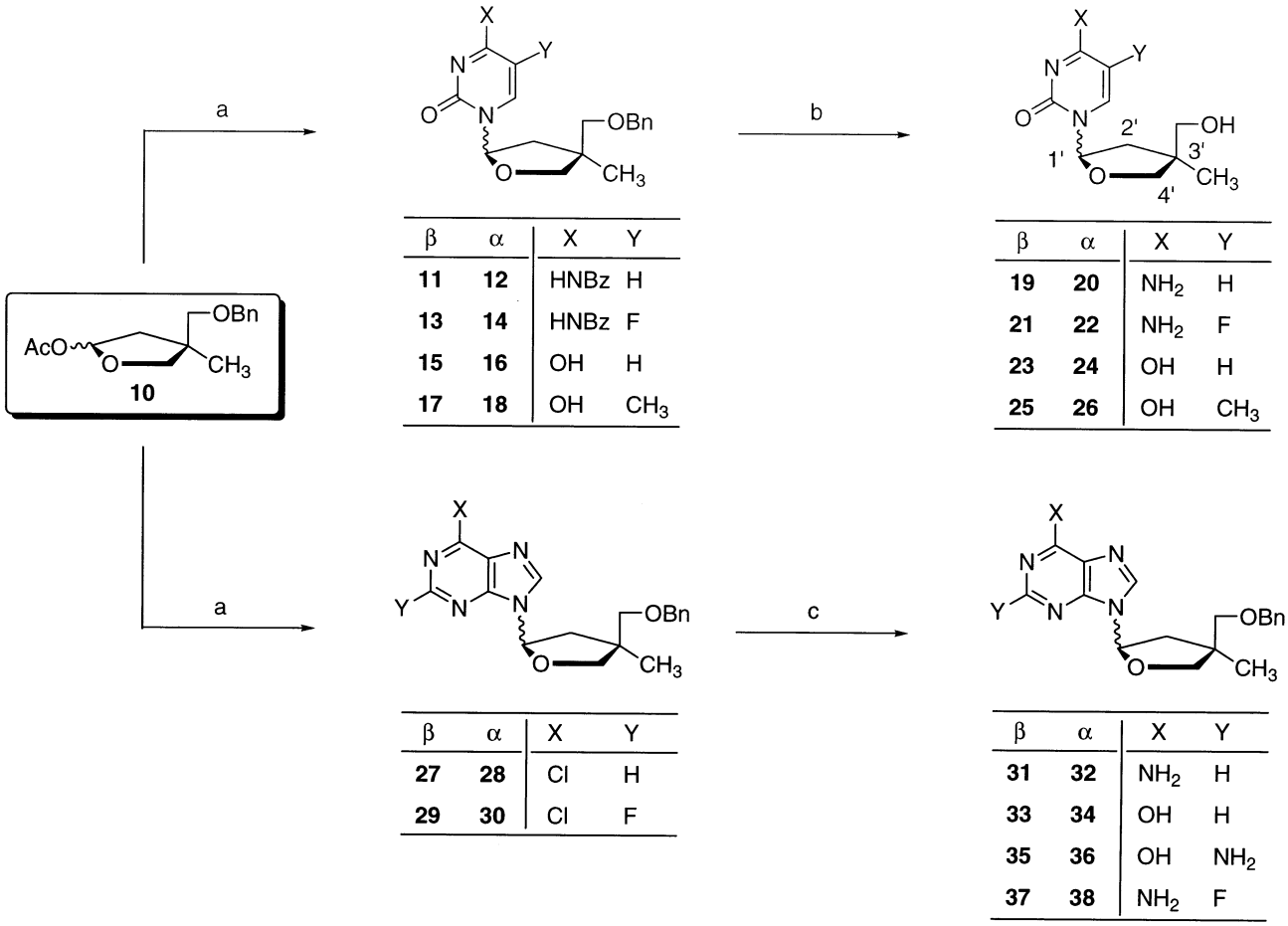
The synthesized nucleosides were assayed against HIV and hepatitis B virus in PBM and 2.2.15 cells, respectively. It was found that compound **37** shows moderate activity against HIV ($EC_{50} = 2.55$ μM). Interestingly, compound **38** shows good activity as well as a significant toxicity ($EC_{50} = 0.073$ μM, $IC_{50} = 1.0$ μM in PBM cells). However, none of these compounds showed any significant anti-HBV activity up to 100 μM.

3. Experimental

General methods.—Melting points (mp) were determined on a Mel-Temp II apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 AMX spectrometer for 400 MHz, with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet) or br d (broad doublet). Mass spectra were measured on a Micromass Autospec high-resolution mass



Scheme 1. Reagents: (a) ethoxycarbonyl ethylidene(triphenyl)phosphorane, CH_2Cl_2, 0 °C; (b) Dibal-H, toluene, −78 °C; (c) BnBr, NaH, THF; (d) 2 N HCl; (e) TBDMSCl, imidazole, CH_2Cl_2; (f) Triethyl orthoacetate, propionic acid, 135 °C; (g) O_3–DMS, MeOH, −78 °C; (h) Dibal-H, toluene, −78 °C; (i) $(Ac)_2O$, pyridine.



β	α	X	Y
11	**12**	HNBz	H
13	**14**	HNBz	F
15	**16**	OH	H
17	**18**	OH	CH_3

β	α	X	Y
19	**20**	NH_2	H
21	**22**	NH_2	F
23	**24**	OH	H
25	**26**	OH	CH_3

β	α	X	Y
27	**28**	Cl	H
29	**30**	Cl	F

β	α	X	Y
31	**32**	NH_2	H
33	**34**	OH	H
35	**36**	OH	NH_2
37	**38**	NH_2	F

Scheme 2. Reagents: (a) silylated bases, TMSOTf, $ClCH_2CH_2Cl$; (b) (i) NH_3–MeOH and 20% $Pd(OH)_2/C$, cyclohexane, MeOH for **19**–**22**; (ii) 20% $Pd(OH_2/C$, cyclohexane, MeOH for **23**–**26**; (c) (i) NH_3–MeOH, 90 °C and 20% $Pd(OH)_2/C$, cyclohexane, MeOH for **31** and **32** or $NSCH_2OH$, NaOMe, MeOH, reflux and Na/THF, −78 °C for **33** and **34**; (ii) NH_3–DME and $HSCH_2CH_2OH$, NaOMe, MeOH, reflux and Na–THF, −78°C for **35** and **36**; (iii) NH_3–DME and 20% $Pd(OH)_2/C$; cyclohexane, MeOH for **37** and **38**.

spectrometer. Optical rotations were performed on a Jasco DIP-370 Digital Polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Silica Gel G (TLC) grade > 440 mesh was used for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

*Ethyl (*E*)(*S*)-3-(2,2-dimethyl[1,3]dioxolane-4-yl)-2-methylacrylate* (**2**).—A solution of carbethoxyethylidene triphenylphosphorane (47.0 g, 129.7 mmol) in CH_2Cl_2 (150 mL) was added dropwise to a solution of **1** (15.5 g, 117.4 mmol) in CH_2Cl_2 (300 mL) at 0 °C. The solvent was evaporated under reduced pressure. The residue was triturated with small amounts of cold diethyl ether to precipitate triphenylphosphine oxide. *n*-Hexane was added to this triturated mixture. The resulting suspension was kept in the refrigerator for 1 h to precipitate additional product. The resulting solid (triphenylphosphine oxide) was filtered off with the aid of Celite and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (23:1 hexane–EtOAc) to give compound **2** as a liquid (19.7 g, 79%); $[\alpha]_D^{26}$ + 19.1° (*c* 3.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.70 (dd, *J* 1.4, 8.1 Hz, 1 H), 4.85 (q, *J* 7.5 Hz, 1 H), 4.23–4.15 (m, 3 H), 3.63 (t, *J* 7.7 Hz, 1 H), 1.90 (d, *J* 1.2 Hz, 3 H), 1.46, 1.42 (s, s, 3 H, 3 H), 1.30 (t, *J* 7.1 Hz, 3 H).

