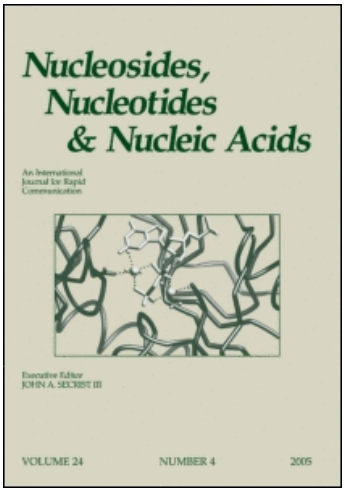

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Synthesis and Anti-HIV Activity of 4′-Cyano-2′,3′-didehydro-3′-deoxythymidine

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ABSTRACT

A new anti-HIV agent 4′-cyano-2′,3′-didehydro-3′-deoxythymidine (**9**) was synthesized by allylic substitution of the 3′,4′-unsaturated nucleoside **14**, having a leaving group at the 2′-position, with cyanotrimethylsilane in the presence of $SnCl_4$. Evaluation of the anti-HIV activity of **9** showed that this compound is much less potent than the recently reported 2′,3′-didehydro-3′-deoxy-4′-(ethynyl)thymidine (**1**).

Key Words: Anti-HIV; Cyano; Didehydro-3′-deoxythymidine; Unsaturated-sugar nucleoside; Phenylselenide anion; Allylic substitution; Organosilicon reagent.

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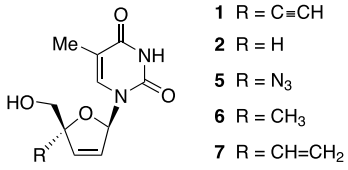
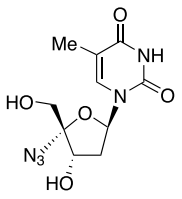
INTRODUCTION

During our recent studies on the reaction of organometallic reagents with 4′,5′-epoxy nucleosides,[1] 2′,3′-didehydro-3′-deoxy-4′-(ethynyl)thymidine (**1**) was synthesized.[2] Biological evaluation of **1** revealed that this compound is a more potent anti-HIV agent than the parent compound stavudine (**2**).[2–6] This finding was quite unexpected, since it has been reported that removal of the 3′-hydroxyl group in the anti-HIV active 4′-azidothymidine (**3**) leads to complete loss of the activity: compounds **4** and **5** are devoid of the activity.[7] An additional advantage of **1** is the fact that this compound is less toxic to CEM cell growth and less inhibitory to mitochondrial DNA synthesis than stavudine (**2**).



1 R = C≡CH
2 R = H
5 R = N_3
6 R = CH_3
7 R = $CH{=}CH_2$
8 R = $C{\equiv}CCH_3$
9 R = CN



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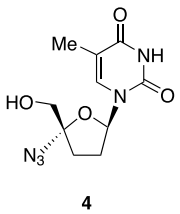

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As a result of our brief examination of structure-activity relationship (SAR) of 4′-carbon-substituted 2′,3′-didehydro-3′-deoxythymidine derivatives, it became apparent that the introduction of a methyl or vinyl group at the 4′-position leads to complete loss of the activity (**6**[8] and **7**),[2] and that alkylation of the ethynyl group of **1** is also discouraging (for example, **8**). From these results, one would readily expect that suitable 4′-substituents should possess an sp-hybridized carbon atom, and its size should be as small as possible. We describe here the synthesis and anti-HIV activity of 4′-cyano-2′,3′-didehydro-3′-deoxythymidine (**9**) motivated by the above considerations.

RESULTS AND DISCUSSION

Nucleosides having a cyano group at the 4′-position have mostly been synthesized by manipulation of the respective 4′-hydroxymethyl precursors.[9] In 1996, an allylic substitution of 3′,4′-unsaturated nucleosides having a leaving group at the 2′-position was reported from our laboratory.[10] This method provides a new entry to the synthesis of 4′-branched 2′,3′-didehydro-2′,3′-dideoxyribonucleosides. Also reported in this paper is the fact that, irrespective of the stereochemistry (''up'' or ''down'') of the 2′-leaving group, incoming nucleophiles attack the 4′-position from both the α- and β-faces, presumably due to the intervention of an oxonium intermediate. Since organosilicon reagents, including cyanotrimethylsilane, can be used as nucleophiles in combination with $SnCl_4$, this methodology was used for the present purpose.

