Syntheses of 4′-*C*-Ethynyl-*β*-D-*arabino*- and 4′-*C*-Ethynyl-2′-deoxy-*β*-D-*ribo*-pentofuranosylpyrimidines and -purines and Evaluation of Their Anti-HIV Activity

Hiroshi Ohrui,*[,†] Satoru Kohgo,[†] Kenji Kitano,[§] Shinji Sakata,[§] Eiichi Kodama,[‡] Kazuhisa Yoshimura,[#] Masao Matsuoka,[‡] Shiro Shigeta,[∥] and Hiroaki Mitsuya[#,⊥]

Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan, Biochemicals Division, Yamasa Corporation, Chiba 288-0056, Japan, Laboratory of Virus Immunology, Research Center for AIDS, Institute for Virus Research, Kyoto University, Kyoto 606-8507, Japan, Department of Microbiology, Fukushima Medical University, Fukushima 960-1295, Japan, Department of Internal Medicine II, Kumamoto University, School of Medicine, Kumamoto 860, Japan, and Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, Maryland 20892

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4′-*C*-Ethynyl-*β*-D-*arabino*- and 4′-*C*-ethynyl-2′-deoxy-*β*-D-*ribo*-pentofuranosylpyrimidine and -purine nucleosides were synthesized and evaluated for their in vitro anti-HIV activity. The key intermediate, 4-*C*-ethynyl- or 4-*C*-triethylsilylethynyl-D-*ribo*-pentofuranose, was prepared from D-glucose and glycosidated with various pyrimidine or purine bases. The *arabino* pyrimidine derivatives were prepared from the corresponding *ribo* derivatives via O^2,2′-anhydro nucleosides. The 2′-deoxy-*ribo* derivatives were synthesized by radical reduction of 2′-bromo or 2′- phenoxythiocarbonyloxy nucleosides. Among these 4′-*C*-ethynyl nucleosides, seven analogues proved to be potent against HIV-1 in vitro with EC_{50} values ranging from 0.0003 to 0.03 μM. These compounds also exerted activity against clinical and multi-dideoxy-nucleoside-resistant HIV-1 strains with comparable EC_{50} values. Three such 4′-*C*-ethynyl-2′-deoxypurine analogues including 4′-*C*-ethynyl-2′-deoxyadenosine and 4′-*C*-ethynyl-2,6-diamino-2′-deoxypurine were less cytotoxic [selectivity indices (SIs): 975−2733] than three 4′-*C*-ethynyl-2′-deoxycytidine analogues (SIs: 63−363). 4′-*C*-Ethynyl-5-fluoro-2′-deoxycytidine was least toxic (SI: >3333) and potent against all HIV strains tested.

Introduction

The human immunodeficiency virus (HIV), the causative agent of aquired immune deficiency syndrome (AIDS), has spread all over the world to become a serious life-threatening disease. In the treatment of AIDS, six nucleoside reverse trascriptase inhibitors, 3′-azido-3′-deoxythymidine (AZT),[1] 2′,3′-dideoxyinosine (ddI),[2] 2′,3′-dideoxycytidine (ddC),[2] 2′,3′-dehydro-2′,3′-dideoxythymidine (d4T),[3] L-1,3-oxathiolanylcytosine (3TC),[4] and abacavir (ABC),[5] all of which function as viral DNA chain terminators, have currently been used as chemotherapeutic agents for AIDS treatment, and the development of new anti-HIV nucleoside derivatives has been enthusiastically studied. However, the emergence of mutants which resist these drugs has been a critical problem in using these chemotherapeutic agents, and there are cases in which these mutants show high levels of cross-resistance. Consequently, the development of structurally new nucleoside derivatives which are active against HIV variants resistant to the existing 2′,3′-dideoxy nucleosides is urgently needed.

All of the six existing therapeutic nucleoside reverse transcriptase inhibitors are modified at the 2′- and 3′-positions of the sugar moiety of natural nucleosides, and these modifications can be easily attained by the chemistry of their hydroxy groups.[6] However, few examples of nucleosides modified at the 4′-position of the sugar moiety have been reported: for example, 4′-cyano-,[7] 4′-azido-,[8] and 4′-ethynylthymidine (**30**)[9] and 4′-ethynyl-2′-deoxycytidine (**58**)[10] which reportedly have potent anti-HIV activity. This may be due to their difficult chemistry. It is proposed that the conformation of the furanose ring of 4′-*C*-azidothymidine is extremely unnatural with a 3′-*C*-*endo*,[8] and its unnatural conformation is closely related to its biological activities.

We have previously described synthetic methods of 4′-*C*-alkyl-substituted nucleosides from 4-*C*-hydroxymethyl ribose derivatives and reported that most of their 2′-deoxy derivatives exhibited various biological activities.[11−17] For example, 4′-*C*-methyl-2′-deoxycytidine (**1**)[12] exhibits remarkable anti-HIV and antileukemia activities.[13] We also have reported the synthesis of 4′-*C*-ethynyl-*ribo* nucleosides (**2**−**4**) as a new series of 4′-*C*-substituted nucleosides.[16,17] However, they exerted no significant antiviral activity.[16] In this report, we describe novel methods for the synthesis of 4′-*C*-ethynyl-D-*arabino*-pentofuranosyl (**5**) and 4′-*C*-ethynyl-2′-deoxy-D-*ribo*-pentofuranosyl (**6**) nucleosides which proved to act as inhibitors of the HIV reverse transcriptase similar to 4′-azido-2′-deoxy nucleosides and **1**.

Chemistry

Although 4′-*C*-ethynyl nucleosides can be prepared from the corresponding natural nucleosides, we used

* To whom correspondence should be addressed. Tel: +81-22-717-8803. Fax: +81-22-717-8806. E-mail: ohrui@biochem.tohoku.ac.jp.
† Tohoku University.
§ Yamasa Corp.
‡ Kyoto University.
∥ Fukushima Medical University.
Kumamoto University, School of Medicine.
⊥ National Cancer Institute.

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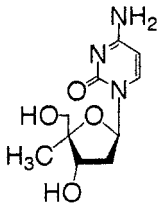
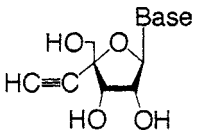
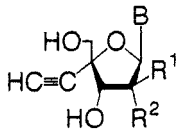


(1)



(2): Base = U
(3): Base = T
(4): Base = C

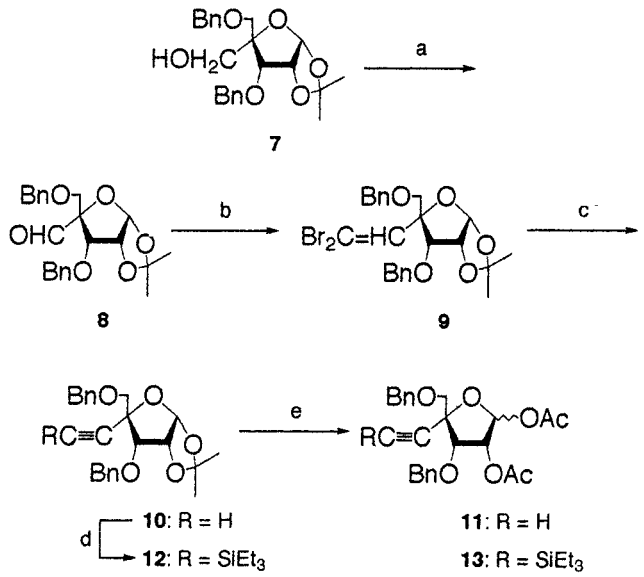


(5): R^1 = OH, R^2 = H
(6): R^1 = R^2 = H
(30): B = T, R^1 = R^2 = H
(58): B = C, R^1 = R^2 = H

4-*C*-hydroxymethyl-3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentofuranose (**7**)[11] as starting material for the synthesis of D-*arabino* and 2′-deoxy-D-*ribo* analogues of 4′-*C*-ethynyl nucleosides. Synthesis of the ribose unit bearing an ethynyl group at the 4-*C*-position is outlined in Scheme 1. The 4-*C*-hydroxymethyl group in **7** was oxidized to a formyl group by Swern oxidation in quantitative yield. Conversion of the aldehyde **8** into an ethynyl group was performed by Corey's protocol.[18] Treatment of **8** with carbon tetrabromide and triphenylphosphine in dichloromethane afforded 4-*C*-dibromovinyl derivative **9** in 95% yield, and the dibromovinyl group was converted to an ethynyl group in 90% yield by treatment of **9** with *n*-butyllithium in tetrahydrofuran. Hydrolysis of the acetonide of **10** in 70% acetic acid containing 10% trifluoroacetic acid followed by acetylation of the resulting hydroxy groups gave **11** as an anomeric mixture in 81% yield (Scheme 1).