(E)(S)-4-(3-Hydroxy-2-methylpropenyl)-2,2-dimethyl[1,3]dioxolane (**3**).—DIBAL-H (170.0 mL, 1 M solution in hexane) was added dropwise at −78 °C under argon to a solution of **2** (18.0 g, 84.1 mmol) in CH_2Cl_2 (365 mL). After stirring for 30 min under the same conditions, the reaction mixture was quenched by a slow addition of MeOH (200 mL) and stirred for another 3 h. The resulting solid was filtered off with the aid of Celite and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (3:2 hexane–EtOAc) to give **3** (14.0 g, 97%); $[\alpha]_D^{23}$ +12.7° (*c* 5.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.41 (ddd, *J* 8.6, 2.8, 1.3 Hz, 1 H), 4.77 (m, 1 H), 4.01 (dd, *J* 5.4, 2.2 Hz, 1 H), 3.96 (s, 2 H), 3.48 (t, *J* 8.0 Hz, 1 H), 1.67 (d, *J* 0.8 Hz, 3 H), 1.33, 1.32 (s, s, 3 H, 3 H).

(E)(S)-4-(3-Benzyloxy-2-methylpropenyl)-2,2-dimethyl[1,3]dioxolane (**4**).—Sodium hydride (3.9 g, 97.5 mmol 60% in oil) was washed twice with anhyd pentane. Anhydrous THF (200 mL) was added to the mixture, and a solution of compound **3** (14.0 g, 81.5 mmol) in tetrahydrofuran (THF) (100 mL) was slowly added, and then stirred for 30 min under nitrogen. Benzyl bromide (89.5 mmol, 15.3 g) was then added slowly with stirring for 3 h under nitrogen at room temperature (rt). A satd NH_4Cl soln was slowly added to quench the excess sodium hydride, and the mixture was extracted twice with diethyl ether. The organic extract was dried over anhyd $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15:1 hexane–EtOAc) to give **4** (21.2 g, 99%); $[\alpha]_D^{26}$ +10.9° (*c* 6.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.25 (m, 5 H), 5.52 (dd, *J* 7.4, 1.0 Hz, 1 H), 4.83 (m, 1 H), 4.48 (s, 2 H), 4.09 (dd, *J* 7.9, 5.9 Hz, 1 H), 3.92 (s, 2 H), 3.54 (t, *J* 8.1 Hz, 1 H), 1.75 (s, 3 H), 1.43, 1.40 (s, s, 3 H, 3 H); ^{13}C NMR ($CDCl_3$): δ 138.47, 138.33, 128.65, 127.96, 127.88, 124.68, 109.29, 76.99, 75.37, 72.78, 72.24. 69.60, 27.06, 26.27, 14.60; HRMS Calcd for $[M+H]^+$: 263.1647; found: 263.1624. Anal. Calcd for $C_{16}H_{22}O_3 \cdot 0.1C_6H_{14}$: C, 73.52; H, 8.64. Found: C, 73.71; H, 8.51.

(E)(S)-5-Benzyloxy-4-methylpent-3-ene-1,2-diol (**5**).—To a solution of compound **4** (21.2 g, 80.9 mmol) in 1,4-dioxane (100 mL), 2 N HCl (200 mL) was added, and the mixture was stirred at rt for 2 h. After the reaction mixture was neutralized with solid $NaHCO_3$, the solvent was evaporated under reduced pressure and co-evaporated twice with EtOH. The residue was dissolved in CH_2Cl_2 and dried over anhyd $MgSO_4$. The solid was filtered off with the aid of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1:2 hexane–EtOAc) to give **5** (15.2 g, 85%); $[\alpha]_D^{26}$ +9.2° (*c* 7.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.26 (m, 5 H, phenyl H), 5.47 (d, *J* 8.3 Hz, 1 H), 4.52–4.48 (m, 3 H), 3.90 (s, 2 H), 3.58 (d, *J* 10.8 Hz, 1 H), 3.48 (dd, *J* 10.3, 8.0 Hz, 1 H), 1.74 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 138.06, 137.15, 128.41, 128.21, 127.75, 75.13, 72.17, 69.08, 66.15, 14.49; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.21; H, 8.19. Found: C, 70.24; H, 8.16.

*(E)(S)-5-Benzyloxy-1-*tert*-butyldimethylsilanyloxy-4-methylpent-3-en-2-ol* (**6**).—Imidazole (2.0 g, 30.0 mmol) was added to a solution of compound **5** (3.3 g, 15.0 mmol) in CH_2Cl_2 (100 mL), and the mixture was then cooled to −10 °C. To this reaction mixture a solution of *tert*-butyldimethylsilyl chloride (2.3 g, 15.2 mmol) in CH_2Cl_2 (50 mL) was slowly added. The reaction solvent was evaporated under reduced pressure. The residue was extracted twice with diethyl ether and water. The combined organic layer was dried over anhyd $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10:1 hexane–EtOAc) to give compound **6** (4.6 g, 92%); $[\alpha]_D^{25}$ +15.8° (*c* 6.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 26–7.17 (m, 5 H), 5.36 (d, *J* 8.2 Hz, 1 H), 4.40–4.36 (m, 3 H), 3.83 (s, 2 H), 3.51 (dd, *J* 10.1, 3.6 Hz, 1 H), 3.35 (t, *J* 9.9 Hz, 1 H), 1.66 (s, 3 H), 0.83 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 138.24, 136.85, 128.31, 127.63, 127.56, 127.51, 127.41, 75.27, 71.83, 68.85, 66.58, 25.90, 25.84, 14.42, 5.35, 5.42; Anal. Calcd for $C_{19}H_{32}O_3Si \cdot 0.6H_2O$: C, 65.70; H, 9.39. Found: C, 65.68; H, 9.28.