Preparation of the 3′,4′-unsaturated thymine nucleoside **14**, to be used as a substrate for the allylic substitution, is shown in Scheme 1. Thus, 1-(β-D-ribofuranosyl) thymine was converted to the 2′,3′-epoxide **10** according to the published procedure.[11] Cleavage of the epoxide ring was conducted by reacting with a phenylselenide anion

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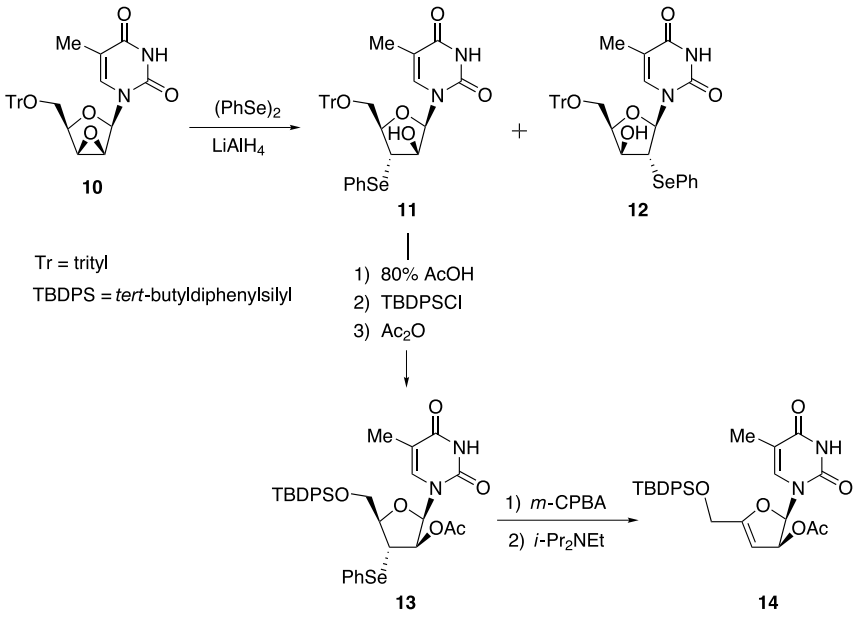
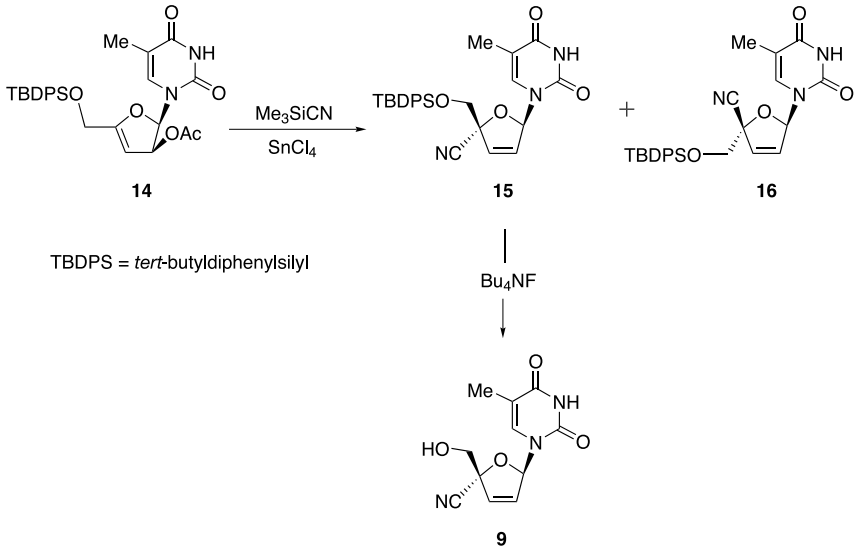


Scheme 1. Preparation of the 3′,4′-unsaturated thymine nucleoside.

prepared by reducing $(PhSe)_2$ with $LiAlH_4$[12] (in dioxane, for 2 h at room temperature) to give the desired 3′-phenylseleno derivative (**11**, 56%) as well as its 2′-isomer (**12**, 42%). The 5′-*O*-trityl group of **11** was replaced with *tert*-butyldiphenylsilyl group from the expectation that the anisotropic effect of this silyl protecting group would serve as a stereochemical determinant of the 4′-substituted products at a later stage. Further



Scheme 2. 3′,4′-Unsaturated thymine nucleoside reacting with cyanotrimethylsilane.

