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Nucleophilic Substitution at the 4′-Position of Nucleosides: New Access to a Promising Anti-HIV Agent 2′,3′-Didehydro-3′-deoxy-4′-ethynylthymidine

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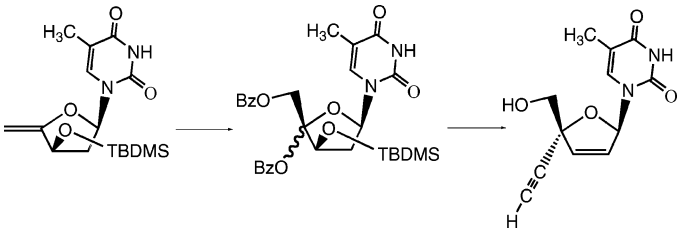
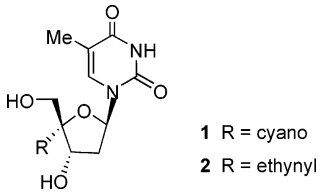


For the synthesis of 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine (**8**: 4′-Ed4T), a recently reported promising anti-HIV agent, a new approach was developed. Since treatment of 1-(2,5-dideoxy-β-L-*glycero*-pent-4-enofuranosyl)thymine with $Pb(OBz)_4$ allowed the introduction of the 4′-benzoyloxy leaving group, nucleophilic substitution at the 4′-position became feasible for the first time. Thus, reaction between the 4′-benzoyloxy derivative (**14**) and $Me_3SiC{\equiv}CAl(Et)Cl$ as a nucleophile led to the isolation of the desired 4′-"down"-ethynyl derivative (**18**) stereoselectively in 62% yield. As an application of this approach, other 4′-substituted nucleosides, such as the 4′-allyl (**24a**) and 4′-cyano (**26a**) derivatives, were synthesized using organosilicon reagents. In these instances, pretreatment of **14** with $MeAlCl_2$ was necessary.

Introduction

Nucleosides constitute an important class of biologically active compounds, especially as antiviral and antitumor agents.[1] Recently, their 4′-carbon-substituted analogues have attracted much attention due to the reported potent anti-HIV activity of 4′-cyanothymidine (**1**)[2] and 4′-ethynylthymidine (**2**).[3] Synthesis of these 4′-carbon-substituted nucleosides has mostly relied on manipulations of the 4′-hydroxymethyl derivative of nucleosides or sugars that can be prepared by the well-known aldol−Cannizzaro reaction of the corresponding aldehyde,[4,5] although several other newer synthetic methods for this class of nucleosides are also available.[6]



1 R = cyano
2 R = ethynyl

With the aim of developing a new synthetic method for this class of nucleosides with a wider scope, we have already carried out ring-opening of 4′,5′-epoxynucleosides with organosilicon[7] or organoaluminum[8] reagents. One example is shown in Scheme 1 for the preparation of the 4′-methyl, 4′-vinyl, and 4′-ethynyl analogues of 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine. Thus, oxidation of the 4′,5′-unsaturated derivative **3**[9] with an acetone

(1) For a review, see: *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993.

(2) O-Yang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. *Tetrahedron Lett*. **1992**, *33*, 37.

(3) Kodama, E.; Kohgo, S.; Kitano, K.; Machida, H.; Gatanda, H.; Shigeta, S.; Matsuoka, M.; Ohrui, H.; Mitsuya, H. *Antimicrob. Agents Chemother*. **2001**, *45*, 1539.

(4) Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. *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. *J. Med. Chem*. **2000**, *43*, 4516.

(6) For an excellent review dealing with the synthesis and anti-HIV activity of 4′-*C*-substituted nucleosides, see: Hayakawa, H.; Kohgo, S.; Kitano, K.; Ashida, N.; Kodama, E.; Mitsuya, H.; Ohrui, H. *Antiviral Chem. Chemother*. **2004**, *15*, 169.

(7) Haraguchi, K.; Takeda, S.; Tanaka, H. *Org. Lett*. **2003**, *5*, 1399.

(8) Haraguchi, K.; Takeda, S.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3775.

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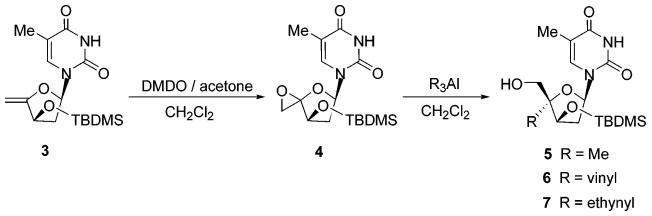
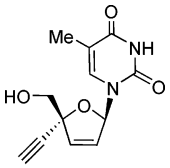
SCHEME 1



solution of dimethyldioxirane (DMDO) gave the epoxide **4**, which was then reacted with organoaluminum reagents (R_3Al) to furnish the 4′-carbon-substituted products (**5**−**7**).[8]

During this study, 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine (**8**: 4′-Ed4T), prepared from **7** by a series of conventional