*Ethyl (E)(S)-3-benzyloxymethyl-6-*tert*-butyldimethylsilanyloxy-3-methylhex-4-enate* (**7**).—A mixture of allylic alcohol **6** (6.8 g, 202.4 mmol), triethyl orthoacetate (100 mL), and catalytic amounts of propionic acid (131.1

μL) was heated to 135 °C in a Claisen apparatus for 4 h under nitrogen. The reaction mixture was cooled to rt and distilled off in vacuo. The resulting residue was purified by silica gel column chromatography (30:1 hexane–EtOAc) to give **7** (5.4 g, 65.4%); $[\alpha]_D^{25}$ −9.7° (*c* 9.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.30–7.21 (m, 5 H), 5.72 (dd, *J* 15.9, 0.9 Hz, 1 H), 5.51 (dt, *J* 10.1, 5.1 Hz, 1 H), 4.45 (s, 1 H), 4.09 (d, *J* 5.1 Hz, 2 H), 4.02 (q, *J* 7.1 Hz, 2 H), 3.32 (d, *J* 8.9 Hz, 1 H), 3.27 (d, *J* 8.6 Hz, 1 H), 2.39 (s, 2 H), 1.17 (t, *J* 7.1 Hz, 3 H), 1.12 (s, 3 H), 0.84 (d, *J* 0.6 Hz, 9 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 171.78, 138.63, 135.11, 128.23, 127.88, 127.38, 76.68, 73.21, 64.10, 59.94, 42.15, 39.49, 25.94, 22.10, 18.38, 14.25, −5.12; MS (*m*/*z*): 277 $[M+H]^+$. Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 68.06; H, 9.34.

*Ethyl (*R*)-3-benzyloxymethyl-3-methyl-4-oxobutyrate* (**8**).—A solution of compound **7** (14.8 g, 36.5 mmol) in MeOH (220 mL) was cooled down to −78 °C, and ozone gas was then bubbled into the reaction mixture until a blue color persisted for an additional 5 min. The reaction mixture was degassed with nitrogen, and methyl sulfide (13.4 mL, 183 mmol) was slowly added at −78 °C. The mixture was stirred for 3 h at rt under nitrogen. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (8:1 hexane–EtOAc) to give **8** as a colorless oil (6.8 g, 70.3%); $[\alpha]_D^{24}$ −5.4° (*c* 4.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 9.65 (s, 1 H), 7.36–7.27 (m, 5 H), 4.49 (s, 2 H), 4.10 (q, *J* 7.1 Hz, 2 H), 3.54 (d, *J* 9.0 Hz, 2 H), 2.81 (d, *J* 5.9, 1 H), 2.58 (d, *J* 5.8 Hz, 1 H), 1.22 (t, *J* 7.1 Hz, 3 H), 1.17 (s, 3 H).

*3-*C*-(Benzyloxymethyl)-2,3-dideoxy-3-*C*-methyl-*D*-glycero-tetrofuranose* (**9**).—To a solution of compound **8** (4.1 g, 15.5 mmol) in toluene (100 mL), 1 M solution of DIBAL-H (33.5 mL, 33.5 mmol) in toluene was added dropwise at −78 °C under nitrogen, and the mixture was then stirred for 30 min at −78 °C. The reaction mixture was quenched with MeOH (33.5 mL), and the temperature was increased to rt. After stirring at rt for 3 h, the resulting solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2:1 hexane–EtOAc) to give **9** (2.4 g, 67.2%): ^1H NMR ($CDCl_3$): δ 7.38–7.28 (m, 5 H), 5.52 (t, *J* 2.6 Hz, 0.3 H), 5.40 (m, 0.7 H), 4.69–4.49 (m, 2 H), 4.01–3.58 (m, 2 H), 3.38–3.19 (m, 2 H), 2.10–1.63 (m, 2 H), 1.23, 1.06 (s, s, 3 H).

*1-*O*-Acetyl-3-*C*-(benzyloxymethyl)-2,3-dideoxy-3-*C*-methyl-*D*-glycero-tetrofuranose* (**10**).—To a solution of compound **9** (2.4 g, 10.8 mmol) in pyridine (73 mL), Ac_2O (1.65 g, 16.2 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co-evaporated with toluene three times. The residue was dissolved in EtOAc and successively washed with 0.01 N HCl, satd $NaHCO_3$ soln, and brine. The extract was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (6:1 hexane–EtOAc) to give **10** (2.3 g, 89.2%): ^1H NMR ($CDCl_3$): δ 7.37–7.28 (m, 5 H), 6.28 (dd, *J* 5.4, 2.4 Hz, 0.4 H), 6.26 (dd, *J* 5.7, 1.6 Hz, 0.6 H), 4.55 (s, 1.2 H), 4.53 (d, *J* 1.4 Hz, 0.8 H), 3.96–3.63 (m, 2 H), 3.42 (s, 0.8 H), 3.27 (dd, *J* 19.8, 11.2 Hz, 1.2 H), 2.22 (dd, *J* 14.0, 5.9 Hz, 0.8 H), 2.06, 2.00 (s, s, 3 H), 1.75 (dd, *J* 13.9, 1.7 Hz, 1.2 H), 1.25, 1.19 (s, s, 3 H).

General procedure for condensation of acetate **10** *with bases.*—N^4-benzoylcytosine (602 mg, 2.8 mmol), anhyd HMDS (40 mL), and a catalytic amount of $(NH_4)_2SO_4$ were refluxed to a clear solution, and the solvent was distilled off under anhyd conditions. The residue was dissolved in anhyd CH_2Cl_2 (10 mL). To this mixture, a solution of **10** (369.3 mg, 1.4 mmol) in dry dichloroethane (10 mL) and Me_3SiOTf (0.5 mL, 2.8 mmol) was added, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was quenched with 5 mL of satd $NaHCO_3$ and stirred for 10 min. The resulting solid was filtered through a Celite pad, and the filtrate was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified and separated by preparative TLC (3:2:1 hexane–EtOAc–MeCN) to give **11** (259 mg, 44%) and **12** (211 mg, 36%).

N^4-Benzoyl-1-[3-C-(benzyloxymethyl)-2,3-dideoxy-3-C-methyl-β-D-glycero-tetrofuranosyl]cytosine (**11**) *and N^4-benzoyl-1-[3-C-(benzyloxymethyl)-2,3-dideoxy-3-C-methyl-α-D-glycero-tetrofuranosyl]cytosine* (**12**).—**11**: $[\alpha]_D^{24}$ +77.2° (*c* 0.9% $CHCl_3$); UV (MeOH) λ_{max} 259.5, 301.5 nm; ^{1}H NMR ($CDCl_3$): δ 7.92–7.27 (m, 12 H), 6.11 (t, *J* 6.2 Hz, 1 H), 4.48, 4.44 (d, d, *J* 12.2, 11.8 Hz, 2 H), 4.16 (d, *J* 8.4 Hz, 1 H), 3.78 (d, *J* 8.5 Hz, 1 H), 3.28, 3.25 (d, d, *J* 8.8, 8.8 Hz, 2 H), 2.52 (dd, *J* 13.4, 6.6 Hz, 1 H), 2.03 (dd, *J* 13.7, 5.4 Hz, 1 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 161.97, 143.93, 137.84, 133.19, 129.10, 128.49, 127.86, 127.67, 127.44, 95.80, 88.82, 77.81, 74.87, 73.33, 43.85, 43.60, 29.70, 22.80; HRMS Calcd for $[M+H]^+$: 420.1923; found: 420.1931. **12**: $[\alpha]_D^{25}$ −38.6° (*c* 0.2, $CHCl_3$): UV (MeOH) λ_{max} 258.5, 304.5 nm; ^{1}H NMR ($CDCl_3$): δ 8.02 (d, *J* 7.4 Hz, 1 H), 7.62 (d, *J* 7.4 Hz, 1 H), 7.90–7.30 (m, 10 H), 6.01 (t, *J* 6.3 Hz, 1 H), 4.56 (s, 2 H), 4.16 (d, *J* 8.6 Hz, 1 H), 3.80 (d, *J* 8.6 Hz, 1 H), 3.39 (d, *J* 8.8 Hz), 3.33 (d, *J* 8.8 Hz, 1 H), 2.81 (dd, *J* 14.0, 6.7 Hz, 1 H), 1.75 (dd, *J* 14.0, 5.7 Hz, 1 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 162.16, 143.43, 138.10, 133.22, 129.16, 128.44, 127.69, 127.53, 89.42, 77.94, 75.17, 73.38, 44.11, 44.04, 29.70, 21.60; HRMS Calcd for $[M+H]^+$: 420.1923; found: 420.1748.