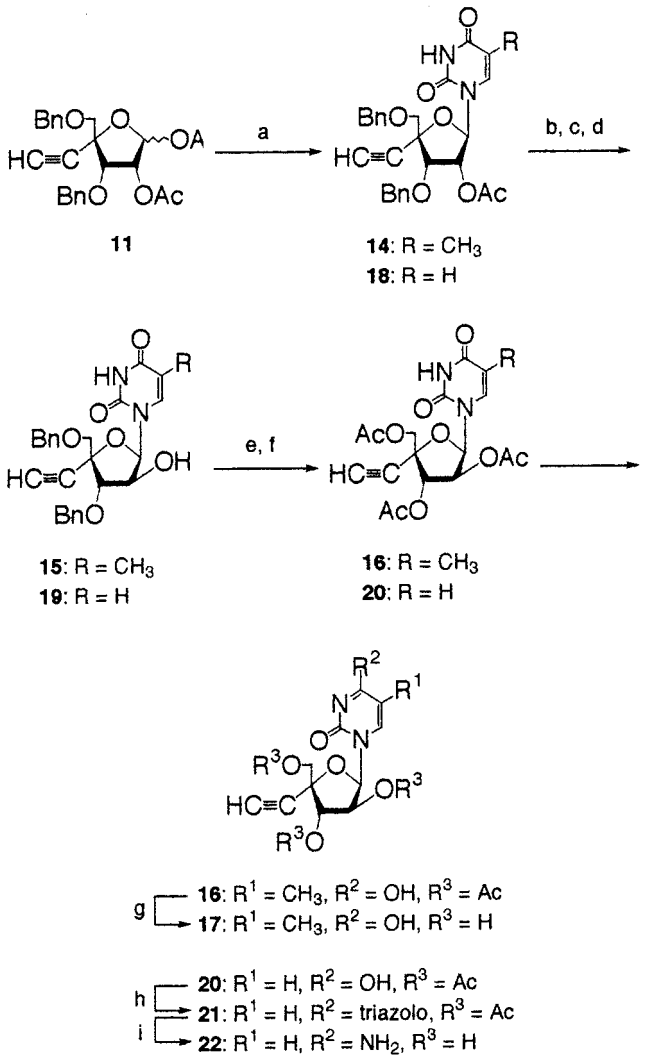
Synthetic routes of 4-*C*-ethynyl-β-D-*arabino*-pentofuranosylthymine (**17**) and -cytosine (**22**) are shown in

Scheme 1[a]



[a] Reagents: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) CBr_4, PPh_3, CH_2Cl_2; (c) *n*-BuLi, THF; (d) *n*-BuLi, THF, then Et_3SiCl; (e) 1. 70% AcOH, TFA, 2. Ac_2O, pyridine.

Scheme 2[a]

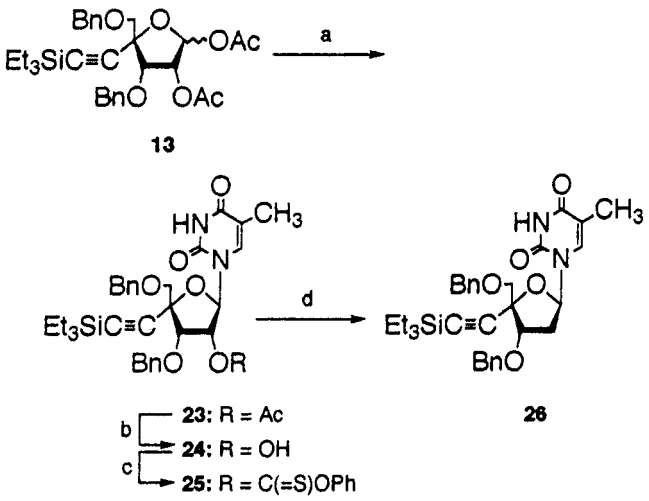


[a] Reagents: (a) silylated base, TMSOTf, 1,2-DCE; (b) NaOH(aq), MeOH; (c) MsCI, pyridine; (d) NaOH(aq), THF; (e) BBr_3, CH_2Cl_2; (f) Ac_2O, pyridine; (g) MeONa, MeOH; (h) 1,2,4-triazole, $Cl_2P(=O)$-OC_6H_4Cl, pyridine; (i) NH_4OH, dioxane.

Scheme 2. Condensation of **11** with silylated thymine and uracil in 1,2-dichloroethane in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst afforded thymine and uracil derivatives **14** and **18** in 96% and 87% yields, respectively. After deacetylation of **14** and **18** in 0.1 N sodium hydroxide in water–methanol, the resulting 2′-α-hydroxy group was methanesulfonylated and inverted to the 2′-β-orientation by treatment with 0.6 N sodium hydroxide in water–tetrahydrofuran through O^2,2′-anhydro nucleoside to give **15** and **19** in 91% and 73% yields, respectively. Deprotection of the 3′- and 5′-*O*-benzyl groups in **15** and **19** with boron tribromide in dichloromethane and subsequent acetylation of the resulting hydroxy groups afforded **16** and **20** in 91% and 94% yields, respectively. 4′-*C*-Ethynyl-*arabino*-furanosylthymine **17** was obtained by deacylation of **16** with sodium methoxide in methanol in an 80% yield. On the other hand, 4′-*C*-ethynyl-*arabino*-furanosylcytosine **22** was obtained in a 75% yield from **20** by Reese's method[19] through 4-triazolouridine derivative **21**.

In deoxygenation of the 2′-hydroxyl group of a *ribo* nucleoside, a radical reduction of the 2′-halo or thiocar-

Scheme 3[a]



[a] Reagents: (a) silylated thymine, TMSOTf, 1,2-DCE; (b) Et_3N, MeOH; (c) ClC(=S)OPh, DMAP, MeCN; (d) *n*-Bu_3SnH, AIBN, toluene.

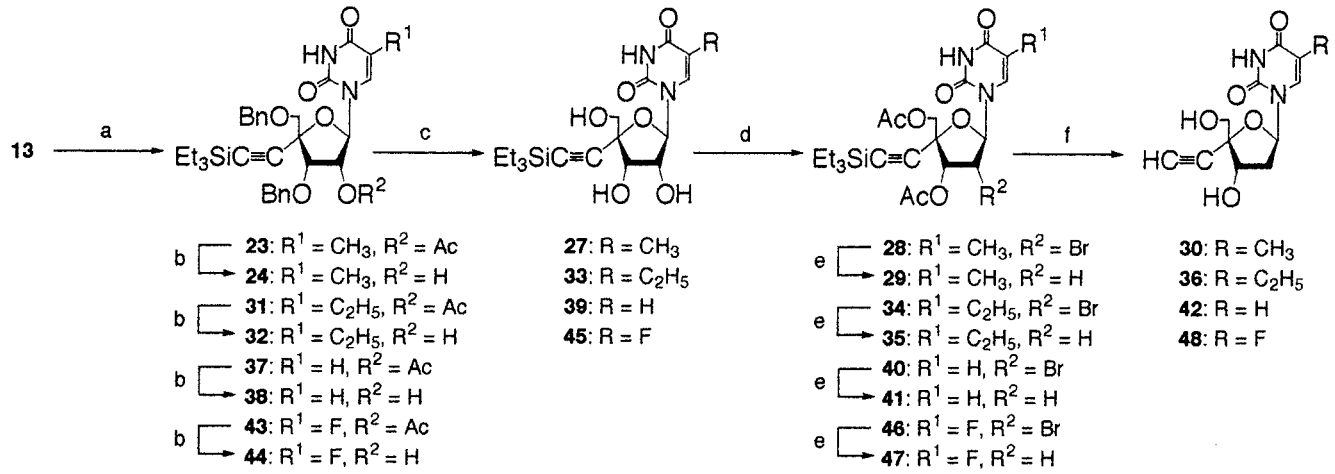
bonate of the *ribo* nucleoside with tri-*n*-butyltin hydride has generally been utilized.[20] Since it is known that the hydrostannylation of terminal alkyne[21,22] could be avoided by protection of the ethynyl group with a bulky group,[22] we planned to protect the ethynyl group in **10** with a triethylsilyl group to prevent hydrostannylation. Treatment of **10** with *n*-butyllithium in tetrahydrofuran and then with chlorotriethylsilane afforded ribose derivative **12** bearing a triethylsilylated ethynyl group in 98% yield. **12** was converted to **13** by the similar procedure to that described for **11** in 80% yield (Scheme 1).

