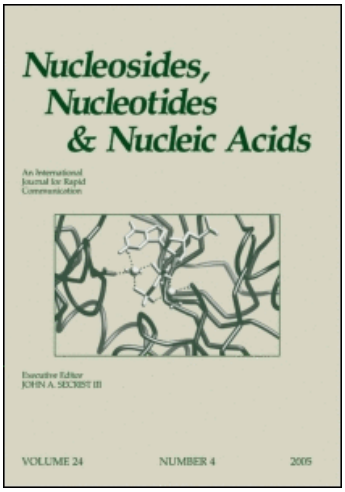

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Synthesis of (±)-4'-Ethynyl and 4'-Cyano Carbocyclic Analogues of Stavudine (d4T)

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SYNTHESIS OF (±)-4′-ETHYNYL AND 4′-CYANO CARBOCYCLIC ANALOGUES OF STAVUDINE (d4T)

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▫ *The synthesis of (±)-4′-ethynyl (**8**) and 4′-cyano (**9**) carbocyclic analogues of the anti-HIV agent stavudine (**5**, d4T) is reported. The carbocyclic unit (**16**) was constructed from readily available β-keto ester **10**. The ethynyl or cyano group of **8** and **9** were prepared, after the introduction of thymine base to **16**, by manipulation of the ester function. Evaluation of the anti-HIV activity of **8** and **9** was also carried out.*

Keywords Stavudine, 4′-ethynyl-d4T, Carbocyclic Nucleoside

INTRODUCTION

The finding that thymidine derivatives bearing 4′-azido (**1**)[1] and 4′-cyano (**2**)[2] substituents show significant inhibitory activity against HIV proliferation has stimulated the synthesis of 4′-substituted nucleoside analogues. In fairy recent studies along this line, 4′-ethynylnucleosides have also been shown to be promising anti-HIV agents.[3–6]

On the other hand, carbocyclic nucleosides have attracted considerable attention as antitumor and antiviral agents.[7–10] In particular, those having a cyclopentene structure, such as carbovir (**3**) and its cyclopropylamino derivative abacavir (**4**), have been known to act as potent anti-HIV (human immunodeficiency virus) agents.[11]

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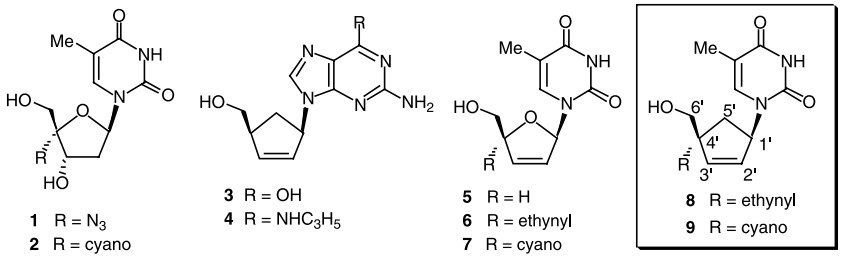
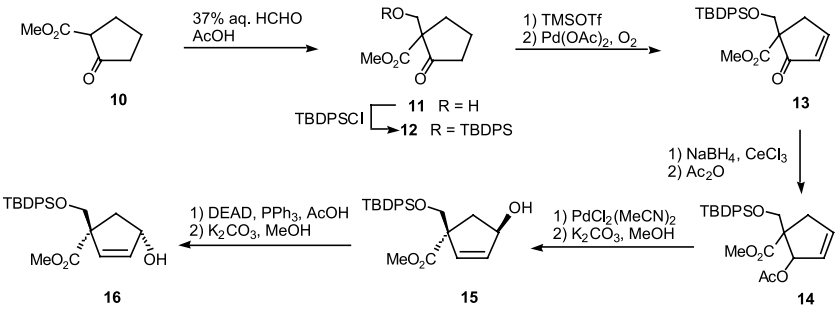
In our recent studies on the C–C bond formation at the 4′-position of nucleosides,[12–14] the synthesis of 4′-ethynyl (**6**)[13] and 4′-cyano (**7**)[14] analogues of anti-HIV agent stavudine (**5**, d4T: 2′,3′-didehydro-3′-deoxythymidine) has been executed. As a result of their antiviral evaluation, both compounds (**6** and **7**) were found to be active against HIV, in particular the activity of 4′-ethynyl-d4T (**6**) was higher than the parent compound d4T (**5**).[13] Furthermore, this compound was found to be less toxic to CEM cell growth and less inhibitory to mitochondrial DNA synthesis than d4T.[15] These findings prompted us to design and synthesize the carbocyclic counterparts of **6** and **7**. In this article, we report the synthesis of the 4′-ethynyl (**8**) and 4′-cyano (**9**) carbocyclic analogues of d4T as racemates.



RESULTS AND DISCUSSION

A synthetic method for 4′-alkylcarbovir derivatives has been reported from our laboratory.[16,17] In this synthesis, alkyl substituents were introduced into the cyclopentane ring by alkylation of the lithium enolate derived from the commercially available methyl 2-oxocyclopentane-carboxylate (**10**). Since such an approach was apparently not readily applicable to the introduction of ethynyl or cyano groups, we considered the possibility of using the carbomethoxy group of **10** as precursor of our requisite 4′-substituents.

We, therefore, initiated the present study with the introduction of a hydroxymethyl group to **10** (Scheme 1). Attempted reactions of the potassium



SCHEME 1 Preparation of the carbocyclic unit 16.