Table 1. Anti-HIV-1 activity in MT-2 cells.[a]

Compound	IC_{50} (μM)[b]	CC_{50} (μM)[c]
9	7.0 ± 2.6	>100
1	0.25 ± 0.14	>100
Stavudine (2)	1.3 ± 0.4	>100

[a]Data represent mean values for two separate experiments.
[b]Inhibitory concentration required to achieve 50% protection of MT-2 cells against the cytopathic effect of HIV-1.
[c]Cytotoxic concentration required to reduce the viability of mock-infected MT-2 cells by 50%.

acetylation of the 2′-hydroxyl group gave **13**. Oxidation of **13** with *m*-CPBA gave the corresponding selenoxide in 70% yield. Subsequent elimination of benzeneselenenic acid was carried out in THF at 70°C for 1 h in the presence of *i*-Pr_2NEt. Despite the presence of two *syn*-hydrogens (H-2′ and H-4′) available for the elimination, exclusive removal of the H-4′ was observed in this reaction to give the 3′,4′-unsaturated derivative **14** as the sole product in 67% yield.

When **14** was reacted with cyanotrimethylsilane (10 equiv.) in the presence of $SnCl_4$ (5 equiv.) in CH_2Cl_2 at −70°C for 5 h, no S_N2 product was formed. Instead two isomeric products **15** (48%) and **16** (43%) resulting from allylic substitution were isolated as shown in Scheme 2. The depicted stereochemistry of **15** at the 4′-position was deduced from the ^1H NMR observation that its 5-Me resonance appeared at a significantly higher field of δ 1.53 when compared with that of **16** (δ 1.95) or **14** (δ 1.92), due to the anisotropic effect of the phenyl ring in the 5′-*O*-protecting group. Finally, removal of the 5′-*O*-silyl group in **15** was carried out with Bu_4NF in THF to give the desired 4′-cyano analogue **9** in almost quantitative yield.

Compound **9** thus synthesized was assayed for its ability to inhibit the replication of HIV-1 in MT-2 cell culture by the reported procedure.[13] In Table 1 are shown the assay results of **9** together with those of **1** and the parent compound stavudine (**2**). Although the 4′-cyano analogue (**9**) was found to be active as we anticipated, its activity is almost five times lower than that of stavudine (**2**). Further SAR studies on this class of compounds are currently under investigation in our laboratory.

EXPERIMENTAL SECTION

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

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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-[2,3-Anhydro-5-*O*-trityl-β-D-lyxofuranosyl]thymine (10). To a pyridine (30 mL) suspension of 1-(β-D-ribofuranosyl)thymine (5.16 g, 20 mmol) was added TrCl (6.69 g, 24 mmol) at 0°C under Ar atmosphere, and the reaction mixture was stirred at rt overnight. To this was added MsCl (4.6 mL, 60 mL), and the mixture was stirred at 0°C for 5 h. The reaction mixture was quenched by adding ice chips and then partitioned between $CHCl_3/H_2O$ (200 mL × 2/100 mL). Column chromatography (4% MeOH in CH_2Cl_2) of the organic layer gave 1-(2,3-di-*O*-mesyl-5-*O*-trityl-β-D-ribofuranosyl)thymine, which was dissolved in EtOH (200 mL). To the EtOH solution of the product was added 1 M NaOH (200 mL), and the mixture was stirred at refluxing temperature for 2 h. The reaction mixture was neutralized with 1 M HCl, evaporated to dryness, and partitioned between EtOAc/H_2O (200 mL/50 mL × 4). Column chromatography (hexane/EtOAc = 1/4) of the organic layer gave **10** (3.80 g, 39%) as a solid: mp 174–175°C; ^{1}H NMR ($CDCl_3$)δ1.83 (3H, d, $J_{5\text{-Me},6}$ = 1.3 Hz, 5-Me), 3.39 (1H, dd, $J_{5'a,5'b}$ = 9.7 and $J_{4',5'a}$ = 5.5 Hz, H-5′), 3.49 (1H, dd, $J_{5'a,5'b}$ = 9.7 and $J_{4',5'b}$ = 5.9 Hz, H-5′), 3.87 (1H, dd, $J_{3',4'}$ = 0.8 and $J_{2',3'}$ = 2.8 Hz, H-3′), 3.91 (1H, dd, $J_{1',2'}$ = 0.7 and $J_{2',3'}$ = 2.8 Hz, H-2′), 4.14–4.17 (1H, m, H-4′), 6.19 (1H, d, $J_{1',2'}$ = 0.7 Hz, H-1′), 7.24–7.33 (9H, m, Tr), 6.98 (1H, d, $J_{5\text{-Me},6}$ = 1.3 Hz, H-6), 7.46–7.49 (6H, m, Tr), 8.61 (1H, br NH); FAB-MS (*m/z*) 483 (M^++ H).