First, we attempted to synthesize 2′-deoxy derivatives using the thymine derivative as a model compound by reduction of the 2′-hydroxy group of 4′-*C*-triethylsilylethynyl-3′,5′-di-*O*-benzyl derivative **24** and subsequent deprotection (Scheme 3). The thymine nucleoside **23** was obtained in 87% yield by condensation of **13** with silylated thymine. This was deacetylated in methanol containing 5% triethylamine to afford **24** in 90% yield. The 2′-hydroxyl group in **24** was phenoxythiocarbonylated with phenyl chlorothionoformate in acetonitrile in the presence of 4-(dimethylamino)pyridine to give **25**, which was reduced to the 2′-deoxy derivative **26** by radical reduction using tri-*n*-butyltin hydride in toluene in the presence of 2,2′-azobis(isobutyronitrile) without the addition of tributyltin radical to the terminal alkyne in 94% yield. However, attempts of debenzylation of **26** by treatment with boron tribromide, boron trichloride, or iodotrimethylsilane were not successful because of the acid lability of the 2′-deoxy nucleoside. Therefore, we then tried another route for the synthesis of 2′-deoxy nucleosides (Scheme 4). **13** was condensed with silylated 5-ethyluracil and uracil, and the corresponding nucleosides **31** and **37** were obtained in 76% and 78% yields, respectively. Deacetylation of **31** and **37** with triethylamine in methanol gave deacetylation products **32** and **38** in 92% and 93%, respectively, and **24**, **32**, and **38** were debenzylated to give free *ribo* nucleosides **27**, **33**, and **39** in 98%, 84%, and 93% yields, respectively. The 2′-hydroxyl groups of these *ribo* nucleosides **27**, **33,** and **39** were deoxygenated by radical reduction with tri-*n*-butyltin hydride in toluene via 3′,5′-di-*O*-acetyl-2′-bromo-2′-deoxypyrimidine nucleosides **28**, **34**, and **40**, which were obtained by treatment of **27**, **33,** and **39** with acetyl bromide in acetonitrile,[23] to give **29**, **35,** and **41** in 66%, 55%, and 81% yields, respectively. 4′-*C*-Ethynylthymidine **30**,[9] 4′-*C*-ethynyl-5-ethyl-2′-deoxyuridine **36**, and 4′-*C*-ethynyl-2′-deoxyuridine **42** were obtained in 92%, 88%, and 97% yields by deprotection of **29**, **35,** and **41.** 4′-*C*-Ethynyl-2′-deoxy-5-methylcytidine **56** and 4′-*C*-ethynyl-2′-deoxycytidine **58**[10] were obtained from **29** and **41** in 49% and 72% yields, respectively, by the similar method described for **22** (Scheme 6).

We also synthesized 2′-deoxy-5-halouridines and cytidines bearing an ethynyl group at the 4′-*C*-position. 5-Fluoro-2′-deoxyuridine derivative **48** was synthesized from 4′-*C*-triethylsilylethynyl-2′-*O*-acetyl-3′,5′-di-*O*-benzyl-5-fluorouridine (**43**) obtained by glycosylation of 5-fluorouracil with **13. 43** was derived to 4′-*C*-triethylsilylethynyl-3′,5′-di-*O*-acetyl-2′-deoxy-5-fluorouridine (**47**) in 57% yield by the method used for synthesizing **29**. **47** was deprotected under alkaline conditions to give 4′-*C*-ethynyl-2′-deoxy-5-fluorouridine (**48**) in 88% yield (Scheme 4). 5-Chloro-, bromo-, and iodo-2′-deoxyuridine derivatives **50**, **52**, and **54** were synthesized by halogenation of 2′-deoxyuridine derivative **41**. **41** was halogenated with lithium chloride, lithium bromide, or iodine in the presence of ammonium cerium nitrate in acetonitrile or acetonitrile−acetic acid[24] to give 5-halouracil derivatives **49**, **51**, and **53** in over 90% yields, respectively (Scheme 5). These were deacetylated under alkaline conditions to give **50**, **52,** and **54** in 94%, 96%, and 97% yields, respectively. 4′-*C*-Ethynyl-2′-deoxy-5-halocytidines **60**, **62**, **64,** and **66** were synthesized in 60%, 58%, 68%, and 44% yields, respectively, by the method used for preparing **22** (Scheme 6).

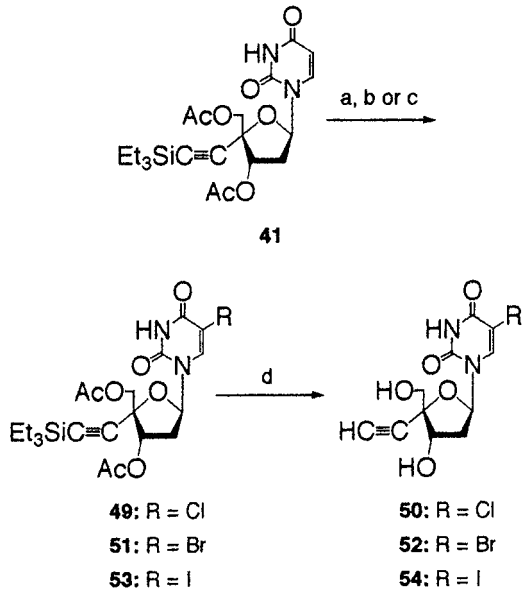
In addition to the syntheses of 4′-*C*-ethynylpyrimidine nucleosides, we attempted to synthesize adenine, 2,6-diaminopurine, hypoxanthine, and guanine nucleosides bearing an ethynyl group at the 4′-*C*-position. The glycosidation of **13** with pertrimethylsilylated adenine, under the conditions described for the synthesis of **23**, gave **67** in 55% yield. In this reaction, no 7-glycosylated product was detected in the reaction mixture by TLC analyses. Deacetylation of **67** with triethylamine in methanol (86% yield) was followed by treatment with phenyl chlorothionoformate and 4-(dimethylamino)-pyridine in acetonitrile. After short silica gel column purification of the thioformate **69**, radical reduction of **69** with tri-*n*-butyltin hydride in the presence of azobis-(isobutyronitrile) was carried out to produce **70** in 68% yield. Desilylation of **70** with tetrabutylammonium fluoride in tetrahydrofuran was followed by debenzylation under the Birch reduction conditions. Together with the target compound **72**, the purine derivative **73** formed by reduction of the C^6-double bond of **72** was produced. Separation using ODS reversed-phase column chromatography gave **72** and **73** in yields of 53% and 8%, respectively. When 8 mol equiv of sodium metal was used, **72** and **73** were produced in the ratio of ca. 1:4.5. 2,6-Diamino-9-(2-deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)purine (**80**) was prepared from **13** by a procedure similar to that described for the preparation of **72**. In the final step of debenzylation, only a trace amount of the deaminated product was formed. Treatment of **72** and **80** with adenosine deaminase, followed by purification of the products with ODS reversed-phase column

Scheme 4[a]



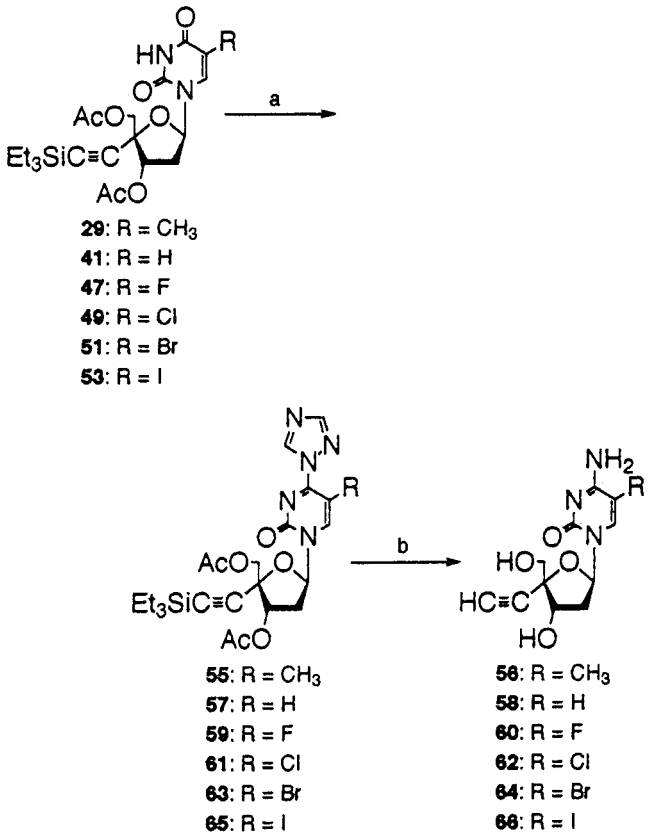
[a] Reagents: (a) silylated base, TMSOTf, 1,2-DCE; (b) Et_3N, MeOH; (c) BCl_3, CH_2Cl_2; (d) AcBr, MeCN; (e) *n*-Bu_3SnH, AIBN, toluene; (f) NaOH(aq), MeOH.