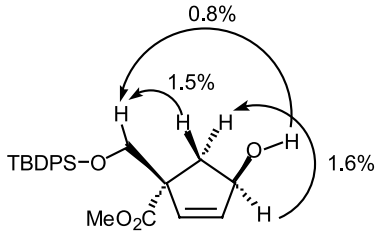


FIGURE 1 NOE correlations observed for 15.

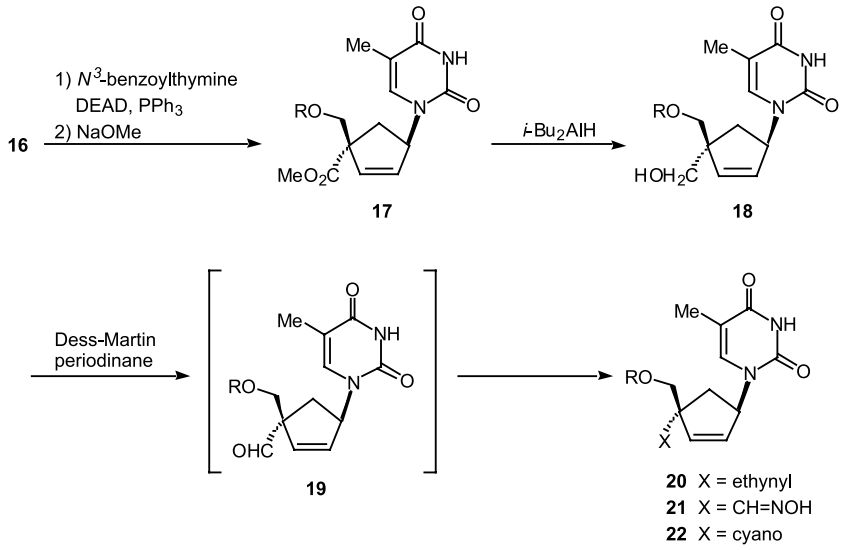
salt of **10** with paraformaldehyde in variety of solvents (DMSO, DMF, HMPA, or H_2O) all met with failure. The desired alcohol **11** was obtained in 77% yield by converting the potassium salt to its tin enolate (Bu_3SnCl/HMPA-THF/0°C/0.5 h) and then reacting with paraformaldehyde for 48 h at room temperature. It was found, however, that direct treatment of **11** simply with 37% aqueous HCHO in the presence of AcOH (at rt for 48 h) gave **11** in quantitative yield.

Conventional silylation of **11** with *tert*-butyldiphenylsilyl chloride gave **12** (77%). Introduction of a double bond to **12** was conducted by Pd-catalyzed dehydrogenation through the corresponding silyl-enolate.[18] The enone **13** was obtained in 88% yield by this procedure. The Luche reduction[19] of **13** followed by acetylation gave the allyl acetate **14** in quantitative yield as a single isomer, although its stereochemistry could not be determined at this stage. Compound **14**, upon Pd-catalyzed allylic rearrangement[20] followed by deacetylation, gave the allyl alcohol **15** in 67% yield. The depicted stereochemistry of **15** came from the results of NOE experiments given in Figure 1. The desired carbocyclic unit **16** was prepared in 83% yield by the Mitsunobu inversion[21] of **15** and subsequent deacetylation.

For the coupling reaction of **16** under the Mitsunobu conditions, N^3-benzoylthymine[22] was employed. The resulting reaction mixture was evaporated and then treated with NaOMe in MeOH to give the carbocyclic nucleoside **17** in 52% yield (Scheme 2). The HMBC (heteronuclear multiple bond connectivity) spectrum of **17** gave a cross peak between H-6 and C-1′, which confirmed the depicted regiochemistry.

There are many methods available for the transformation of aldehydes to alkynes.[2][a] Reduction of the ester function of **17** was carried out with *i*-Bu_2AlH. However, it turned out that, even at low temperature (−70°C in CH_2Cl_2), only a small amount of the desired aldehyde **19** was formed, the main product being the hydroxymethyl derivative **18**, as evidenced by TLC analysis (hexane/EtOAc = 1/3). Compound **18** was, therefore, reoxidized with Dess-Martin periodinane in CH_2Cl_2 and the aldehyde **19** formed was used for further transformations without characterization.

[a]For example, see Ref. [23].



SCHEME 2 (R = TBDPS) Synthesis of 4′-ethynyl and 4′-cyano carbocyclic d4T.

For the preparation of the 4′-ethynyl derivative (**20**), the method reported by Agrofoglio and co-workers[24] was used. Thus, treatment of **19** with a diazophosphonate $CH_3COC(N_2)P(O)(OMe)_2$[b] in MeOH in the presence of K_2CO_3 furnished **20** in 47% yield. Its ^{13}CNMR spectrum showed the presence of two ^{13}C-resonances apparently derived from carbon atoms of the ethynyl group: δ 71.1 (C ≡ *C*H) and 84.8 (*C* ≡ CH). In addition, an NOE enhancement (0.5%) was observed between H-6 and CH_2-6′ of **20**, supporting the depicted stereochemistry. The 4′-cyano derivative **22** was prepared in 81% yield through the oxime intermediate **21**, which underwent spontaneous elimination upon treatment with MsCl in pyridine. In the ^{13}C NMR spectrum of **22**, the 4′-CN appeared at δ 120.2, which is typical for nitrile resonances.[c] Desilylation of **20** and **22** was carried out by conventional procedure (Bu_4NF in THF). The target compounds **8** (60%) and **9** (32%) were obtained after purification through the respective 6′-*O*-acetate.