1-(3-Deoxy-3-phenylseleno-5-*O*-trityl-β-D-arabinofuranosyl)thymine (11) and 1-(2-Deoxy-2-phenylseleno-5-*O*-trityl-β-D-xylofuranosyl)thymine (12). To a dioxane (20 mL) suspension of the phenylselenide anion,[12] prepared from $(PhSe)_2$ (3.94 g, 12.61 mmol) and $LiAlH_4$ (359 mg, 9.46 mmol), was added **10** (3.80 g, 7.88 mmol) dissolved in dioxane (20 mL), and the mixture was stirred at rt for 2 h under Ar atmosphere. Neutralization of the reaction mixture with AcOH followed by column chromatography (hexane/EtOAc = 1/2) gave **11** (2.82 g, 56%, foam) and **12** (2.12 g, 42%, foam).

Physical data of **11**: ^{1}H NMR ($CDCl_3$, after addition of D_2O)δ2.05 (3H, s, 5-Me), 3.43 (1H, dd, $J_{5'a,5'b}$ = 11.0 and $J_{4',5'a}$ = 3.6 Hz, H-5′), 3.59–3.65 (2H, m, H-5′ and H-3′), 3.97–4.01 (1H, m, H-4′), 4.48 (1H, dd, $J_{2',3'}$ = 5.4 and $J_{1',2'}$ = 5.2 Hz, H-2′), 6.05 (1H, d, $J_{1',2'}$ = 5.2 Hz, H-1′), 7.21–7.32, 7.32–7.38 and 7.46–7.53 (20H, each as m, Tr and SePh), 7.71 (1H, s, H-6); FAB-MS (KI, *m/z*) 679 (M^++ K).

Physical data of **12**: ^{1}H NMR ($CDCl_3$, after addition of D_2O)δ1.65 (3H, d, $J_{5\text{-Me},6}$ = 1.2 Hz, 5-Me), 3.51 (1H, dd, $J_{5'a,5'b}$ = 10.6 and $J_{4',5'a}$ = 4.0 Hz, H-5′), 3.58 (1H, dd, $J_{5'a,5'b}$ = 10.6 and $J_{4',5'b}$ = 4.4 Hz, H-5′), 3.76 (1H, dd, $J_{3',4'}$ = 4.6 and $J_{2',3'}$ = 3.2 Hz, H-3′), 4.23–4.25 (1H, m, H-4′), 4.29 (1H, dd, $J_{2',3'}$ = 3.2 and $J_{1',2'}$ = 4.4 Hz, H-2′), 6.01 (1H, d, $J_{1',2'}$ = 4.4 Hz, H-1′), 7.25–7.34, 7.41–7.44 and 7.61–7.63 (21H, each as m, Tr and SePh), 6.98 (1H, d, $J_{5\text{-Me},6}$ = 1.3 Hz, H-6); FAB-MS (KI, *m/z*) 679 (M^+ + K).