N^4-Benzoyl-1-[3-C-(benzyloxymethyl)-2,3-dideoxy-3-C-methyl-β-D-glycero-tetrofuranosyl]5-fluorocytosine (**13**) *and N^4-benzoyl-1-[3-C-(benzyloxymethyl)-2,3-deoxy-3-methyl-α-D-glycero-tetrofuranosyl]5-fluorocytosine* (**14**).—Silylated N^4-benzoyl-5-fluorocytosine, which was prepared from N^4-benzol-5-fluorocytosine (644 mg, 1.4 mmol), anhyd HMDS (10 mL), and a catalytic amount of $(NH_4)_2SO_4$, was reacted with **10** (243 mg, 0.9 mmol) and Me_3SiOTf (0.5 mL, 2.8 mmol) in dry dichloroethane (20 mL) at rt for 2 h under nitrogen. After a workup similar to that for **11** and **12**, purification by preparative TLC (60:12:5 hexane–EtOAc–MeCN) gave **13** (238 mg, 30%) and **14** (193 mg, 24%): **13**: $[\alpha]_D^{25}$ +68.9° (*c* 2.1, $CHCl_3$); UV (MeOH) λ_{max} 257.5, 326.5 nm; ^{1}H NMR ($CDCl_3$): δ 8.22 (d, *J* 7.4 Hz, 1 H), 7.64–7.25 (m, 10 H), 6.01 (t, *J* 6.7 Hz, 1 H), 4.44 (s, 2 H), 4.05, 3.65 (d, d, *J* 8.6, 8.6 Hz, 2 H), 3.24 (d, *J* 8.6 Hz, 2 H), 2.25 (dd, *J* 13.9, 6.7 Hz, 1 H), 2.01 (dd, *J* 13.9, 6.0 Hz, 1 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 152.45, 152.11, 139.25, 137.47, 132.84, 128.78, 128.11, 127.45, 127.41, 87.48, 76.84, 75.47, 73.94, 44.17, 43.58, 22.04. **14**: $[\alpha]_D^{25}$ −41.1° (*c* 2.1, $CHCl_3$); UV (MeOH) λ_{max} 256.5, 324.5 nm; ^{1}H NMR ($CDCl_3$): δ 8.29 (d, *J* 7.5 Hz, 1 H), 7.63–7.26 (m, 10 H), 5.97 (t, *J* 6.4 Hz, 1 H), 4.55 (s, 2 H), 4.09, 3.79 (d, d, *J* 8.7, 8.7 Hz, 2 H), 3.34 (d, *J* 8.6 Hz, 2 H), 2.68 (dd, *J* 13.9, 6.5 Hz, 1 H), 1.72 (dd, *J* 13.9, 6.2 Hz, 1 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 152.14, 151.24, 137.44, 132.97, 129.93, 128.47, 127.46, 127.54, 124.44, 124.26, 88.50, 77.66, 75.10, 73.41, 44.07, 43.50, 21.66.

1-[3-C-(Benzyloxymethyl)-2,3-dideoxy-3-C-methyl-β-D-glycero-tetrofuranosyl]uracil (**15**) *and 1-[3-C-(benzyloxymethyl)-2,3-dideoxy-3-C-methyl-α-D-glycero-tetrofuranosyl]uracil* (**16**).—Silylated uracil (prepared from uracil (254 mg, 2.3 mmol), anhyd HMDS (10 mL), and a catalytic amount of $(NH_4)_2SO_4$) was reacted with **10** (300 mg, 1.1 mmol) and Me_3SiOTf (0.4 mL, 2.3 mmol) in dry dichloroethane (20 mL) at rt for 2 h under nitrogen. After a workup similar to that of **11** and **12**, purification by silica gel column chromatography (15:1 $CHCl_3$–MeOH) gave **15** and **16** as inseparable anomeric mixtures (354 mg, 99%): ^{1}H NMR ($CDCl_3$): δ 7.56 (d, *J* 7.2 Hz, 0.5 H), 7.50 (d, *J* 7.2, 0.5 Hz), 7.38–7.28 (m, 5 H), 6.03 (t, 6.7 Hz, 1 H), 5.64 (d, d, *J* 7.2, 7.2 Hz, 1 H), 4.51 (s, 1 H), 3.96, 3.58 (d, d, *J* 8.2, 8.2 Hz, 1 H), 3.30, 3.32 (s, s, 2 H), 2.11 (m, 1 H), 1.80 (m, 1 H), 1.13, 1.15 (2s, 3 H).

1-[3-C-(Benzyloxymethyl)-2,3-dideoxy-3-C-methyl-β-D-glycero-tetrofuranosyl]thymine (**17**) *and 1-[3-C-(benzy-loxymethyl)-2,3-dideoxy-3-C-methyl-α-D-glycero-tetrofuranosyl]thymine* (**18**).—Silylated thymine (prepared from thymine (484 mg, 3.8 mmol), anhyd HMDS (20 mL), and a catalytic amount of $(NH_4)_2SO_4$) were reacted with **10** (508 mg, 1.9 mmol) and Me_3SiOTf (0.7 mL, 3.8 mmol) in dry dichloroethane (20 mL) at rt for 2 h under nitrogen. After a workup similar to that of **11** and **12**, purification by silica gel column chromatography (5:1 $CHCl_3$–MeOH) gave **17** and **18** as an inseparable anomeric mixture (632 mg, 99.5%): ^{1}H NMR ($CDCl_3$): δ 7.57,

7.59 (s, s, 1 H), 6.04, 6.11 (t, t, *J* 7.4, 7.4 Hz, 1 H), 4.99, 5.04 (t, t, *J* 5.2, 5.4 Hz, 1 H, D_2O exchangeable), 3.81, 3.83 (s, s, 2 H), 3.37–3.41 (m, 2 H), 2.30–2.33 (m, 1 H), 1.861.88 (s, s, 3 H), 1.76–1.79 (m, 1 H), 1.14, 1.11 (s, s, 3 H).