Finally, **8** and **9** were assayed for their ability to inhibit the replication of HIV-1 in MT-4 cell culture, the results of which are summarized in Table 1 together with the data of stavudine and 4′-ethynylstavudine (**6**). Unfortunately, both **8** and **9** did not display any inhibitory activity.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were measured on a JEOL JNM-LA 500 (500 MHz). Chemical shifts are reported relative to Me_4Si. Mass

[b]For the preparation of the diazophosphonate: Ref. [25].
[c]Synthesis of 4′-cyano-2′-deoxy purine nucleosides has recently been reported: Ref. [26].

TABLE 1 Anti-HIV-1 Activity in MT-4 Cells

Compound	EC_{50} (μM)	CC_{50} (μM)
Stavudine	0.47	>100
6	0.14	>100
8	>100	>100
9	>100	>100

spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix on a JEOL JMS-700. Ultraviolet spectra (UV) were recorded on a JASCO V-530 spectrophotometer. Column chromatography was carried out on silica gel (Micro Bead Silica Gel PSQ 100B, Fuji Silysia Chemical Ltd.). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck). Where necessary, analytical samples were purified by high-performance liquid chromatography (HPLC). HPLC was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H)· KIT column (2 × 25 cm). THF was distilled from benzophenone ketyl.

1-Hydroxymethyl-2-oxocyclopentanecarboxylic acid methyl ester (11). A mixture of **10** (5.0 g, 35.2 mmol), 37% aqueous HCHO (33 mL, *ca.* 370 mmol), and AcOH (4.03 mL, 70.3 mmol) was stirred for 23 h at rt. The reaction mixture was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), and purified by column chromatography (hexane/EtOAc = 1/1). This gave **11** (6.05 g, 100%) as an oil: ^{1}HNMR ($CDCl_3$) δ 1.97–2.18 (2H, m, CH_2), 2.21–2.25 (1H, m, CH_2), 2.29–2.53 (3H, m, OH and CH_2), 2.62–2.66 (1H, m, CH_2), 3.74 (3H, s, Me), 3.81 (1H, dd, J = 11.2 and 8.0 Hz, CH_2OH), 3.89 (1H, dd, J = 11.2 and 4.4 Hz, CH_2OH); FAB-MS *m/z* 173 (M^++ H). Anal Calcd for $C_8H_{12}O_4 \cdot 1/5H_2O$: C, 54.65; H, 7.11. Found: C, 54.54; H 6.96.

1-(*tert*-Butyldiphenylsilyloxymethyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (12). A mixture of **11** (10.35 g, 60.1 mmol), imidazole (8.18 g, 120.2 mmol), and TBDPSCl (15.6 ml, 60.1 mmol) in DMF (40 mL) was stirred for 16 h at room temperature under positive pressure of dry Ar. The mixture was partitioned between EtOAc and sat. aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated. The resulting syrupy residue was treated with MeOH (*ca.* 40 mL) to give the precipitated **12**. This procedure was repeated further three times to give **12** (18.97 g, 77%) as a white solid: mp 89–91°C; ^{1}HNMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*t*), 2.03–2.11 (2H, m, CH_2), 2.26–2.35 (1H, m, CH_2), 2.41–2.53 (3H, m, CH_2), 3.65 (3H, s, Me), 3.87 (1H, d, J = 9.6 Hz, CH_2OSi), 4.09 (1H, d, J = 9.6 Hz, CH_2OSi), 7.37–7.46 (6H, m, Ph), 7.61–7.65 (4H, m, Ph); FAB-MS *m/z* 411 (M^++ H). Anal Calcd for $C_{24}H_{30}O_4Si \cdot 1/10H_2O$: C, 69.90; H, 7.38. Found: C, 69.89; H, 7.43.

1-(*tert*-Butyldiphenylsilyloxymethyl)-2-oxo-3-cyclopentenecarboxylic acid methyl ester (13). To a stirring mixture of **12** (3.58 g, 8.72 mmol) and Et_3N (6.1 ml, 43.6 mmol) was added $Me_3SiOSO_2CF_3$ (2.56 mL, 13.0 mmol) at 0°C under positive pressure of dry Ar. The mixture was stirred for 30 min at the same temperature and then partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated. The residue was dissolved in DMSO (12 mL). To this solution was added $Pd(OAc)_2$ (98 mg, 0.44 mmol), and the mixture was stirred for 36 h under positive pressure of O_2. The mixture was partitioned between EtOAc and brine. Column chromatography (hexane/EtOAc = 5/1) of the organic layer gave **13** (3.13 g, 88%) as a white solid: mp 103–105°C; ^{1}HNMR ($CDCl_3$) δ 0.97 (9H, s, SiBu-*t*), 2.99–3.05 (1H, m, CH_2), 3.21–3.26 (1H, m, CH_2), 3.66 (3H, s, Me), 3.98 (1H, d, J = 10.0 Hz, CH_2OSi), 4.18 ((1H, d, J = 10.0 Hz, CH_2OSi),6.24–6.26 (1H, m, CH = CH), 7.37–7.45 (6H, m, Ph), 7.58–7.62 (4H, m, Ph), 7.86–7.88 (1H, m, CH = CH); FAB-MS *m/z* 409 (M^++ H). Anal Calcd for $C_{24}H_{28}O_4Si \cdot 1/10H_2O$: C, 70.24; H, 6.93. Found: C, 70.19; H, 6.94.