Scheme 5[a]



[a] Reagents: (a) LiCl, CAN, AcOH−MeCN; (b) LiBr, CAN, MeCN; (c) I_2, CAN, MeCN; (d) NaOH(aq), MeOH.

Scheme 6[a]



[a] Reagents: (a) 1,2,4-triazole, $Cl_2P(=O)OC_6H_4Cl$, pyridine; (b) 1. NH_4OH, dioxane, 2. NaOH(aq), MeOH.

chromatography, gave 4′-*C*-ethynyl-2′-deoxyinosine **74** and 4′-*C*-ethynyl-2′-deoxyguanosine **81** in yields of 72% and 50%, respectively (Scheme 7).

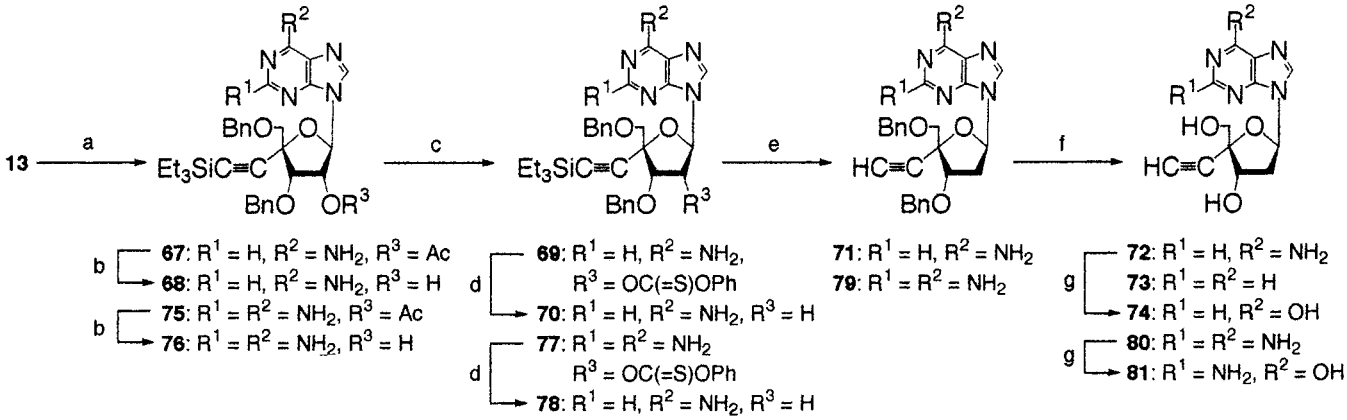
In Vitro Antiviral Activity of 4′-Substituted Nucleosides

Among 19 4′-substituted nucleoside analogues examined for antiviral activity against a wild-type laboratory strain HIV-1_{LAI}, 7 4′-*C*-ethynyl nucleoside analogues (compounds **22**, **56**, **58**, **60**, **72**, **80,** and **81**) were potent against HIV-1 in vitro (Table 1). These compounds also exerted potent antiviral activity against a wild-type clinical HIV-1 strain (HIV-1_{104pre}) and a multi-dideoxynucleoside-resistant infectious molecular clone (HIV-1_{MDR}). It was noted, however, that three 4′-*C*-ethynylcytidine analogues (compounds **22**, **56**, and **58**) were relatively more cytotoxic than the three 4′-*C*-ethynylpurine analogues (compounds **72**, **80,** and **81**). Selective indices (CC_{50}/EC_{50}) of the formers ranged from 63 to 363, while those of the latter ranged from 975 to 2733.

Interestingly, the substitution of a hydrogen atom at position 5 of cytosine of 4′-*C*-ethynyl-2′-deoxycytidine (compound **58**) with fluorine, generating 4′-*C*-ethynyl-2′-deoxy-5-fluorocytidine (compound **60**), substantially decreased the cytotoxicity of compound **58**. The selective index of compound **60** was greater than 3333 (Table 1). However, the substitution of the same with other halogen atoms (chlorine, bromine, and iodine) converted compound **58** to inert compounds **62**, **64**, and **66**, respectively.

It is of note that although HIV-1_{MDR} carrying five amino acid substitutions (Ala62Val, Val75Leu, Phe77Leu,

Scheme 7[a]



[a] Reagents: (a) silylated base, TMSOTf, 1,2-DCE; (b) Et_3N, MeOH; (c) ClC(=S)OPh, DMAP, MeCN; (d) *n*-Bu_3SnH, AIBN, toluene; (e) TBAF, THF; (f) Na, NH_3(liq), THF; (g) adenosine deaminase, Tris-HCl buffer.

Table 1. In Vitro Antiviral Activity of 4′-*C*-Ethynyl Nucleosides[a]

	MTT assay			MAGI assay	
compd	EC_{50} (μM) HIV-I_{LAI}	CC_{50} (μM)	SI	EC_{50} (μM) HIV-1_{104pre}	EC_{50} (μM) HIV-I_{MDR}
17	>350	>350	ND	NE	NE
22	0.0048	1.74	363	0.0048	0.0078
30	0.61	>380	>623	0.4	0.24
36	>360	>360	ND	NE	NE
42	>100	>100	ND	NE	NE
48	>10	3.4	ND	NE	NE
50	6.0	81.7	13.6	NE	NE
52	2.3	>100	>44	NE	NE
54	0.34	>260	>765	0.36	0.62
56	0.011	0.70	63	0.0057	0.0045
58	0.0048	0.92	192	0.00096	0.0015
60	0.030	>100	>3333	0.002	0.009
62	>100	>100	ND	NE	NE
64	>100	>100	ND	NE	NE
66	>100	>100	ND	NE	NE
72	0.012	11.7	975	0.0068	0.0054
73	117	>380	>3.2	132	145
74	0.15	216	14.4	0.83	0.65
80	0.0003	0.82	2733	0.0019	0.0013
81	0.0014	1.5	1071	0.0071	0.0054
AZT	0.038	>100	>2632	0.002	24.9

[a] MT-4 cells and HIV-1_{LAI} were employed in the MTT assay (except for compounds **42**, **48**, **50**, and **52**), while HeLa-CD4-LTR-β-gal cells and HIV-1_{MDR} were used in the MAGI assay as target cells and infectious virions, respectively. For testing compounds **42**, **48**, **50**, and **52**, MT-2 cells and HIV-1_{LAI} were employed in the MTT assay. EC_{50}, compound concentration that suppresses the replication of HIV-1 by 50%; SI, selectivity index (CC_{50}/EC_{50}); ND, not determined; NE, not examined.

Phe116Tyr, and Gln151Met) showed a high level of resistance against all the currently available nucleoside reverse transcriptase inhibitors,[25,26] which have a 2′,3′-dideoxy configuration, the 4′-*C*-ethynyl-2′-deoxy nucleoside analogues potent against HIV-l_{LAI} were also highly active against HIV-1_{MDR} (Table 1).

From the results of anti-HIV activities of 4′-ethynlyl-2′-deoxy nucleosides and the previous result[13] that 4′-*C*-methyl-2′-deoxycytidine triphosphate was both a strong inhibitor of polymerase α and a chain terminator for DNA polymerase α-catalyzed chain elongation of DNA strands, it may be concluded that some 4′-*C*-substituted-2′-deoxy (and *arabino*) nucleosides may have strong affinity for deoxy nucleoside kinases at the nucleoside level due to the presence of the 3′-down hydroxy group and also for reverse transcriptases in their triphosphate form. However, despite the presence of the 3′-OH, they might be able to act as chain terminators as well as reverse transcriptase inhibitors because of the sharply diminished reactivity of the 3′-OH due to the neopentyl alcohol character of the 3′-OH and the severe steric hindrance to it by the vicinal *cis* 4′-substituent.

Although both **74** and **81** were prepared from **72** and **80**, respectively, by treatment with adenosine deaminase, the different biological activities between **72** and **74**, and between **80** and **81**, indicated that both **72** and **80** were not deaminated so easily by adenosine deaminase under the physiological conditions used for the antviral activity test. These results may be ascribed to the conformational change of the furanose ring of 4-substituted nucleosides.[8]

Experimental Section

General. Melting point data were obtained with a Shibata melting apparatus and are uncorrected. ^1H NMR spectra were recorded with a JEOL JNMEX-400 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were recorded with a Hitachi M-80B spectrometer at 70 eV. Specific rotation was measured with a Jasco DIP-360 at 589 nm. Merck silica gel art. #9385 was used for column chromatography and Merck silica gel art. #5554 for analytical thin-layer chromatography.