*1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]cytosine* (**19**).—Compound **11** (258.7mg, 0.6 mmol) was treated with satd methanolic ammonia at rt overnight. The solvent was evaporated under reduced pressure. After purification by silica gel column chromatography (15: $CHCl_3$–MeOH, 192.3 mg, 99%), cytosine analogue (192.3 mg, 0.6 mmol) was refluxed with $Pd(OH)_2/C$ (135.5 mg) in MeOH (38.9 mL) and cyclohexene (10.1 mL) overnight. The reaction mixture was filtered and evaporated. The residue was purified by silica gel column chromatography (5:1 $CHCl_3$–MeOH) to give compound **19** (105 mg, 77.1%): mp 177–179 °C; $[\alpha]_D^{26}$ +77.8° (*c* 0.3, MeOH); UV (H_2O) λ_{max} 271.5 nm (ε 10,800) (pH 7), 276.5 nm (ε 18,800) (pH 2), 270.5 nm (ε 17,000) (pH 11); ^{1}H NMR (DMSO-d_6): δ 7.61 (d, *J* 7.5 Hz, 1 H), 7.18 (br d, 2 H, D_2O exchangeable), 6.04 (t, *J* 6.7 Hz, 1 H), 5.74 (d, *J* 7.5 Hz, 1 H), 4.88 (t, *J* 6.2 Hz, 1 H, D_2O exchangeable), 3.96, 3.50 (d, d, *J* 8.2, 8.2 Hz, 2 H), 3.35 (d, *J* 7.9 Hz, 2 H), 2.00 (dd, *J* 13.2, 6.6 Hz, 1 H), 1.77 (dd, *J* 13.2, 7.2 Hz, 1 H), 1.07 (s, 3 H); ^{13}C NMR (DMSO-d_6): δ 169.02, 168.95, 168.88, 158.51, 144.14, 144.09, 97.42, 97.37, 97.32, 89.63, 79.65, 69.61, 69.49, 48.21, 45.09, 25.58; HRMS Calcd for $[M+H]^+$: 226.1192; found: 226.1187. Anal. Calcd for $C_{10}H_{15}N_3O_3 \cdot 0.4H_2O$: C, 51.67; H, 6.79; N,18.06. Found: C, 51.60; H, 6.65; N, 18.04.

*1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]cytosine* (**20**).—Compound **12** (211 mg, 0.5 mmol) was converted into compound **20** (83 mg, 72.3%) by a similar method to that of **19**: mp 199–201 °C; $[\alpha]_D^{26}$ −48.4° (*c* 0.2, MeOH); UV (H_2O) λ_{max} 270.5 nm (ε 7740) (pH 7), 279.5 nm (ε 8730) (pH 2), 271.5 nm (ε 9100) (pH 11); ^{1}H NMR (DMSO-d_6): δ 7.65 (d, *J* 7.4 Hz, 1 H), 7.14 (br d, 2 H, D_2O exchangeable), 5.95 (t, *J* 6.7 Hz, 1 H), 5.74 (d, *J* 7.3 Hz, 1 H), 4.92 (t, *J* 5.5 Hz, 1 H, D_2O exchangeable), 3.80, 3.71 (d, d, *J* 8.2, 8.2 Hz, 2 H), 3.33 (s, 2 H), 2.31 (dd, *J* 13.3, 6.6 Hz, 1 H), 1.56 (dd, *J* 13.3, 6.9 Hz, 1 H), 1.01 (s, 3 H); ^{13}C NMR (DMSO-d_6): δ 164.37, 164.29, 153.86, 139.60, 92.63, 92.58, 92.53, 85.45, 74.45, 64.91, 64.78, 43.57, 43.55, 40.52, 19.38; HRMS Calcd for $[M+H]^+$: 226.1192; found: 226.1196. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.30; H, 6.71; N, 18.62.

*1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]-5-fluorocytosine* (**21**).—Compound **13** (93 mg, 0.2 mmol) was also converted into compound **21** (28.9 mg, 36.9%) by a method similar to that of **19**: mp 181–183 °C; $[\alpha]_D^{25}$ +214.9° (*c* 0.2, MeOH); UV (H_2O) λ_{max} 281.5 nm (ε 7950) (pH 7), 290.0 nm (ε 9440) (pH 2), 280.0 nm (ε 7920) (pH 11); ^{1}H NMR (MeOH-d_4): δ 7.77 (d, *J* 6.3 Hz, 1 H), 5.93 (t, *J* 6.4 Hz, 1 H), 3.99, 3.57 (d, d, *J* 8.5, 8.5 Hz, 2 H), 3.21, (d, *J* 1.3 Hz, 2 H), 2.14 (dd, *J* 13.5, 7.0 Hz, 1 H), 1.82 (dd, *J* 13.5, 6.5 Hz, 1 H), 1.06 (s, 3 H); ^{13}C NMR (MeOH-d_4): δ 159.65, 159.51, 156.46, 126.29, 125.97, 89.27, 78.06, 68.13, 67.96, 43.33, 22.46; HRMS Calcd for $[M+H]^+$: 244.1097; found: 244.1098. Anal. Calcd for $C_{10}H_{14}FN_3O_3 \cdot 0.4EtOH$: C, 49.50; H, 6.26; N, 16.05. Found: C, 49.35; H, 5.97; N, 15.95.

*1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]-5-fluorocytosine* (**22**).—Compound **14** (158 mg, 0.4 mmol) was converted into compound **22** (26.9 mg, 37.7%) by a method similar to that of **19**: mp 190–192 °C; $[\alpha]_D^{23}$ −48.2° (*c* 0.3, MeOH); UV (H_2O) λ_{max} 280.5 nm (ε 8530) (pH 7), 289.5 nm (ε 11,300) (pH 2), 280.5 nm (ε 7200) (pH 11); ^{1}H NMR (MeOH-d_4): δ 7.85 (d, *J* 6.5 Hz, 1 H), 5.93 (t, *J* 6.4 Hz, 1 H), 3.96, 3.83 (d, d, *J* 8.6, 8.5 Hz, 2 H), 3.47, 3.43 (d, d, *J* 10.9, 10.8, 2 H), 2.53 (dd, *J* 13.7, 6.5 Hz, 1 H), 1.70 (dd, *J* 13.7, 6.5 Hz, 1 H), 1.11 (s, 3 H); ^{13}C NMR (MeOH-d_4): δ 159.68, 159.64, 156.47, 126.27, 125.95, 89.84, 77.78, 68.18, 43.80, 20.87; HRMS Calcd for $[M+H]^+$: 244.1097; found: 244.1096. Anal. Calcd for $C_{10}H_{14}FN_3O_3 \cdot 0.4MeOH$: C, 48.74; H, 5.62; N, 16.40. Found: C, 48.93; H, 5.88; N, 16.13.