2-Acetoxy-1-(*tert*-butyldiphenylsilyloxy)methyl-3-cyclopentenecarboxylic acid methyl ester (14). A mixture of $NaBH_4$ (628 mg, 16.6 mmol) and MeOH (50 mL) was cooled and stirred at −70°C. To this was added a mixture of **13** (3.39 g, 8.3 mmol) and $CeCl_3 \cdot 7H_2O$ (3.1 g, 8.3 mmol) in THF/MeOH = 1/1 (50 mL) drop-wise for 15 min. The resulting suspension was stirred for 1 h at −70°C. The reaction was quenched by adding AcOH (*ca.* 1 mL). The reaction mixture was evaporated. The residue was suspended in MeCN (15 ml). To this suspension were added DMAP (1.02 g, 8.3 mmol), *i*-Pr_2NEt (1.45 mL, 8.3 mmol) and Ac_2O (1.57 mL, 16.6 mmol). The mixture was stirred for 30 min at 0°C under positive pressure of dry Ar and partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 4/1) of the organic layer gave **14** (3.74 g, 100%) as an oil: ^{1}HNMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*t*), 1.87 (3H, s, Ac), 2.50–2.55 (1H, m, CH_2), 2.91–2.97 (1H, m, CH_2), 3.71 (3H, s, Me), 3.87 (1H, d, J = 9.6 Hz, CH_2OSi), 4.08 (1H, d, J = 9.6 Hz, CH_2OSi), 5.76–5.78 (1H, m, CH = CH), 5.99–6.00 (1H, m, CH = CH), 6.07–6.08 (1H, m, AcOCH), 7.29–7.45 (4H, m, Ph), 7.61–7.65 (4H, m, Ph); FAB-MS *m/z* 453 (M^++ H). Anal Calcd for $C_{26}H_{32}O_5Si \cdot 1/2H_2O$: C, 67.65; H, 7.21. Found: C, 67.73; H, 7.03.

1-(*tert*-Butyldiphenylsilyloxy)methyl-(trans-4-hydroxy)-2-cyclopentenecarboxylic acid methyl ester (15). A mixture of **14** (1.87 g, 4.13 mmol), $PdCl_2(MeCN)_2$ (106 mg, 0.41 mmol), and *p*-benzoquinone (224 mg, 2.07mmol) in THF (17 mL) was refluxed for 3 h under positive pressure of dry Ar. The mixture was partitioned between CH_2Cl_2 and sat. aqueous $Na_2S_2O_3$. The organic layer was dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (5 ml) and treated with K_2CO_3 (685 mg, 4.96 mmol) for 1 h with stirring. The mixture was partitioned between $CHCl_3$ and brine. Column chromatography (hexane/EtOAc = 6/1) of the organic layer gave **15** (1.14 g, 67%) as an oil: ^{1}HNMR

($CDCl_3$) δ 1.02 (9H, s, SiBu-*t*), 1.87 (1H, dd, *J* = 14.4 and 2.4 Hz, CH_2), 2.73 (1H, dd, *J* = 14.4 and 7.2 Hz, CH_2), 3.65 (3H, s, Me), 3.79 (1H, d, *J* = 9.6 Hz, CH_2OSi), 3.85 (1H, d, *J* = 9.6 Hz, CH_2OSi), 4.82–4.87 (1H, m, CHOH), 5.84–5.87 (1H, m, CH = CH), 6.02–6.04 (1H, m, CH = CH), 7.38–7.44 (6H, m, Ph), 7.63–7.65 (4H, m, Ph); FAB-MS *m/z* 411 (M^++ H). Anal Calcd for $C_{24}H_{30}O_4Si \cdot 1/10H_2O$: C, 69.90; H, 7.38. Found: C, 69.89; H, 7.40.

1-(*tert*-Butyldiphenylsilyloxy)methyl-(*cis*-4-hydroxy)-2-cyclopentenecarboxylic acid methyl ester (16). A mixture of **15** (1.08 g, 2.63 mmol) , Ph_3P (897 mg, 3.42 mmol), and AcOH (301 μL, 5.26 mmol) in THF (10 mL) was cooled to 0°C under positive pressure of dry Ar. To this was added drop-wise diethyl azodicarboxylate (2.3 M solution in toluene, 1.49 mL, 3.42 mol). After stirring for 30 min, the mixture was partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated. The residue was treated with K_2CO_3 (727 mg, 5.26 mmol) in MeOH (5 mL) for 1 h. The mixture was partitioned between $CHCl_3$ and brine. Column chromatography (hexane/EtOAc = 4/1) of the organic layer gave **16** (892 mg, 83%) as an oil: ^{1}HNMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*t*), 2.20–2.31 (3H, m, CH_2 and OH), 3.70 (1H, d, *J* = 9.6 Hz, CH_2OSi), 3.71 (3H, s, Me), 3.87 (1H, d, *J* = 9.6 Hz, CH_2OSi), 4.76–4.81 (1H, m, CHOH), 5.88 (1H, d, *J* = 5.6 Hz, CH = CH), 6.03 (1H, dd, *J* = 5.6 and 2.4 Hz, CH = CH), 7.36–7.46 (6H, m, Ph), 7.61–7.65 (4H, m, Ph); FAB-MS *m/z* 411 (M^++ H). Anal Calcd for $C_{24}H_{30}O_4Si \cdot 1/10H_2O$: C, 69.90; H, 7.38. Found: C, 69.85; H, 7.46.