3,5-Di-*O*-benzyl-4-*C*-formyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentofuranose (8). To a solution of oxalyl chloride (3.38 mL, 38.7 mmol) in dichloromethane (80.0 mL) was dropwised dimethyl sulfoxide (5.50 mL, 77.5 mmol) at −60 °C. The mixture was stirred for 15 min at the same temperature, and then a solution of **7**[11] (10.3 g, 25.7 mmol) in dichloromethane (100 mL) was added dropwise. After stirring of mixture at −60 °C for 30 min, triethylamine (10.9 mL, 78.2 mmol) was added and the mixture was stirred for 30 min at room temperature. The reaction mixture was partitioned with water and the organic layer was dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (2:1 *n*-hexane/ethyl acetate) to give **8** as a colorless oil (9.68 g, 24.3 mmol, 94.6%): $[\alpha]_D$ +24.5° (*c* = 1.03, $CHCl_3$).

3,5-Di-*O*-benzyl-4-*C*-(2,2-dibromoethenyl)-1,2-*O*-isopropylidene-α-D-*ribo*-pentofuranose (9). To a solution of **8** (9.50 g, 23.8 mmol) in dichloromethane (200 mL) were added carbon tetrabromide (15.8 g, 47.6 mmol) and triphenylphosphine (25.0 g, 95.3 mmol) at 0 °C and the mixture was stirred for 1 h. Triethylmine (20.0 mL, 142 mmol) was added and the mixture was poured into *n*-hexane (1000 mL). After filtration of insoluble precipitate, the filtrate was evaporated. The residue was purified by silica gel column chromatography (3:1

n-hexane/ethyl acetate) to give **9** as a colorless oil (12.6 g, 22.7 mmol, 95.4%): $[\alpha]_D$ +6.20° (*c* = 1.00, $CHCl_3$).

3,5-Di-*O*-benzyl-4-*C*-ethynyl-1,2-*O*-isopropylidene-D-*ribo*-pentofuranose (10). To a solution of **9** (12.4 g, 22.4 mmol) in dry tetrahydrofuran (160 mL) was added *n*-butyllithium (1.6 M solution in *n*-hexane, 30.7 mL, 49.1 mmol) at −78 °C under an argon atmosphere and the mixture was stirred for 30 min at the same temperature. After addition of water, ethyl acetate was added and the organic layer was washed with water. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (3:1 *n*-hexane/ethyl acetate) to give **10** as a colorless oil (7.95 g, 20.2 mmol, 90.2%): $[\alpha]_D$ +22.6° (*c* = 1.00, $CHCl_3$).

1,2-Di-*O*-acetyl-3,5-di-*O*-benzyl-4-*C*-ethynyl-D-*ribo*-pentofuranose (11). To a solution of **10** (6.00 g, 15.2 mmol) in 70% acetic acid (100 mL) was added trifluoroacetic acid (10.0 mL) and the solution was stirred for 4 h at 40 °C. The mixture was evaporated and the residue was coevaporated with toluene. To the solution of the residue in pyridine (50.0 mL) was added acetic anhydride (14.3 mL, 0.15 mol), and the mixture was stirred for 12 h at room temperature. The mixture was evaporated and the residue was coevaporated with toluene. The residue was dissolved in ethyl acetate and the organic layer was washed with water. The solvent was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (3:1 *n*-hexane/ethyl acetate) to give **11** as a colorless oil (5.40 g, 12.3 mmol, 80.9%): for α-anomer (second eluting), $[\alpha]_D$ −7.980° (*c* = 1.015, $CHCl_3$); for *β*-anomer (first eluting), $[\alpha]_D$ −22.54° (*c* = 1.065, $CHCl_3$).

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-4-*C*-triethylsilylethynyl-α-D-*ribo*-pentofuranose (12). To a solution of **10** (5.00 g, 12.7 mmol) in dry tetrahydrofuran (100 mL) was added *n*-butyllithium (1.6 M solution in *n*-hexane, 9.50 mL, 15.2 mmol) at −78 °C under an argon atmosphere and the mixture was stirred for 5 min at the same temperature. After stirring, chlorotriethylsilane (2.55 mL, 15.2 mmol) was added at −78 °C under an argon atmosphere and stirred for 30 min at same temperature. After addition of water, ethyl acetate was added and the organic layer was washed with water. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (3:1 *n*-hexane/ethyl acetate) to give **12** as a colorless oil (6.32 g, 12.4 mmol, 97.6%): $[\alpha]_D$ −27.27° (*c* = 1.045, $CHCl_3$).

1,2-Di-*O*-acetyl-3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-D-*ribo*-pentofuranose (13). Under the conditions analogous to those used for the preparation of **11**, compound **12** (5.55 g, 10.9 mmol) gave **13** as an anomeric mixture (α:*β* = 1:6.6) as a colorless oil (4.80 g, 8.68 mmol, 79.6%): for α-anomer (second eluting), $[\alpha]_D$ −21.8° (*c* = 1.00, $CHCl_3$); for *β*-anomer (first eluting), $[\alpha]_D$ −58.0° (*c* = 1.00, $CHCl_3$).

1-(2-*O*-Acetyl-3,5-di-*O*-benzyl-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)thymine (14). A mixture of **11** (2.00 g, 4.56 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (6.76 mL, 27.4 mmol) and thymine (l.15 g, 9.12 mmol) in 1,2-dichloroethane (50.0 mL) was refluxed for 1 h. After cooling to room temperature, to the reaction mixture was added trimethylsilyl trifluoromethanesulfonate (1.65 mL, 6.05 mmol) and the resulting mixture was refluxed for 12 h. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate and the mixture was stirred. Insoluble precipitate was removed by filtration. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (2:3 *n*-hexane/ethyl acetate) to give **14** as a colorless gum (2.21 g, 4.38 mmol, 96.1%): $[\alpha]_D$ +10.0° (*c* = 1.04, $CHCl_3$).

1-(3,5-Di-*O*-benzyl-4-*C*-ethynyl-*β*-D-*arabino*-pentofuranosyl)thymine (15). To a solution of **14** (2.00 g, 3.96 mmol) in methanol (90 mL) was added 1 N sodium hydroxide solution (10 mL) and the mixture was stirred for 1 h at room temperature. After neutralization of the reaction mixture by addition of acetic acid, the solvent was removed by evaporation. The residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. The residue was coevaporated with pyridine and dissolved in pyridine (50 mL). To the solution was added methanesulfonyl chloride (0.45 mL, 5.77 mmol) at 0 °C and the mixture was stirred for 1 h at room temperature. The mixture was evaporated and the residue was dissolved in ethyl acetate. The organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was coevaporated with toluene and dissolved in tetrahydrofuran (30 mL). To the solution was added 1 N sodium hydroxide solution (50 mL) and the resulting mixture was refluxed for 1 h. The mixture was neutralized and evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (1:2 *n*-hexane/ethyl acetate) to give **15** as a white powder (1.67 g, 3.61 mmol, 91.2%): $[\alpha]_D$ +30.6° (*c* = 1.00, $CHCl_3$).

1-(2,3,5-Tri-*O*-acetyl-4-*C*-ethynyl-*β*-D-*arabino*-pentofuranosyl)thymine (16). To a solution of **15** (1.50 g, 3.24 mmol) in dichloromethane (40.0 mL) was added boron tribromide (1.0 M in dichloromethane, 16.2 mL, 16.2 mmol) at −78 °C under an argon atmosphere and the mixture was stirred for 2 h at the same temperature. To the solution was added a mixture of pyridine (7.00 mL) and methanol (10.0 mL) and the mixture was stirred for 10 min at −78 °C and evaporated. The residue was coevaporated with pyridine and dissolved in pyridine (50 mL). The solution was added acetic anhydride (4.59 mL, 48.7 mmol) and stirred for 12 h at room temperature. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (1:2 *n*-hexane/ethyl acetate) to give **16** as a white powder (1.20 g, 2.94 mmol, 90.7%): $[\alpha]_D$ +7.20° (*c* = 1.00, $CHCl_3$).

1-(4-*C*-Ethynyl-*β*-D-*arabino*-pentofuranosyl)thymine (17). To a solution of **16** (1.00 g, 2.45 mmol) in methanol (50.0 mL) was added sodium methoxide (0.20 g, 3.70 mmol) and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was neutralized with cation exchanger resin (Dowex 50W×8, 200−400 mesh, H^+ form) and evaporated. The residue was purified by silica gel column chromatography (9:1−4:1 chloroform/methanol) and the desired fraction was crystalized from methanol−ether to give **17** (0.55 g, 1.95 mmol, 79.6%): $[\alpha]_D$ +49.86° (*c* = 1.035, CH_3OH).

1-(2-Di-*O*-acetyl-3,5-di-*O*-benzyl-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)uracil (18). Under the conditions analogous to those used for the preparation of **14, 11** (2.50 g, 5.70 mmol) gave **18** as a colorless gum (2.44 g, 4.97 mmol, 87.2%): $[\alpha]_D$ +29.0° (*c* = 1.00, $CHCl_3$).