*1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]uracil* (**23**) *and 1-[2,3-deoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrafuranosyl]uracil* (**24**).—Compound **15** and **16** (354 mg, 1.1 mmol) was refluxed with $Pd(OH)_2/C$ (499 mg) in MeOH (143 mL) and cyclohexene (37 mL)

overnight. The reaction mixture was filtered and evaporated. The residue was purified and separated by preparative TLC (30:1 $CHCl_3$–MeOH) to give **23** (74.1 mg, 29.2%) and **24** (82.3 mg, 32.5%). **23**: mp 122–124 °C; $[\alpha]_D^{27}$ −4.0° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 261.5 nm (ε 8470) (pH 7), 263.5 nm (ε 8110) (pH 2), 262.5 nm (ε 8000) (pH 11); ^{1}H NMR (MeOH-d_4): δ 7.62 (d, *J* 8.0 Hz, 1 H), 5.91 (t, *J* 6.7 Hz, 1 H), 5.62 (d, *J* 8.1 Hz, 1 H), 3.84, 3.75 (d, d, *J* 8.5, 8.4 Hz, 2 H), 3.37, 3.34 (d, d, *J* 8.8, 10.8 Hz, 2 H), 2.36 (dd, *J* 13.6, 6.6 Hz, 1 H), 1.69 (dd, *J* 13.7, 6.8 Hz, 1 H), 1.04 (s, 3 H); ^{13}C NMR (MeOH-d_4): δ 164.76, 150.49, 140.40, 100.75, 87.35, 76.02, 66.44, 44.58, 41.20, 18.99; Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.80; H, 6.27; N, 12.23; HRMS Calcd for $[M+H]^+$: 227.1032; found: 227.1040. **24**: mp 134–136 °C; $[\alpha]_D^{26}$ +17.0° (*c* 0.9, MeOH); UV (H_2O) λ_{max} 261.0 (ε 8695) (pH 7), 261.5 (ε 9212) (pH 2), 260.0 (ε 8539) (pH 11); ^{1}H NMR (MeOH-d_4): δ 7.64 (d, *J* 8.1 Hz, 1 H), 6.00 (t, *J* 6.7 Hz, 1 H), 5.62 (d, *J* 8.1 Hz, 1 H), 3.97, 3.55 (d, d, *J* 8.4, 8.4 Hz, 2 H), 3.37 (s, 2 H), 2.06 (dd, *J* 13.5, 6.6 Hz, 1 H), 1.91 (dd, *J* 13.4, 6.8 Hz, 1 H), 1.07 (s, 3 H); ^{13}C NMR (MeOH-d_4): δ 166.74, 152.59, 142.47, 102.93, 88.75, 78.49, 68.31, 46.58, 42.97, 22.89; HRMS Calcd for $[M+H]^+$: 227.1032; found: 227.1046. Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.13; H, 6.26; N, 12.28.

*1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]thymine* (**25**) *and 1-[3-deoxy 3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]thymine* (**26**).—Compounds **25** (185 mg, 44.9%) and **26** (196 mg, 47.7%) were obtained from **17** and **18** (566 mg, 1.7 mmol) by a similar method to that of **23** and **24**. **25**: mp 172–174 °C; $[\alpha]_D^{23}$ +7.9° (*c* 0.4, MeOH); UV (H_2O) λ_{max} 265.5 nm (ε 10,100) (pH 7), 268.0 nm (ε 9840) (pH 2), 268.0 nm (ε 6680) (pH 11); ^{1}H NMR (DMSO-d_6): δ 11.31(s, 1 H, D_2O exchangeable), 7.58 (s, 1 H), 6.04 (t, *J* 7.4 Hz, 1 H), 4.99 (t, *J* 5.2 Hz, 1 H, D_2O exchangeable), 3.81 (s, 2 H), 3.37 (s, 2 H), 2.31 (dd, *J* 13.3, 6.5 Hz, 1 H), 1.86 (s, 3 H), 1.76 (dd, *J* 13.1, 6.5 Hz, 1 H), 1.14 (s, 3 H): ^{13}C NMR (DMSO-d_6): δ 167.27, 153.84, 139.66, 113.03, 89.19, 79.12, 69.54, 48.45, 44.01, 23.70, 15.59; HRMS Calcd for $[M+H]^+$: 241.1188; found: 241.1176. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.84; H, 6.62; N, 11.57. **26**: mp 154–156 °C; $[\alpha]_D^{23}$ +25.5° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 266.0 nm (ε 8700) (pH 7), 268.5 nm (ε 9210) (pH 2), 280.0 nm (ε 8540) (pH 11); ^{1}H NMR (DMSO-d_6): δ 11.28 (s, 1 H, D_2O exchangeable), 7.50 (s, 1 H), 6.06 (t, *J* 7.1 Hz, 1 H), 4.92 (t, *J* 5.3 Hz, 1 H, D_2O exchangeable), 3.98, 3.49 (d, d, *J* 8.2, 8.2 Hz, 2 H), 3.31 (s, 2 H), 1.92 (m, 2 H), 1.79 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (DMSO-d_6): δ 164.14, 150.75, 136.27, 109.84, 85.53, 76.68, 66.55, 45.14, 40.78, 22.41, 12.52; HRMS Calcd for $[M+H]^+$: 241.1188; found: 241.1198. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.02; H, 6.71; N, 11.64.

*9-[3-*C*-(Benzyloxymethyl)-2,3-dideoxy-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]6-chloropurine* (**27**) *and 9-[3-*C*-(benzyloxymethyl)-2,3-dideoxy-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]6-chloropurine* (**28**).—Silylated 6-chloropurine (prepared from 6-chloropurine (410.5 mg, 2.7 mmol), anhyd HMDS (23 mL), and a catalytic amount of $(NH_4)_2SO_4$) was reacted with **10** (351.0 mg, 1.3 mmol) and Me_3SiOTf (0.5 mL, 2.7 mmol) in dry dichloroethane (20 mL) at rt for 2 h under nitrogen. After a similar workup to that of **11** and **12**, purification by silica gel column chromatography (3:1 hexane–EtOAc) gave **27** and **28** (295.3 mg, 62.0%) as an inseparable anomeric mixture: ^{1}H NMR ($CDCl_3$): δ 8.75, 8.72 (s, s, 1 H), 8.40, 8.26 (s, s, 1 H), 7.38–7.19 (m, 5 H), 6.45, 6.29 (d, d, t, *J* 7.2, 5.7 Hz, 1 H), 4.60, 4.53 (s, s, 2 H) 4.19, 4.02 (d, d, *J* 8.5, 8.5 Hz, 2 H), 3.76, 3.56 (d, d, *J* 9.5, 9.5 Hz, 2 H), 2.69 (dd, *J* 14.2, 5.8 Hz, 1 H), 2.37 (dd, *J* 13.8, 7.2 Hz, 1 H), 2.09–1.98 (m, 2 H), 1.25, 1.11 (s, s, 3 H); HRMS Calcd for $[M+H]^+$: 359.1275; found: 329.1310.