1-[*cis*-1-(*tert*-Butyldiphenylsilyloxy)methyl-*trans*-1-methoxycarbonyl-2-cyclopenten-4-yl]thymine (17). To a THF (30 mL) solution of PPh_3 (1.93 g, 7.35 mmol) was added drop-wise DEAD (2.3 M toluene solution, 3.08 mL, 7.08 mmol) at 0°C under positive pressure of dry Ar, and the mixture was stirred for 0.5 h. To this was added a THF (45 mL) suspension containing **16** (1.16 g, 2.83 mmol) and N^3-benzoylthymine (976 mg, 4.25 mmol), and the reaction mixture was stirred for 45 h at room temperature. After evaporation of the solvent, the residue was treated with 2M NaOMe in MeOH (5.5 mL) for 2 h with stirring. The mixture was neutralized by adding AcOH (1.15 mL) and then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **17** (758 mg, 52%) as a white foam: UV (MeOH) λ_{max} 272 nm (ε 9800), λ_{min} 240 nm (ε 2200); ^{1}HNMR ($CDCl_3$) δ 1.05 (9H, s, SiBu-*t*), 1.74 (3H, d, *J* = 1.2 Hz, 5-Me), 1.75 (1H, dd, *J* = 14.0 and 6.8 Hz, H-5′), 3.01 (1H, dd, *J* = 14.0 and 8.4 Hz, H-5′), 3.70 (3H, s, CO_2Me), 3.87 (1H, d, *J* = 10.0 Hz, H-6′), 3.90 (1H, d, *J* = 10.0 Hz, H-6′), 5.79 (1H, dd, *J* = 5.2 and 2.0 Hz, H-2′), 5.83–5.88 (1H, m, H-1′), 6.10 (1H, dd, *J* = 5.2 and 2.4 Hz, H-3′), 6.88 (1H, q, *J* = 1.2 Hz, H-6), 4.36–7.47 (6H, m, Ph), 7.61–7.64 (4H, m, Ph), 8.89 (1H, br, NH); FAB-MS *m/z* 519 (M^++ H). Anal Calcd for $C_{29}H_{34}N_2O_5Si \cdot 1/10H_2O$: C, 66.92; H, 6.62; N, 5.38. Found: C, 66.71; H, 6.59; N, 5.61.

1-[*cis*-1-(*tert*-Butyldiphenylsilyloxy)methyl-*trans*-1-hydroxymethyl-2-cyclopenten-4-yl]thymine (18). To a CH_2Cl_2 (30 mL) solution of **17** (2.1 g, 4.05 mmol) was added drop-wise *i*-Bu_2AlH (1.01 M in toluene, 16 mL, 16.2 mmol) at −70°C under positive pressure of dry Ar. After stirring for 40 min, the reaction was quenched by adding AcOH, and the mixture was partitioned between $CHCl_3$ and aqueous NH_4Cl. Column chromatography ($CHCl_3$/MeOH = 20/1) of the organic layer gave **18** (1.75 g, 88%) as a foam: UV (MeOH) λ_{max} 272 nm (ε 9300), λ_{min} 240 nm (ε 1800); ^{1}HNMR ($CDCl_3$) δ 1.07 (9H, s, SiBu-*t*), 1.50 (1H, dd, *J* = 14.0 and 6.8 Hz, H-5′), 1.75 (3H, d, *J* = 0.8 Hz, 5-Me), 1.90 (1H, t, *J* = 5.8 Hz, OH), 2.43 (1H, dd, *J* = 14.0 and 8.6 Hz, H-5′), 3.58–3.64 (2H, m, C*H*$_2$OH), 3.67 (1H, d, *J* = 10.0 Hz, H-6′), 3.71 (1H, d, *J* = 10.0 Hz, H-6′), 5.72–5.76 (2H, m, H-1′ and H-2′), 6.09 (1H, dd, *J* = 5.6 and 2.2 Hz, H-3′), 6.88 (1H, q, *J* = 0.8 Hz, H-6), 7.36–7.47 (6H, m, Ph), 7.63–7.65 (4H, m, Ph), 8.26 (1H, br, NH); FAB-MS *m/z* 491 (M^++ H). Anal. Calcd for $C_{28}H_{34}N_2O_4Si \cdot H_2O$: C, 66.11; H, 7.13; N. 5.51. Found: C, 66.48; H, 6.92; N, 5.50.

1-[*cis*-1-(*tert*-Butyldiphenylsilyloxy)methyl-*trans*-1-ethynyl-2-cyclopenten-4-yl]thymine (20). To a solution of **18** (66 mg, 1.35 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (1.15 g 2.70 mmol). After stirring for 1.5 h, the reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated to give the crude aldehyde **19**, which was dissolved in MeOH (30 mL). After adding K_2CO_3 (747 mg, 5.40 mmol), the MeOH solution of **19** was reacted with dimethyl (1-diazo-2-oxopropyl)phosphonate (648 mg, 3.38 mmol) at room temperature for 2 h. The reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **20** (305 mg, 47%) as a foam: UV (MeOH) λ_{max} 271 nm (ε 9600), λ_{min} 238 nm (ε 1800); ^{1}HNMR ($CDCl_3$) δ 1.07 (9H, s, SiBu-*t*), 1.71 (3H, d, *J* = 1.2 Hz, 5-Me), 2.02 (1H, dd, *J* = 13.2 and 7.6 Hz, H-5′), 2.20 (1H, s, C ≡ CH), 2.70 (1H, dd, *J* = 13.2 and 8.0 Hz, H-5′), 3.69 (1H, d, *J* = 9.6 Hz, H-6′), 3.83 (1H, d, *J* = 9.6 Hz, H-6′), 5.76 (1H, dd, *J* = 5.2 and 2.0 Hz, H-2′), 5.91–5.95 (1H, m, H-1′), 6.02 (1H, dd, *J* = 5.2 and 2.4 Hz, H-3′), 6.98 (1H, q, *J* = 1.2 Hz, H-6), 7.37–7.48 (6H, m, Ph), 7.63–7.66 (4H, m, Ph), 8.20 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.3 (5-Me), 19.5 (*C*Me$_3$), 26.9 (C*Me*$_3$), 40.2 (C5′), 49.2 (C4′), 60.6 (C1′), 67.7 (C6′), 71.1 (C ≡*C*H), 84.8 (*C*≡ CH), 111.3 (C5), 127.9, 130.0 135.5 and 135.6 (Ph-tertiary), 130.8 (C2′), 132.8 (Ph-quaternary), 136.3 (C6), 139.6 (C3′), 150.7 (C2), 163.4 (C4); FAB-MS *m/z* 485 (M^++ H). Anal. Calcd for $C_{29}H_{32}N_2O_3Si \cdot 3/4H_2O$: C, 69.91; H, 6.78; N, 5.62. Found: C, 70.10; H, 6.73; N, 6.02.