1-(3,5-Di-*O*-benzyl-4-*C*-ethynyl-*β*-D-*arabino*-pentofuranosyl)uracil (19). Under the conditions analogous to those used for the preparation of **15**, **18** (2.30 g, 4.69 mmol) gave **19** as a white powder (1.54 g, 3.43 mmol, 73.1%): $[\alpha]_D$ +40.7° (*c* = 1.00, $CHCl_3$).

1-(4-*C*-Ethynyl-2,3,5-tri-*O*-acetyl-*β*-D-*arabino*-pentofuranosyl)uracil (20). Under the conditions analogous to those used for the preparation of **16, 19** (1.40 g, 3.12 mmol) gave **20** as a white powder (1.15 g, 2.92 mmol, 93.6%): $[\alpha]_D$ +18.2° (*c* = 1.00, $CHCl_3$).

1-(4-*C*-Ethynyl-*β*-D-*arabino*-pentofuranosyl)cytosine (22). To a solution of **20** (1.00 g, 2.54 mmol) in pyridine (50.0 mL) was added 4-chlorophenyl phosphorodichloridate (1.05 mL, 6.38 mmol) at 0 °C and the resulting mixture was stirred for 5 min at the same temperature. 1,2,4-Triazole (1.75 g, 25.3 mmol) was added to the solution and the mixture was stirred for 7 days at room temperature. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. The residue was coevaporated with toluene and purified by silica gel column chromatography (1:3 *n*-hexane/ethyl acetate) to give **21**. To a solution of **21** in dioxane (60.0 mL) was added 25% ammonium hydroxide (20.0 mL) and stirred for 24 h at room temperature. The reaction mixture was evaporated and the residue was purified by

reverse phase column chromatography (Wakosil 40C18, 3% acetonitrile in water) and the desired fraction was crystalized from methanol-ether to give **22** (0.51 g, 1.91 mmol, 75.2%): $[\alpha]_D$ +95.7° (c = 1.00, CH_3OH).

1-(2-*O*-Acetyl-3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*- pentofuranosyl)thymine (23). Under the conditions analogous to those used for the preparation of **14**, **13** (4.50 g, 8.14 mmol) gave **23** as a colorless gum (4.40 g, 7.11 mmol, 87.4%): $[\alpha]_D$ −22.3° (c = 1.00, $CHCl_3$).

1-(3,5-Di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)thymine (24). A solution of **23** (4.00 g, 6.46 mmol) in methanol (100 mL) containing 5% triethylamine was stirred for 12 h at room temperature. The mixture was evaporated and the residue was purified by silica gel column chromatography (1:1 *n*-hexane/ethyl acetate) to give **24** as a white powder (3.35 g, 5.81 mmol, 89.9%): $[\alpha]_D$ −18.2° (c = 0.99, $CHCl_3$).

1-(3,5-Di-*O*-benzyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)thymine (26). To a solution of **24** (1.00 g, 1.73 mmol) in acetonitrile (20.0 mL) were added 4-(dimethylamino)pyridine (0.63 g, 5.16 mmol) and phenyl chlorothionoformate (0.29 mL, 2.09 mmol) and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was dissolved in ethyl acetate and the organic layer was washed with 5% citric acid solution and water. The solution was dried over magnesium sulfate and evaporated to give crude **25** as a yellowish gum. To the solution of crude **25** in toluene (20.0 mL) were added tri-*n*-butyltin hydride (2.79 mL, 10.4 mmol) and a small amount of azobis-(isobutyronitrile) at 85 °C and the mixture was stirred for 1 h at the same temperature. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (3:1 toluene/ethyl acetate) to give **26** as a colorless gum (0.92 g, 1.64 mmol, 94.8%): $[\alpha]_D$ −3.21° (c = 1.09, $CHCl_3$).

1-(4-*C*-Triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-thymine (27). To a solution of **24** (1.00 g, 1.73 mmol) in dichloromethane (50.0 mL) was added boron trichloride (1.0 M in dichloromethane, 17.3 mL, 17.3 mmol) at −78 °C under an argon atmosphere and the mixture was stirred for 2 h at the same temperature. To the mixture was added a mixture of pyridine (10.0 mL) and methanol (20.0 mL), and the mixture was stirred for 10 min at −78 °C and evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (9:1 chloroform/methanol) to give **27** as a white powder (0.67 g, 1.69 mmol, 97.7%): $[\alpha]_D$ − 1.86° (c = 1.02, CH_3OH).

1-(3,5-Di-*O*-acetyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)thymine (29). To a suspension of **27** (0.67 g, 1.69 mmol) in acetonitrile (25.0 mL) was added dropwise acetyl bromide (1.50 mL, 20.3 mmol) in acetonitrile (20.0 mL) over 30 min at 85 °C and the resulting mixture was refluxed for 2 h. The reaction mixture was evaporated and the residue was dissolved in ethyl acetate. After washing of the organic layer with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution, the organic layer was dried over magnesium sulfate and evapolated to give crude bromide **28** as a brownish foam. The residue was coevaporated with toluene and dissolved in toluene (50 mL). To the solution were added tri-*n*-butyltin hydride (0.86 mL, 3.33 mmol) and a small amount of azobis-(isobutyronitrile) at 85 °C and the mixture stirred for 1 h at the same temperature. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (1:1 toluene/ethyl acetate) to give **29** as a colorless gum (0.52 g, 1.12 mmol, 66.3%): $[\alpha]_D$ −11.40° (c = 1.035, $CHCl_3$).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)thymine (30). To a solution of **29** (0.36 g, 0.77 mmol) in methanol (24.0 mL) was added 1 N aqueous sodium hydroxide solution (6.00 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was neutralized with cation exchanger resin (Dowex 50W×8, 200−400 mesh, H^+ form) and evaporated. The residue was purified by silica gel column chromatography (9:1 chloroform/methanol) and the desired fraction was crystalized from methanol−ether to give **30** (0.19 g, 0.71 mmol, 92.2%): $[\alpha]_D$ +40.2° (c = 1.00, CH_3OH).

1-(2-*O*-Acetyl-3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-ethyluracil (31). Under the conditions analogous to those used for the preparation of **14, 13** (1.80 g, 3.26 mmol) gave **31** as a colorless gum (1.60 g, 2.53 mmol, 77.6%): $[\alpha]_D$ −21.7° (c = 1.15, $CHCl_3$).

1-(3,5-Di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-ethyluracil (32). Under the conditions analogous to those used for the preparation of **24**, **31** (1.50 g, 2.37 mmol) gave **32** as a white foam (1.29 g, 2.18 mmol, 92.0%): $[\alpha]_D$ −12.1° (c = 1.20, $CHCl_3$).

1-(4-*C*-Triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-ethyluracil (33). Under the conditions analogous to those used for the preparation of **27**, **32** (1.25 g, 2.12 mmol) gave **33** as a white powder (0.73 g, 1.78 mmol, 84.0%): $[\alpha]_D$ +5.100 (c = 1.00, CH_3OH).

1-(3,5-Di-*O*-acetyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-ethyluracil (35). Under the conditions analogous to those used for the preparation of **29**, compound **33** (0.63 g, 1.53 mmol) gave **35** as a white powder (0.40 g, 0.84 mmol, 54.9%): $[\alpha]_D$ −10.0° (c = 1.00, $CHCl_3$).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-ethyluracil (36). Under the conditions analogous to those used for the preparation of **30**, **35** (0.33 g, 0.69 mmol) gave **36** as a white foam (0.17 g, 0.61 mmol, 88.4%): $[\alpha]_D$ +37.9° (c = 1.00, CH_3OH).

1-(2-Acetyl-3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)uracil (37). Under the conditions analogous to those used for the preparation of **14**, **13** (3.00 g, 5.43 mmol) gave **37** as a colorless gum (2.50 g, 4.13 mmol, 76.1%): $[\alpha]_D$ −21.97° (c = 1.015, $CHCl_3$).

1-(3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)uracil (38). Under the conditions analogous to those used for the preparation of **24**, **13** (2.00 g, 3.31 mmol) gave **38** as a white powder (1.72 g, 3.06 mmol, 92.5%): $[\alpha]_D$ −21.56° (c = 1.025, $CHCl_3$).

1-(4-*C*-Triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-uracil (39). Under the conditions analogous to those used for the preparation of **27**, **38** (1.50 g, 2.67 mmol) gave **39** as a white powder (0.95 g, 2.48 mmol, 92.9%): $[\alpha]_D$ −4.50° (c = 1.00, CH_3OH).

1-(3,5-Di-*O*-acetyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)uracil (41). Under the conditions analogous to those used for the preparation of **29**, **39** (0.77 g, 2.01 mmol) gave **41** as a colorless gum (0.73 g, 1.62 mmol, 80.6%); $[\alpha]_D$ −11.7° (c = 1.04, $CHCl_3$).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-uracil (42). Under the conditions analogous to those used for the preparation of **30**, **41** (0.30 g, 0.67 mmol) gave **42** as a white foam (165 mg, 0.65 mmol, 97.0%): $[\alpha]_D$ +37.8° (c = 0.51, CH_3OH).