*9-[3-*C*-(Benzyloxymethyl)-2,3-dideoxy-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]-6-chloro-2-fluoropurine* (**29**) *and 9-[3-*C*-(benzyloxymethyl)-2,3-dideoxy-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]-6-chloro-2-fluoropurine* (**30**).—Silylated 6-chloro-2-fluoropurine (prepared from 6-chloro-2-fluoropurine (432 mg, 2.8 mmol), anhyd HMDS (20 mL), and a catalytic amount of $(NH_4)_2SO_4$) was reacted with **10** (500 mg, 1.9 mmol) and Me_3SiOTf

(0.5 mL, 2.8 mmol) in dry dichloroethane (20 mL) at rt for 2 h under nitrogen. After a similar workup to that of **11** and **12**, purification by silica gel column chromatography (5:1 hexane–EtOAc) gave **29** and **30** (396 mg, 56%) as an inseparable anomeric mixture: ^{1}H NMR (MeOH-d_4): δ 8.59, 8.57 (s, s, 1 H), 7.54–7.27 (m, 5 H), 6.35, 6.28 (t, t, J 6.3, 6.6 Hz, 1 H), 4.51–4.48 (m, 2 H), 4.21, 3.91 (m, 2 H), 3.35–3.33 (m, 2 H), 2.70–2.58 (m, 1 H), 2.43–2.30 (m, 1 H), 1.13, 1.15 (s, s, 3 H).

*9-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]adenine* (**31**).—Anomeric mixtures **27** and **28** (200.0 mg, 0.6 mmol) were treated with satd methalonic ammonia for 15 h at 90 °C in a steel bomb. After removal of the solvent, the residue was purified by preparative TLC (10:1 $CHCl_3$–MeOH) to give the β isomer (55.9 mg, 29.5%) and the α isomer (59.7 mg, 31.6%). The β isomer (71.0 mg, 0.2 mmol) was refluxed with $Pd(OH)_2$/C (46.4 mg) in MeOH (10.4 mL) and cyclohexene (3.2 mL) overnight. The reaction mixture was filtered, and the solvent was evaporated. The residue was purified by silica gel column chromatography (5:1 $CHCL_3$–MeOH) to give **31** (32.4 mg, 62.1%) as a white solid: mp 217–219 °C; $[\alpha]_D^{25}$ −55.4° (c 0.2, DMF); UV (H_2O) λ_{max} 259.0 nm (ε 14,100) (pH 7), 258.0 (ε 21,300) (pH 2), 260.0 nm (ε 16,700) (pH 11); ^{1}H NMR (DMSO-d_6): δ 8.41 (s, 1 H), 8.24 (s, 1 H), 7.36 (br s, 2 H, D_2O exchangeable), 6.42 (t, J 6.9 Hz, 1 H), 5.06 (t, J 5.2 Hz, 1 H, D_2O exchangeable), 4.14, 3.64 (d, d, J 8.2, 8.2 Hz, 2 H), 3.56 (d, J 10.3 Hz, 2 H), 2.62 (dd, J 13.2, 6.9 Hz, 1 H), 2.25 (dd, J 13.2, 7.2 Hz, 1 H), 1.23 (s, 3 H); ^{13}C NMR (DMSO-d_6): δ 159.52, 159.46, 156.03, 152.64, 142.50, 122.58, 87.84, 79.60, 69.64, 69.52, 48.87, 48.85, 25.60; HRMS Calcd for $[M+H]^+$: 250.1304; found: 250.1292. Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.88; H, 6.09; N, 27.95.

*9-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]adenine* (**32**).—The α isomer (89.7 mg, 0.3 mmol) obtained from **27** and **28** was converted into **32** (41.3 mg, 57.9%): mp 158–160 °C; $[\alpha]_D^{28}$ +33.5° (c 1.1, MeOH); UV (H_2O) λ_{max} 260.0 nm (ε 11,800) (pH 7), 257.5 nm (ε 14,400) (pH 2), 260.0 nm (ε 16,100) (pH 11); ^{1}H NMR (DMSO-d_6): δ 8.52 (s, 1 H), 8.33 (s, 1 H), 7.44 (br s, 2 H, D_2O exchangeable), 6.43 (t, J 6.8 Hz, 1 H), 5.14 (t, J 5.3 Hz, 1 H, D_2O exchangeable), 4.06, 4.01 (d, d, J 8.2, 8.1 Hz, 2 H), 3.51 (s, 2 H), 2.57 (dd, J 7.0, 1.2 Hz, 1 H), 2.44 (dd, J 7.0, 1.8 Hz, 1 H),1.35 (s, 3 H); ^{13}C NMR (DMSO-d_6): δ 159.53, 159.46, 155.98, 152.57, 142.93, 122.76, 87.95, 78.73, 69.60, 69.47, 48.89, 48.87, 23.34; HRMS Calcd for $[M+H]^+$: 250.1304; found: 250.1278. Anal. Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 53.13; H, 6.13; N, 28.03.

*1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]hypoxanthine* (**33**) *and 1-[2,3-dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl] hypoxanthine* (**34**).—The anomeric mixture of **27** and **28** (177 mg, 0.5 mmol) was refluxed with MeOH (8.5 mL, 2.0 mmol), CH_3ONa (2.6 mL, 2.0 mmol), and 2-mercaptoethanol (0.13 mL, 2.0 mmol) for 3 h. The solvent was removed under reduced pressure. The residue was purified by preparative TLC to give an anomeric mixture (137.1 mg, 82.1%), which was dissolved in anhyd THF (2 mL) and cooled down to −78 °C in a Dewar flask. Around 3 mL of ammonia gas was collected in the reaction mixture. To this reaction mixture, small particles of sodium metal were added until a blue color appeared at −78 °C under nitrogen. When the blue color started to appear, the reaction mixture was immediately quenched with MeOH (disappearance of color) and elevated in temperature to rt to remove the ammonia gas. The reaction mixture was neutralized with AcOH until the pH was around 7.5. The solvent was removed under reduced pressure. The residue was purified by preparative TLC (5:1 $CHCl_3$–MeOH) to give **33** (19.6 mg, 23.6%) and **34** (22.6 mg, 18.6%). **33**: mp 178–180 °C; $[\alpha]_D^{28}$ −21.2° (c 0.2, MeOH); UV (H_2O) λ_{max} 248.5 nm (ε 10,800) (pH 7), 249.0 nm (ε 12,300) (pH 2), 255.0 nm (ε 10,500) (pH 11); ^{1}H NMR (MeOH-d_4): δ 8.18 (s, 1 H), 7.95 (s, 1 H), 6.30 (t, J 6.8 Hz, 1 H), 4.10, 3.90 (d, d J 8.4, 8.4 Hz, 2 H), 3.51, 3.38 (d, d, J 10.9, 10.9 Hz, 2 H), 2.48 (dd, J 13.6, 6.5 Hz, 1 H), 2.20 (dd, J 13.5, 7.2 Hz, 1 H), 1.15 (s, 3 H); HRMS Calcd for $[M+H]^+$: 251.1144; found: 251.1122. Anal. Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H,

5.64; N, 22.39. Found: C, 52.08; H, 6.00; N, 21.92. **34**: mp 170–173 °C; $[\alpha]_D^{26}$ +40.5° (*c* 0.3, MeOH); UV (H_2O) λ_{max} 249.0 nm (ε 12,500) (pH 7), 249.0 nm (ε 13,600) (pH 2), 255.5 nm (ε 12,300) (pH 11); ^{1}H NMR (MeOH-d_4): δ 8.12 (s, 1 H), 7.95 (s, 1 H), 6.21 (t, *J* 6.8 Hz, 1 H), 3.92, 3.87 (d, d, *J* 8.4, 8.5 Hz, 2 H), 3.44, 3.38 (d, d, *J* 10.8, 10.9 Hz, 2 H), 2.46 (dd, *J* 13.7, 7.0 Hz, 1 H), 2.30 (dd, *J* 13.7, 6.6 Hz, 1 H), 1.14 (s, 3 H); HRMS Calcd for $[M+H]^+$: 251.1144; found: 251.1125. Anal. Calcd for $C_{11}H_{14}N_4O_3 \cdot 0.3MeOH$: C, 52.03; H, 5.83; N, 21.48. Found: C, 51.96; H, 5.64; N, 21.26.