1-[2-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-phenylseleno-β-D-arabinofuranosyl]thymine (13). An 80% AcOH (40 mL) solution of **11** (1.67 g, 2.61 mmol) was stirred at 80°C for 1h. Evaporation of the reaction mixture followed by column chromatography (3% MeOH in CH_2Cl_2) gave 1-(3-deoxy-3-phenylseleno-β-D-arabinofuranosyl)thymine (0.57 g, 55%) as a syrup. To a pyridine (7 mL) solution of this

product (563.9 mg, 1.42 mmol) was added *t*-butyldiphenylsilyl chloride (0.55 mL, 2.13 mmol). After stirring overnight at rt, the reaction mixture was quenched with EtOH and evaporated to dryness. Column chromatography (hexane/AcOEt = 1/4) of the residue gave 1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-phenylseleno-β-D-arabinofuranosyl]thymine (675.8 mg, 75%) as a syrup. A mixture of this product (633.4 mg, 1.0 mmol), *i*-Pr_2NEt (0.52 mL, 3.0 mmol), Ac_2O (0.19 mL, 2.0 mmmol), and DMAP (24.4 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 1 h. The reaction mixture was partitioned between $CHCl_3$/sat. $NaHCO_3$ (150 mLx2/50 mL). Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **13** (599.3 mg, 88%) as a foam: ^{1}H NMR ($CDCl_3$)δ1.09 (9H, s, *t*-Bu), 1.65 (3H, s, 5-Me), 1.89 (3H, s, Ac), 3.82 (1H, dd, $J_{3',4'}$ = 8.6 and $J_{2',3'}$ = 6.0 Hz, H-3′), 3.89–3.95 (2H, m, H-5′), 4.01–4.04 (1H, m, H-4′), 5.54 (1H, dd, $J_{2',3'}$ = 6.0 and $J_{1',2'}$ = 5.2 Hz, H-2′), 6.09 (1H, d, $J_{1',2'}$ = 5.2 Hz, H-1′), 7.29–7.48, 7.59–7.67 (16H, each as m, SiPh, SePh, and H-6), 8.18 (1H, br, NH); FAB-MS (*m/z*) 679 (M^++ H), 621 (M^+-*t*-Bu).

1-[2-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-β-L-*glycero*-pent-3-enofuranosyl] thymine (14). To a CH_2Cl_2 (8 mL) solution of **13** (563.8 mg, 0.83 mmol) was added *m*-CPBA (172.6 mg, 1.0 mmol) in CH_2Cl_2 (4 mL) at 0°C, and the mixture was stirred for 30 min. The reaction mixture was neutralized with Et_3N and partitioned between $CHCl_3$/sat. $NaHCO_3$ (150 mL × 3/50 mL). Column chromatography (3% MeOH in CH_2Cl_2) of the organic layer gave the corresponding selenoxide (403.4 mg, 70%) as a foam. A mixture of this selenoxide (372.3 mg, 0.54 mmol) and *i*-Pr_2NEt (0.74 mL, 1.61 mmol) in THF (7 mL) was stirred at 70°C under Ar atmosphere for 1 h. Evaporation of the reaction mixture followed by column chromatography (hexane/EtOAc = 2/1) gave **14** (188.4 mg, 67%) as a foam: ^{1}H NMR ($CDCl_3$)δ1.09 (9H, s, *t*-Bu), 1.92 (3H, d, $J_{5\text{-Me},6}$ = 1.2 Hz, 5-Me), 1.95 (3H, s, Ac), 4.27 (1H, ddd, $J_{5'a,5'b}$ = 15.0 and $J_{2',5'a}$ = $J_{3',5'a}$ = 1.6 Hz, H-5′), 4.32 (1H, ddd, $J_{5'a,5'b}$ = 15.0 and $J_{2',5'b}$ = $J_{3',5'b}$ = 1.2 Hz, H-5′), 5.29–5.30 (1H, m, H-3′), 5.83 (1H, m, H-2′), 6.66 (1H, d, $J_{1',2'}$ = 7.2 Hz, H-1′), 7.01 (1H, q, $J_{5\text{-Me},6}$ = 1.2 Hz, H-6), 7.39–7.49 and 7.66–7.70 (10H, m, SiPh), 8.20 (1H, br, NH); FAB-MS (*m/z*) 521 (M^++ H) and 463 (M^+-*t*-Bu).