1-(2-*O*-Acetyl-3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-fluorouracil (43). A mixture of **13** (2.00 g, 3.62 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (5.37 mL, 21.7 mmol) and 5-fluorouracil (0.71 g, 5.46 mmol) in 1,2-dichloroethane (60.0 mL) was refluxed for 1 h. To the reaction mixture was added trimethylsilyl trifluoromethanesulfonate (0.85 ml, 4.70 mmol) at room temperature and the mixture was stirred at 50 °C for 24 h. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate and the mixture was stirred. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (2:1 *n*-hexane/ethyl acetate) to give **43** as a colorless gum (0.80 g, 1.28 mmol, 35.4%): $[\alpha]_D$ −23.3° (c = 0.18, $CHCl_3$).

1-(3,5-Di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-fluorouracil (44). A solution of **43** (0.77 g, 1.24 mmol) in methanol containing 10% triethylamine (50.0 mL) was stirred for 48 h at 30 °C. The mixture was coevaporated with tetrahydrofuran and the residue was purified by silica gel column chromatography (2:1 *n*-hexane/ethyl acetate) to give **44** as a white powder (0.68 g, 1.17 mmol, 94.4%): $[\alpha]_D$ −16.3° (c = 1.05, $CHCl_3$).

1-(4-*C*-Triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-fluorouracil (45). Under the conditions analogous to those used for the preparation of **27**, compound **44** (1.00 g, 1.73 mmol) gave **45** as a white powder (0.64 g, 1.60 mmol, 93.0%): $[\alpha]_D$ −2.30° (*c* = 1.00, CH_3OH).

1-(3,5-Di-*O*-acetyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-fluorouracil (47). Under the conditions analogous to those used for the preparation of **29**, compound **45** (0.54 g, 1.35 mmol) gave **47** as a white powder (0.41 g, 0.88 mmol, 65.2%): $[\alpha]_D$ −12.9° (*c* = 1.00, $CHCl_3$).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-fluorouracil (48). Under the conditions analogous to those used for the preparation of **30**, compound **47** (0.20 g, 0.43 mmol) gave **48** as a white powder (103 mg, 0.38 mmol, 88.4%): $[\alpha]_D$ +45.2° (*c* = 1.02, CH_3OH).

1-(3,5-Di-*O*-acetyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-chlorouracil (49). To a solution of **41** (0.30 g, 0.67 mmol) in a mixture of acetonitrile (5.50 mL) and acetic acid (5.50 mL) were added lithium chloride (34.0 mg, 0.80 mmol) and ammonium cerium nitrate (0.73 g, 1.34 mmol) and the mixture was refluxed for 6 h. The reaction mixture was diluted with ethyl acetate and then washed with saturated aqueous sodium hydrogen carbonate and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (1:1 *n*-hexane/ethyl acetate) to give **49** as a white powder (0.30 g, 0.62 mmol, 92.5%): $[\alpha]_D$ − 12.7° (*c* = 1.00, $CHCl_3$).

1-(2-Deoxy-4-*C*-*β*-D-*ribo*-pentofuranosyl)-5-chlorouracil (50). Under the conditions analogous to those used for the preparation of **30**, **49** (0.25 g, 0.52 mmol) gave **50** as a white foam (0.14 g, 0.49 mmol, 94.2%): $[\alpha]_D$ +43.8° (*c* = 1.00, CH_3OH).

1-(3,5-Di-*O*-acetyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-bromouracil (51). To a solution of **41** (0.30 g, 0.67 mmol) in acetonitrile (11.0 mL) were added lithium bromide monohydrate (84.0 mg, 0.80 mmol) and ammonium cerium nitrate (0.73 g, 1.34 mmol) and the mixture was refluxed for 2 h. The reaction mixture was diluted with ethyl acetate and then washed with saturated aqueous sodium chloride and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (1:1 *n*-hexane/ethyl acetate) to give **51** as a white powder (0.33 g, 0.62 mmol, 92.5%): $[\alpha]_D$ −14.8° (*c* = 1.00, $CHCl_3$).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-bromouracil (52). Under the conditions analogous to those used for the preparation of **30**, **51** (0.25 g, 0.47 mmol) gave **52** as a white foam (0.15 g, 0.45 mmol, 95.7%): $[\alpha]_D$ +36.1° (*c* = 1.00, CH_3OH).

1-(3,5-Di-*O*-acetyl-2-deoxy-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)-5-iodouracil (53). To a solution of **41** (0.95 g, 2.11 mmol) in acetonitrile (35.0 mL) were added iodine (0.32 g, 11.3 mmol) and ammonium cerium nitrate (0.56 g, 1.02 mmol) and the mixture was refluxed for 2 h. The reaction mixture was evaporated and the residue was coevaporated with toluene. The residue was partitioned between ethyl acetate and water and the organic layer was dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (1:1 *n*-hexane/ethyl acetate) to give **53** as a white powder (1.11 g, 1.93 mmol, 91.5%): $[\alpha]_D$ −10.73° (*c* = 1.025, $CHCl_3$).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-iodouracil (54). Under the conditions analogous to those used for the preparation of **30**, compound **53** (0.20 g, 0.35 mmol) gave **54** as a white foam (0.13 g, 0.34 mmol, 97.1%): $[\alpha]_D$ +32.8° (*c* = 1.00, CH_3OH).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-methylcytosine (56). To a solution of **29** (0.75 g, 1.61 mmol) in pyridine (50.0 mL) was added 4-chlorophenyl phosphorodichloridate (1.31 mL, 7.96 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature. To the mixture was added 1,2,4-triazole (1.67 g, 24.2 mmol) and the mixture was stirred for 7 days at room temperature. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. The residue was coevaporated with toluene and purified by silica gel column chromatography (1:3 *n*-hexane/ethyl acetate) to give **55.** To a solution of **55** in dioxane (60.0 mL) was added 25% aqueous ammonium hydroxide solution (20.0 mL) and the mixture was stirred for 24 h at room temperature. The reaction mixture was evaporated. The residue was dissolved in methanol (45.0 mL). To the solution was added 1 N aqueous sodium hydroxide solution (5.00 mL). After being stirred for 2 h, the reaction mixture was neutralized with acetic acid (0.29 mL, 5.00 mmol) and evaporated under reduced pressure to give a syrup. The syrup was purified by reverse phase gel column chromatography (Wakosil 40C18, 5% acetonitrile in water) and the desired fraction was crystalized from methanol−ether to give **56** (0.21 g, 0.79 mmol, 49.1%): $[\alpha]_D$ +58.93° (*c* = 1.061, CH_3OH).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-cytosine (58). Under the conditions analogous to those used for the preparation of **56**, compound **41** (0.30 g, 0.67 mmol) gave **58** as a white powder (0.12 g, 0.48 mmol, 71.6%): $[\alpha]_D$ +75.0° (*c* = 1.00, CH_3OH).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-fluorocytosine (60). To a solution of **47** (0.35 g, 0.75 mmol) in pyridine (5.00 mL) was added 4-chlorophenyl phosphorodichloridate (0.62 mL, 3.77 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature. To the mixture was added 1,2,4-triazole (0.78 g, 11.3 mmol) and the mixture was stirred for 24 h at 30 °C. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. The residue was coevaporated with toluene and purified by silica gel column chromatography (ethyl acetate) to give **59**. To a solution of **59** in dioxane (15.0 mL) was added 25% aqueous ammonium hydroxide solution (5.00 mL) and the mixture was stirred for 24 h at room temperature. The reaction mixture was evaporated. The residue was dissolved in methanol (45.0 mL) and added 1 N aqueous sodium hydroxide (5.00 mL). After being stirred for 2 h, the reaction mixture was neutralized with acetic acid (0.29 mL, 5.00 mmol). The mixture was evaporated and the residue was purified by silica gel column chromatography (4:1 chloroform/ethanol) and the desired fraction was crystallized from methanol−ether to give **60** (120 mg, 0.45 mmol, 60.0%): $[\alpha]_D$ +77.9° (*c* = 1.00, CH_3OH).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-chlorocytosine (62). Under the conditions analogous to those used for the preparation of **60**, **49** (0.35 g, 0.72 mmol) gave **62** (121 mg, 0.42 mmol, 58.3%): $[\alpha]_D$ +58.6° (*c* = 0.49, CH_3OH).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-bromocytosine (64). Under the conditions analogous to those used for the preparation of **60**, compound **51** (0.30 g, 0.57 mmol) gave **64** (128 mg, 0.39 mmol, 68.4%): $[\alpha]_D$ +50.0° (*c* = 1.05, CH_3OH).