*9-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]guanine* (**35**) *and 9-[2,3-deoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]guanine* (**36**).—Ammonia gas was slowly bubbled into the mixture of **29** and **30** (280 mg, 0.7 mmol) in ethylene glycol dimethyl ether (DME, 45 mL) for 24 h. The solvent was removed under reduced pressure. The residue was purified by preparative TLC to give 2-amino-6-chloropurine analogues as an inseparable anomeric mixture (120.5 mg, 32.2%) and 6-amino-2-fluoro-purine analogues as an inseparable anomeric mixture (48.2 mg, 13.5%). The 2-amino-6-chloropurine analogues (66.2 mg, 0.2 mmol) were refluxed with MeOH (3.5 mL), CH_3ONa (0.9 mL, 0.7 mmol), and 2-mercaptoethanol (0.05 mL, 0.7 mmol) for 18 h. After concentration of the mixture, the residue was purified by preparative TLC to give guanine analogues (44.2 mg, 70.4%) as an inseparable anomeric mixture, which was debenzylated by the dissolving metal method similar to that of **33** and **34** to give **35** (22.5 mg, 8.6% from **29** and **30**) and **36** (26.2 mg, 10.0% from **29** and **30**). **35**: mp 231–233 °C; $[\alpha]_D^{27}$ −43.7° (*c* 0.2, MeOH); UV (H_2O) λ_{max} 253.0 nm (ε 12,600) (pH 7), 253.5 nm (ε 10,200) (pH 2), 262.5 nm (ε 11,000) (pH 11); ^{1}H NMR (MeOH-d_4): δ 7.83 (s, 1 H), 6.11 (t, *J* 6.9 Hz, 1 H), 4.04, 3.52 (d, d, *J* 8.4, 8.3 Hz, 2 H), 3.48 (d, *J* 2.7 Hz, 2 H), 2.40 (dd, *J* 13.5, 6.8 Hz, 1 H), 2.10 (dd, *J* 13.3, 7.2 Hz, 1 H), 1.14 (s, 3 H); HRMS Calcd for $[M+H]^+$: 266.1253; found: 266.1259. Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot 1.0H_2O \cdot 0.4MeOH$: C, 47.88; H, 5.60; N, 24.94. Found: C, 48.06; H, 5.22; N, 24.58. **36**: mp 218–220 °C; $[\alpha]_D^{26}$ +25.7° (*c* 0.3, MeOH); UV (H_2O) λ_{max} 253.0 nm (ε 13,100) (pH 7), 254.5 nm (ε 12,000) (pH 2), 262.0 nm (ε 12,700) (pH 11); ^{1}H NMR (MeOH-d_4): δ 7.77(s, 1 H), 6.03 (t, *J* 6.8 Hz, 1 H), 3.86, 3.81 (d, d, *J* 8.5, 8.4 Hz, 2 H), 3.39, 3.33 (d, d, *J* 6.7, 6.7 Hz, 2 H), 2.36 (dd, *J* 13.4, 7.0 Hz, 1 H), 2.24 (dd, *J* 13.6, 6.7 Hz, 1 H), 1.12 (s, 3 H); HRMS Calcd for $[M+H]^+$: 266.1253; found: 266.1255. Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot 1.0H_2O \cdot 0.2MeOH$: C, 46.44; H, 4.77; N, 24.18. Found: C, 46.66; H, 5.10; N, 24.18.

*6-Amino-9-[2,3-dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-β-*D*-glycero-tetrofuranosyl]-2-fluoropurine* (**37**) *and 6-amino-9-[2,3-dideoxy-3-*C*-(hydroxymethyl)-3-*C*-methyl-α-*D*-glycero-tetrofuranosyl]-2-fluoropurine* (**38**).—A mixture of 6-amino-2-fluoro-purine analogues (96.0 mg, 0.3 mmol) in EtOH (10 ml) was treated with palladium-on-charcoal (50 mg) and stirred overnight under an atmosphere of hydrogen. After checking for the complete disappearance of the starting materials, the reaction mixture was filtered and concentrated. The residue was purified and separated by preparative TLC (10:1 $CHCl_3$–MeOH) to give **37** (26.7 mg, 37.2%) and **38** (30.5 mg, 42.4%). **37**: mp 208–210 °C; $[\alpha]_D^{26}$ −32.2° (*c* 0.6, MeOH); UV (H_2O) λ_{max} 261.0 nm (ε 22,900) (pH 7), 261.0 nm (ε 22,400) (pH 2), 261.0 nm (ε 23,300) (pH 11); ^{1}H NMR (MeOH-d_4): δ 8.15 (s, 1 H), 6.19 (t, *J* 6.8 Hz, 1 H), 4.08 (d, *J* 8.4 Hz, 1 H), 3.58 (d, *J* 8.4 Hz, 1 H), 3.53, 3.49 (d, d, *J* 10.9, 10.9 Hz, 2 H), 2.47 (dd, *J* 13.6, 6.5 Hz, 1 H), 2.17 (dd, *J* 13.6, 7.2 Hz, 1 H), 1.13 (s, 3 H); HRMS Calcd for $[M+H]^+$: 268.1210; found: 268.1231. Anal. Calcd for $C_{11}H_{14}FN_5O_2 \cdot 0.2MeOH$: C, 49.04; H, 5.45; N, 25.43. Found: C, 49.06; H, 5.50; N, 25.08. **38**: mp 200–202 °C; $[\alpha]_D^{26}$ +21.5° (*c* 0.2, MeOH); UV (H_2O) λ_{max} 261.5 nm (ε 20,600) (pH 7), 261.5 nm (ε 21,100) (pH 2), 261.5 nm (ε 20,500) (pH 11); ^{1}H NMR (MeOH-d_4): δ 8.08 (s, 1 H), 6.10 (t, *J* 6.7 Hz, 1 H), 3.88, 3.84 (d, d, *J* 8.4, 8.4 Hz, 2 H), 3.43, 3.38 (d, d, *J* 11.0, 11.0 Hz, 2 H), 2.42 (dd, *J* 13.9, 7.4 Hz, 1 H), 2.31 (dd, *J* 13.8, 6.6 Hz, 1 H), 1.14 (s, 3 H); HRMS Calcd for $[M+H]^+$: 268.1210; found: 268.1232. Anal. Calcd for $C_{11}H_{14}FN_5O_2 \cdot 1.3MeOH$: C, 47.79; H, 5.96; N, 22.67. Found: C, 47.40; H, 5.50; N, 23.04.

Acknowledgements

This research was supported by US Public Health Service Research Grants (AI 33655 and AI 323521) from the National Institutes of Health and the Department of Veterans Affairs.

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