1-(*tert*-Butyldiphenylsilyloxy)methyl-*trans*-4-(thymin-1-yl)-2-cyclopentenecarbaldehyde oxime (21). To a solution of **18** (1.7 g, 3.46 mmol) in CH_2Cl_2 (45 mL) was added Dess-Martin periodinane (2.93 g, 6.93 mmol). After stirring for 1.5 h, the mixture was partitioned between CH_2Cl_2 and

saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated to give the crude aldehyde **19**, which was dissolved in pyridine (50 mL) containing $NH_2OH{\cdot}HCl$ (482 mg, 6.93 mmol). After stirring for 20 h at room temperature, the reaction mixture was partitioned between CH_2Cl_2 and brine. Column chromatography (hexane/EtOA = 1/2) of the organic layer gave **21** (1.18 g, 68%) as a foam: UV (MeOH) λ_{max} 272 nm (ε 9300), λ_{min} 240 nm (ε 2400); ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s, Bu-*t*), 1.80 (3H, d, *J* = 1.0 Hz, 5-Me), 1.81 (1H dd, *J* = 13.2 and 8.8 Hz, H-5′), 2.92 (1H, dd, *J* = 13.2 and 7.8 Hz, H-6′), 3.79 (1H, d, *J* = 10.2 Hz, H-6′), 5.76–5.80 (2H, m, H-1′ and H-2′), 6.10 (1H, dd, *J* = 5.8 and 2.4 Hz, H-3′), 7.00 (1H, q, *J* = 1.0 Hz, H-6), 7.37–7.47 (7H m, C*H* = NOH and Ph), 7.61–7.65 (4H, m, Ph), 9.05 (1H, br, NH), 9.32 (1H, br, CH = NO*H*); FAB-MS *m/z* 504 (M^++ H). Anal. Calcd for $C_{28}H_{33}N_3O_4Si$: C, 66.77; H, 6.60; N, 8.34. Found: C, 66.68; H, 6.78; N, 8.15.

1-[*cis*-1-(*tert*-Butyldiphenylsilyloxy)methyl-*trans*-1-cyano-2-cyclopenten-4-yl]thymine (22). To a pyridine (10 mL) solution containing **21** (1.0 g, 1.99 mmol) and DMAP (366 mg, 3.0 mmol) was added MsCl (461 μL, 5.96 mmol) at 0°C. After stirring for 30 h at room temperature, the reaction mixture was partitioned between CH_2Cl_2 and brine. Column chromatography (hexane/EtOAc = 1/2) of the organic layer gave **22** (787 mg, 81%) as a foam: UV (MeOH) λ_{max} 271 nm (ε 9900), λ_{min} 238 nm (ε 2000); ^{1}H NMR ($CDCl_3$) δ 1.09 (9H, s, Bu-*t*), 1.75 (3H, d, *J* = 1.2 Hz, 5-Me), 1.88 (1H, dd *J* = 14.4 and 7.2 Hz, H-5′), 2.96 (1H, dd, *J* = 14.4 and 8.4 Hz, H-5′), 3.78 (1H, d, *J* = 10.0 Hz, H-6′), 3.83 (1H, d, *J* = 10.0 Hz, H-6′), 5.86–5.91 (1H, m, H-1′), 5.97 (1H, dd, *J* = 5.2 and 2.0 Hz, H-2′), 6.08 (1H, dd, *J* = 5.2 and 2.0 Hz, H-3′), 6.76 (1H, q, *J* = 1.2 Hz, H-6), 7.38–7.49 (6H, m, Ph), 7.61–7.65 (4H, m, Ph), 8.28 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.4 (5-Me), 19.4 (*C*Me_3), 26.8 (C*Me*$_3$), 38.4 (C5′), 49.9 (C4′), 60.3 (C1′), 66.9 (C6′), 111.7 (C5), 120.2 (CN), 128.0 130.2, 130.3, 135.5, and 135.6 (Ph-tertiary), 132.0 and 132.1 (Ph-quaternary), 134.3 (C2′), 134.5 (C3′), 135.4 (C6), 150.4 (C2), 163.1 (C4); FAB-MS *m/z* 486 (M^++ H). Anal. Calcd for $C_{28}H_{31}N_2O_3Si \cdot 1/4H_2O$: C, 68.61; H, 6.48; N, 8.57. Found: C, 68.42; H, 6.46; N, 8.35.