1-(2-Deoxy-4-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)-5-iodocytosine (66). Under the conditions analogous to those used for the preparation of **60**, **53** (0.36 g, 0.62 mmol) gave **66** (103 mg, 0.27 mmol, 43.5%): $[\alpha]_D$ +41.2° (*c* = 0.99, CH_3OH).

9-(2-*O*-Acetyl-3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-*β*-D-*ribo*-pentofuranosyl)adenine (67). A mixture of **13** (1.10 g, 2.0 mmol), adenine (405 mg, 3.0 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (2.70 mL, 11.0 mmol) in 1,2-dichloroethane (17.0 mL) was stirred at reflux for 1.5 h. To the mixture was added dropwise trimethylsilyl trifluoromethanesulfonate (0.77 mL, 4.0 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 15 min and then at reflux for 24 h. The mixture was quenched with saturated aqueous sodium hydrogen carbonate at room temperature and filtered through a pad of Celite. The filtrate was extracted with chloroform and the organic phase was washed with saturated aqueous sodium chloride and dried over sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatog-

raphy over silica gel (AcOEt−hexanes−EtOH, 20:20:1) to give **67** (690 mg, 55%) as an oil.

9-(3,5-Di-*O*-benzyl-4-*C*-triethylsilylethynyl-β-D-*ribo*-pentofuranosyl)adenine (68). To a solution of **67** (354 mg, 0.565 mmol) in methanol (14.0 mL) was added triethylamine (3.3 mL) and the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel (AcOEt−hexanes−EtOH, 20:10:1) to give **68** (283 mg, 86%) as colorless prisms.

9-(3,5-Di-*O*-benzyl-2-deoxy-4-*C*-triethylsilylethynyl-β-D-*ribo*-pentofuranosyl)adenine (70). To a acetonitrile solution (7.00 mL) of **68** (112 mg, 0.191 mmol) and 4-(dimethylamino)pyridine (70.5 mg, 0.573 mmol) was added phenyl chlorothionoformate (40.0 μL, 0.287 mmol) at room temperature under an argon atmosphere, and the mixture was stirred at the same temperature for 1 h. After the solvent was removed under reduced pressure, the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and brine and dried over sodium sulfate. The filtrate was concentrated under reduced pressure, and the residue was passed through a short silica gel column to give an oily **69.** To a toluene solution (6.00 mL) of **69** were added 2,2′-azobis-(isobutyronitrile) (7.9 mg, 0.048 mmol) and tri-*n*-butyltin hydride (0.26 mL, 1.15 mmol), and the mixture was stirred at 85 °C under an argon atmosphere for 1 h. The mixture was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (AcOEt−hexanes−EtOH, 20:10:1) to give **70** (74.0 mg, 68%) as a paste.

9-(2-Deoxy-4-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)adenine (72) and 9-(2-Deoxy-4-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)purine (73). To a solution of **70** (189 mg, 0.332 mmol) in tetrahydrofuran (8.00 mL) was added a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.37 mL, 0.37 mmol) at room temperature. After stirring at the same temperature for 30 min, the solvent was removed under reduced pressure. The residue was passed through a short silica gel column to give an oily **71**. To a solution of **71** in tetrahydrofuran (1.5 mL) was introduced ammonia gas dried with potassium hydroxide at −78 °C. To a solution of the oil in a mixture of liquid ammonia (ca. 15 mL) and tetrahydrofuran (15 mL) was added sodium metal (38.0 mg, 1.66 mmol) in several pieces at −78 °C. The mixture was vigorously stirred at the same temperature for 10 min. To the reaction mixture was added ammonium chloride (270 mg), and the mixture was stirred at room temperature for 2 h. To the resulting mixture was added ethanol, and the suspension was passed through a pad of Celite. The pad was washed with ethanol and the combined filtrates were concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (MeOH−$CHCl_3$, 1:10) to give a mixture of **72** and **73**. The mixture was separated by ODS reversed-phase column chromatography (5−7.5% ethanol in water) to give **73** (7.0 mg, 8%) as white powder and **72** (48 mg, 53%) as white powder.

9-(2-Deoxy-4-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)hypoxanthine (74). A mixture of **72** (22.0 mg, 0.08 mmol) and adenosine deaminase (44.0 μL, 20 units) in Tris-HCl buffer (6 mL, pH 7.5) was stirred at 40 °C for 2 h. The solution was cooled to room temperature and applied to an ODS silica gel column. After washing the column with water (500 mL), the eluate of 2.5% ethanol in water was collected and concentrated under reduced pressure to give a residue. The residue was triturated with 2-propanol to give **74** (16.0 mg, 72%) as an amorphous crystals.

9-(2-*O*-Acetyl-3,5-di-*O*-benzyl-4-*C*-triethylsilylethynyl-β-D-*ribo*-pentofuranosyl)-2,6-diaminopurine (75). Compound **13** (1.10 g, 2.0 mmol) was treated as described in the synthesis of **67**. After purification by column chromatography over silica gel (AcOEt−hexanes−EtOH, 20:10:1), **75** (850 mg, 66%) was obtained as a foam.

9-(3,5-Di-*O*-benzyl-4-*C*-triethylsilylethynyl-β-D-*ribo*-pentofuranosyl)-2,6-diaminopurine (76). Compound **75** (850 mg, 1.32 mmol) was treated as described in the synthesis of **68.** After purification by column chromatography over silica gel (AcOEt−hexanes−EtOH, 30:10:1), **76** (740 mg, 93%) was obtained as a foam.

9-(3,5-Di-*O*-benzyl-2-deoxy-4-*C*-triethylsilylethynyl-β-D-*ribo*-pentofuranosyl)-2,6-diaminopurine (78). Compound **76** (470 mg, 0.783 mmol) was treated as described in the synthesis of **70**. After purification by column chromatography over silica gel (AcOEt−hexanes−EtOH, 30:10:1), **78** (276 mg, 60%) was obtained as an oil.

9-(2-Deoxy-4-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)-2,6-diaminopurine (80). Compound **78** (263 mg, 0.45 mmol) was deprotected as described in the synthesis of **72**. After purification by column chromatography over silica gel (MeOH−$CHCl_3$, 1:8) and trituration with methanol, **80** (56.0 mg, 43%) was obtained as amorphous crystals.

9-(2-Deoxy-4-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)guanine (81). Compound **80** (30.0 mg, 0.103 mmol) was treated as described in the synthesis of **74.** After desalting and purification by reversed-phase column chromatography over ODS silica gel (2.5−5% EtOH in H_2O), recystallization from water gave **81** (15.0 mg, 50%) as an amorphous crystals.

Antiviral Assay Against HIV-1. A laboratory HIV-1 strain (HIV-1_{LAI}),[27] a wild-type clinical HIV-1 strain (HIV-1_{104pre}),[25] and an infectious molecular clone which contains five amino acid substitutions (Ala62Val, Val75Leu, Phe77Leu, Phe116Tyr, and Gln115Met) and shows a high level of resistance against a variety of 2′,3′-dideoxy nucleoside analogues[26] were employed as a source of infectious virions.

Antiviral activity of compounds against HIV-1 was conducted as previously described.[28] Briefly, MT-2 or MT-4 cells (2×10^4/mL) were exposed to 100 $TCID_{50}$ of the HIV-1_{LAI} in the presence of various concentrations of drugs in 96-well microculture plates and incubated at 37 °C for 7 days. After 100 μL of the medium was removed from each well, 10 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (7.5 mg/mL) in phosphate-buffered saline (PBS) was added to each well in the plate. The plate was then incubated at 37 °C for 2 h. After incubation, to dissolve the formazan crystals, 100 μL of acidified 2-propanol containing 4% (v/v) Triton X-100 was added to each well. The optical density (wavelength 570 nm) was measured in a microplate reader (model 3550, Biorad). All assays were performed in triplicate.

The MAGI assay using HeLa-CD4-LTR-β-gal indicator cells was conducted as previously described.[29] Briefly, HeLa-CD4-LTR-β-gal cells were seeded (10^4 cells/well) and cultured in 96-well microculture plates for 24 h and exposed to HIV-1_{104pre} or HIV-1_{MDR} at a 30 $TCID_{50}$ dose for 2 h at 37 °C. Various concentrations of drugs were added to the culture 2 h prior to or 2 h after viral exposure. The drugs were continuously present and no cell washing was performed throughout the culture. In 48 h of culture, the cells were fixed with 1% formaldehyde and 0.2% glutaraldehyde in PBS and stained with 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside (X-Gal). Infected cells were counted in situ by virtue of their blue color after incubation with X-Gal under the inverted microscope.

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Supporting Information Available: Elemental analysis or mass and ^{1}H NMR spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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