5′-*O*-(*tert*-Butyldiphenylsilyl)-4′-cyano-2′,3′-didehydro-3′-deoxythymidine (15) and Its 4′-epimer (16). To a CH_2Cl_2 (3.5 mL) solution of **14** (52.1 mg, 0.1 mmol) was added Me_3SiCN (0.13 mL, 1.0 mmol) and then $SnCl_4$ (0.5 mL, 0.5 mmol) at −70°C under Ar atmosphere. After being stirred at −70°C for 5 h, the reaction mixture was partitioned between $CHCl_3$/sat. $NaHCO_3$ (60 mL × 3/20 mL). Purification of the organic layer by preparative TLC (hexane/AcOEt = 1/1) gave **15** (23.3 mg, 48%, syrup) and **16** (20.8 mg, 43%, syrup). Physical data of **15**: ^{1}H NMR ($CDCl_3$)δ1.11 (9H, s, *t*-Bu), 1.53 (3H, d, $J_{5\text{-Me},6}$ = 1.2 Hz, 5-Me), 3.94 (1H, d, $J_{5'a,5'b}$ = 11.2 Hz, H-5′), 4.04 (1H, d, $J_{5'a,5'b}$ = 11.2 Hz, H-5′), 6.15 (1H, dd, $J_{1',3'}$ = 1.2 and $J_{2',3'}$ = 6.0 Hz, H-3′), 6.39 (1H, dd, $J_{1',2'}$ = 2.0 and $J_{2',3'}$ = 6.0 Hz, H-2′), 6.80 (1H, d, $J_{5\text{-Me},6}$ = 1.2 Hz, H-6), 7.23 (1H, dd, $J_{1',3'}$ = 1.2 and $J_{1',2'}$ = 2.0 Hz, H-1′), 7.37–7.49 and 7.62–7.67 (10H, each as m, SiPh), 8.87 (1H, br, NH); FAB-MS (*m/z*) 488 (M^++ H). Physical data of **16**: ^{1}H NMR ($CDCl_3$) δ1.09 (9H, s, *t*-Bu), 1.95 (3H, d, $J_{5\text{-Me},6}$ = 1.2 Hz, 5-Me), 3.77 (1H, d, $J_{5'a,5'b}$ = 10.0 Hz, H-5′), 3.93 (1H, d, $J_{5'a,5'b}$ = 10.0 Hz, H-5′), 6.13 (1H, dd, $J_{1',3'}$ = 1.8 and $J_{2',3'}$ = 6.0 Hz, H-3′), 6.40 (1H, dd, $J_{1',2'}$ = 1.8 and $J_{2',3'}$ = 6.0 Hz, H-2′),

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6.99 (1H, d, $J_{5\text{-Me},6}$ = 1.2 Hz, H-6), 7.10 (1H, t, $J_{1',2'} = J_{1',3'}$ = 1.8 Hz, H-1′), 7.40–7.49 and 7.63–7.67 (10H, each as m SiPh), 8.75(1H, br, NH); FAB-MS (*m/z*) 488 ($M^+ + H$).

4′-Cyano-2′,3′-didehydro-3′-deoxythymidine (9). To a THF (4 mL) solution of **15** (48.1 mg, 0.099 mmol) was added $Bu_4NF{\cdot}3H_2O$ (39.2 mg, 0.15 mmol) at 0°C, and the mixture was stirred at rt for 1 h. Evaporation of the reaction mixture followed by column chromatography (3% MeOH in CH_2Cl_2) of the residue gave **9** (24.5 mg, 99%) as a solid: mp 234–237°C; IR (KBr) 2260 cm^{-1} (CN); UV(MeOH)λ_{max} 267 nm (ε12700),λ_{min} 235 nm (ε5900); ^{1}H NMR (DMSO-d_6 after addition of D_2O) δ1.74 (3H d, $J_{5\text{-Me},6}$ = 1.2 Hz, 5-Me), 3.74 (1H, d, J_{gem} = 11.9 Hz, H-5′), 3.79 (1H, d, J_{gem} = 11.9 Hz, H-5′), 6.33 (1H, dd, $J_{1',3'}$ = 1.3, $J_{2',3'}$ = 5.8 Hz, H-3′), 6.55 (1H, dd, $J_{1',2'}$ = 2.2, $J_{2',3'}$ = 5.8 Hz, H-2′), 7.03 (1H, dd, $J_{1',2'}$ = 2.2, $J_{2',3'}$ = 1.3 Hz, H-1′), 7.33 (1H, d, $J_{5\text{-Me},6}$ = 1.2 Hz, H-6); FAB-MS (*m/z*) 250 ($M^+ + H$). *Anal*. Calcd for $C_{11}H_{11}N_3O_4{\cdot}1/5CH_2Cl_2$: C, 52.05; H, 4.44; N, 16.26. Found: C, 52.11; H, 3.90; N, 16.13.

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