1-(*trans*-1-Ethynyl-*cis*-1-hydroxymethyl-2-cyclopenten-4-yl)thymine (8). A mixture of **20** (101 mg, 0.21 mmol) and Bu_4NF (1M solution in THF, 230 μL, 0.23 mmol) in THF (3 mL) was stirred for 2 h at room temperature. To this mixture were added 4-dimethylaminopyridine (51 mg, 0.42 mmol), *i*-Pr_2NEt (73 μL, 0.42 mmol), and Ac_2O (80 μL, 0.84 mmol). The reaction mixture was stirred for 30 min, and then partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. Column chromatography (EtOAc) of the organic layer gave the acetate (52 mg) as a solid. This acetate was treated with NH_3/MeOH (35 ml) below 0°C for 12 h. During evaporation of the solvent, precipitation occurred. The precipitate was washed with hot benzene (50 mL) to give an analytically pure sample of **8** (31 mg, 60%) as a solid: mp 205–208°C; UV (MeOH) λ_{max} 272 nm (ε 10,300), λ_{min} 237 nm

(ε 1600); ^{1}HNMR (DMSO-d_6) δ 1.73 (3H, d, J = 0.8 Hz 5-Me), 1.89 (1H, dd, J = 14.0 and 6.2 Hz, H-5′), 2.46 (1H, dd, J = 14.0 and 8.8 Hz, H-5′), 3.09 (1H, s, C ≡ CH), 3.41 (1H, dd, J = 10.8 and 6. Hz, H-6′), 4.58 (1H, dd, J = 10.8 and 5.4 Hz, H-6′), 5.22–5.25 (1H, m, OH), 5.60–5.63 (1H, m, H-1′), 5.77–5.79 (1H, m, H-2′), 5.93–5.95 (1H, m, H-3′) 7.31 (1H, q, J = 0.8 Hz, H-6) 11.2 (1H, br, NH); ^{13}C NMR (DMSO-d_6) δ 12.2 (5-Me), 39.8 (C5′), 49.1 (C4′), 59.9 (C1′), 66.4 (C6′), 72.8 (C ≡ *C*H), 86.5 (*C* ≡ CH), 108.8 (C5), 130.7 (C2′), 137.3 (C6), 139.0 (C3′), 150.8 (C2), 163.8 (C4). Anal. Calcd for $C_{13}H_{14}N_2O_3 \cdot$ 1/5 H_2O : C, 62.49; H, 5.81; N, 11.21. Found: C, 62.57; H, 5.65; N, 11.22.

1-(*trans*-1-Cyano-*cis*-1-hydroxymethyl-2-cyclopenten-4-yl)thymine (9). A mixture of **22** (251 mg, 0.52 mmol) and Bu_4NF (1M solution in THF, 579 μL, 0.57 mmol) in THF (7 mL) was stirred for 2 h at room temperature. To this mixture were added 4-dimethylaminopyridine (128 mg, 1.04 mmol), *i*-Pr_2NEt (181 μL, 1.04 mmol), and Ac_2O (196 μL, 2.08 mmol). The reaction mixture was stirred for 30 min, and then partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. Column chromatography (EtOAc) of the organic layer gave the acetate (98 mg) as a solid. This acetate was treated with NH_3/MeOH (20 ml) below 0°C for 12 h. During evaporation of the solvent, precipitation occurred. The precipitate was washed with hot benzene (50 ml) to give an analytically pure sample of **9** (41 mg, 32%) as a solid: mp 228–230°C; UV (MeOH) λ_{max} 271 nm (ε 10,000), λ_{min} 240 nm (ε 1700); ^{1}H NMR (DMSO-d_6) δ 1.74 (3H, d, J = 0.8 Hz, 5-Me), 1.90 (1H, dd, J = 14.4 and 6.4 Hz, H-5′), 2.73 (1H, dd, J = 14.4 and 8.8 Hz, H-5′), 3.62 (1H, dd, J = 10.8 and 6.0 Hz, H-6′), 3.65 (1H, dd, J = 10.8 and 5.6 Hz, H-6′), 5.61–5.66 (2H, m, H-1′ and OH), 6.06–6.11 (2H, m, H-2′ and H-3′), 7.23 (1H, q, J = 0.8 Hz, H-6), 11.31 (1H, br, NH); ^{13}C NMR (DMSO-d_6) δ 12.1 (5-Me), 37.8 (C5′), 49.9 (C4′), 60.0 (C1′), 65.1 (C6′), 109.2 (C5), 121.8 (CN), 133.5 (C3′), 134.6 (C2′), 137.1 (C6), 150.8 (C2), 163.1 (C4); FAB-MS *m/z* 248 (M^++ H). Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.27; H, 5.22; N, 16.71.

REFERENCES

1. Maag, H.; Rydzewski, R.M.; McRoberts, M.J.; Crawford-Ruth, D.; Verheyden, J.P.H.; Prisbe, E.J. Synthesis and anti-HIV activity of 4′-azido- and 4′-methoxy-nucleosides. J. Med. Chem. **1992**, 35, 1440.
2. O-Yang, C.; Wu, H.Y.; Fraser-Smith, E.B.; Walker, K.A.M. Synthesis of 4′-*C*-cyanothymidine and analogues as potent inhibitors of HIV. Tetrahedron Lett. **1992**, 33, 37.
3. Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. Synthesis of 4′α_branched thymidines as a new type of antiviral agent. Bioorg. Med. Chem. Lett. **1999**, 9, 385.
4. Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. Synthesis and biological activities of 4′α-*C*-branched-chain sugar pyrimidine nucleosides. J. Med. Chem. **1999**, 42, 2901.
5. Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. Synthesis of 4′-*C*-ethynyl β-arabino-and 4′-*C*-ethynyl-2′-deoxy-β-D-ribo-pentofuranosylpyrimidines and –purines and evaluation of their anti-HIV activity. J. Med. Chem. **2000**, 43, 4516.
6. Kodama, E.; Kohgo, S.; Kitano, K.; Machida, H.; Gatanaga, H.; Shigeta, S.; Matsuoka, M.; Ohrui, H.; Mitsuya, H. 4′-Ethynyl nucleoside analogues: potent inhibitors of multidrug-resistant human immunodeficiency virus variant in vitro. Antimicrob. Agent Chemother. **2001**, 45, 1539.
7. Vince, R.; Hua, M. Synthesis and anti-HIV activity of carbocyclic 2′,3′-didehydro-2′,3′-dideoxy-2,6-disubstituted purine nucleosides. J. Med. Chem. **1990**, 33, 17.

8. Daluge, S.M. Therapeutic Nucleosides. U.S. patent 1991, Patent number 5034394.
9. Daluge, S.M.; Good, S.S.; Faletto, M.B.; Miller, W.H.; St. Clair, M.H.; Boone, L.R.; Tisdale, M.; Parry, N.R.; Reardon, J.E.; Dornsife, R.E.; Averett, D.R.; Krenitsky, T.A. 1592U89, A novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity. Antimicrob. Agents Chemother. **1997**, 41, 1082.
10. Weller, S.; Radomski, K.M.; Lou, Y.; Stein, D.S. Population pharmacokinetics and pharmavodinamic modeling of abacavir (1592U89) from a dose-ranging, double-blind, randomized monotherapy trial with human immunodeficiency virus-inkected subjects. Antimicrob. Agents Chemother. **2000**, 44, 2052.
11. Mansuri, M.M.; Hitchcock, M.J.M.; Buroker, R.A.; Bregman, C.L.; Ghazzouli, L.; Deaiderio, J.V.; Starrett, J.E.; Sterzyski, R.Z.; Martin, J.C. Comparison of in vivo biological properties and mouse toxicities of three thymidine analogues active against human immunodeficiency virus. Antimicrob. Agents Chemother. **1990**, 34, 637.
12. Haraguchi, K.; Takeda, S.; Tanaka, H. Ring opening of 4′,5′-epoxynucleosides: a novel stereoselective entry to 4′-*C*-branched nucleosides. Org. Lett. **2003**, 5, 1399.
13. Haraguchi, K.; Takeda, S.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G.E.; Cheng, Y. Synthesis of a highly active new anti-HIV agent 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine. Bioorg. Med. Chem. Lett. **2003**, 13, 3775.
14. Haraguchi, K.; Itoh, Y.; Takeda, S.; Honma, Y.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G.E.; Cheng, Y. Synthesis and anti-HIV activity of 4′-cyano-2′,3′-didehydro-3′-deoxythymidine. Nucleosides, Nucleotides Nucleic Acids **2004**, 23, 647.
15. Dutschman, G.E.; Grill, S.P.; Gullen, E.A.; Haraguchi, K.; Takeda, S.; Tanaka, H.; Baba, M.; Cheng, Y.-C. Novel 4′-substituted stavudine analog with improved anti-immunodeficiency virus activity and decreased cytotoxicity. Antimicrob. Agents Chemother. **2004**, 48, 1640.
16. Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T. Enantio- and diastereoselective synthesis of 4′-α-substituted carbocyclic nucleosides. Tetrahedron Asymmetry **1998**, 9, 911.
17. Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T.; Baba, M. Stereoselective synthesis of 4′-α-alkylcarbovir derivatives based on an asymmetric synthesis or chemoenzymatic procedure. Chem. Pharm. Bull. **1999**, 47, 1256.
18. Larock, R.C.; Hightower, R.T.; Kraus, A.G.; Hahn, P.; Zheng, D. A simple, effective, new, palladium-catalyzed conversion of enol silanes to enones and enals. Tetrahedron. Lett. **1995**, 36, 2423.
19. Luche, J.L.; Genal, A.L. Lanthanoids in organic synthesis. 5. selective reductions of ketones in the presence of aldehydes. J. Am. Chem. Soc. **1979**, 101, 5848.
20. Oehlschlager, A.C.; Mishra, P.; Dhami, S. Metal-catalyzed rearrangements of allylic seters. Can. J. Chem. **1984**, 62, 791.
21. Mitsunobu, O. The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. Synthesis **1981**, 1.
22. Choi, Y.; George, C.; Comin, M.J.; Barchi, J.J., Jr.; Kim, H.S.; Jacobson, K.A.; Balzarini, J.; Mitsuya, H.; Boyer, P.L.; Hughes, S.H.; Marquez, V.E. A conformationally locked analogue of the anti-HIV agent stavudine. An important correlation between pseudorotation and maximum amplitude. J. Med. Chem. **2003**, 46, 3292.
23. Corey, E.J.; Fuchs, P.L. A synthetic method for formyl ethynyl conversion (RCHO → RC ≡ CH or RC ≡ CR′). Tetrahedron Lett. **1972**, 3769.
24. Gillaizeau, I.; Lagoja, I.M.; Nolan, S.P.; Aueagne, V.; Rozenski, J.; Herdewijin, P.; Agrofoglio, L.A. Straightforward synthesis of labeled and unlabeled pyrimidine d4Ns via 2′,3′-diyne seco analogues through olefin metathesis reactions. Eur. J. Org. Chem. **2003**, 666.
25. Callant, P.; Haenens, L.D.; Vandewalle, M. An efficient preparation and the intramolecular cyclopropanation of α-diazo-β-ketophosphonates and α-diazophosphonoacatates. Synth. Commun. **1984**, 14, 155.
26. Kohgo, S.; Yamada, K.; Kitano, K.; Iwai, Y.; Sakata, S.; Ashida, N.; Hayakawa, H.; Nameki, D.; Kodama, E.; Matsuoka, M.; Mitsuya, H.; Ohrui, H. Design, efficient synthesis, and anti-HIV activity of 4′-*C*-cyano- and 4′-*C*-ethynyl-2′-deoxy purine nucleosides. Nucleosides, Nucleotides Nucleic Acids **2004**, 23, 671–690.