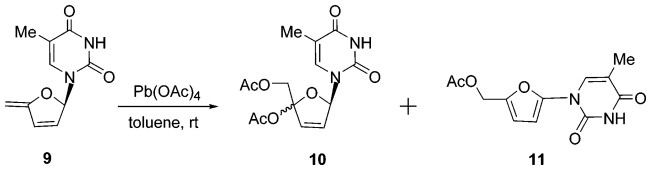
reactions, was found to be more potent against HIV than the parent compound stavudine (d4T) and much less toxic to various cells and also to mitochondrial DNA synthesis.[10] This compound has several additional advantages as a promising anti-HIV agent: (1) it is a better substrate for human thymidine kinase than d4T, (2) it is very much resistant to catabolism by thymidine phosphorylase, and (3) its activity enhances in the presence of a major mutation K103N, a known resistant mutation for some non-nucleoside reverse transcriptase inhibitors.[10,11]

To further evaluate 4′-Ed4T (**8**) in animal studies, we were in need of an alternative synthetic method suitable for its large scale preparation, since the route shown in Scheme 1 is frustrated by inaccessibility of a highly concentrated acetone solution of DMDO. One apparent means of settling this problem is to introduce a leaving group to the 4′-position and execute nucleophilic ethynylation. However, to the best of our knowledge, there have been no precedents available for the introduction of a leaving group to the 4′-position of nucleosides. These situations led us to carry out the present study. In this paper, we demonstrate that the reaction between 1-(2,5-dideoxy-β-L-*glycero*-pent-4-enofuranosyl)thymine and $Pb(OCOR)_4$ allows introduction of an acyloxy leaving group to the 4′-position, and that nucleophilic ethynylation of the resulting 4′-acyloxy derivative with an organoaluminum reagent enabled us to prepare the title compound (**8**) in a fairly large scale. Introduction of allyl and cyano groups was also examined briefly by the use of organosilicon reagents.

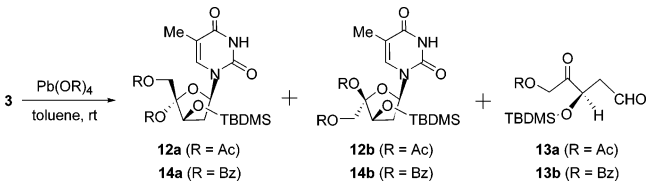
Results and Discussion

Diacyloxylation of 4′,5′-Unsaturated Thymine Nucleosides. Although vicinal diacetoxylation of olefins with $Pb(OAc)_4$ has been known for a long time, this reaction usually leads to a complex mixture of products due to concomitant occurrence of other reaction pathways such as substitution of hydrogen at the allylic position, skeletal rearrangement, double bond migration, and C−C bond cleavage.[12] Nevertheless, some successful examples have been reported in the case of electron-rich olefins such as enol ethers,[13,14] since the initial step of the diacetoxylation is considered to be electrophilic in nature.

SCHEME 2



SCHEME 3



We first thought that reaction of $Pb(OAc)_4$ with the conjugated diene **9**[15] (Scheme 2) would allow regioselective vicinal diacetoxylation to give the 4′-acetoxy-d4T derivative **10** due to the presence of an enol ether structure and that this reaction, when combined with subsequent nucleophilic 4′-ethynylation, might constitute the most straightforward route to 4′-Ed4T (**8**).

Upon reacting $Pb(OAc)_4$ (1.5 equiv) with **9** prepared by the published procedure[16] in toluene at room temperature for 5 h, two products (**10** and **11**) were detected by TLC analysis (hexane/EtOAc = 1/2: **10**, R_f 0.2; **11**, R_f 0.38). Although silica gel column chromatography allowed the isolation and structural confirmation of these products (**10**, ca. 35%; **11**, 50%), the 4′-acetoxy derivative **10** appeared to be too unstable for further reaction, liberating **11** during evaporation of the solvent or even on standing at room temperature. This fact led us to examine diacyloxylation of the previously employed 4′,5′-unsaturated derivative (**3**).[8]

When the reaction of **3** with $Pb(OAc)_4$ was carried out under similar reaction conditions to those employed for **9**, the 4′-acetoxy derivative **12a** was obtained (Scheme 3),[17] but the yield was only 28%. The main product in this reaction was devoid of UV absorption, and its FAB-MS [*m*/*z* 289 (M^+ + H)] and ^1H NMR [δ 9.71 (1H, t, J = 1.3 Hz, CHO)] spectra suggested the depicted aldehyde structure **13a** (60%).

It is conceivable that acidic reaction media encourages protonation to the 4′-acetoxy group of **12**, which renders attack of a nucleophile (acetate anion?) to its carbonyl group feasible. On the basis of this assumption, the diacetoxylation was re-

(9) For the preparation of **3** and **19**, see Supporting Information.

(10) Dutschman, G. E.; Grill, S. P.; Gullen, E. A.; Haraguchi, K.; Takeda, S.; Tanaka, H.; Baba, M.; Cheng, Y.-C. *Antimicrob. Agents Chemother*. **2004**, *48*, 1640.

(11) Nitanda, T.; Wang, X.; Kumamoto, H.; Haraguchi, K.; Tanaka, H.; Cheng, Y.-C.; Baba, M. *Antimicrob. Agents Chemother*. **2005**, *49*, 3355.

(12) Mihailovic, M. L.; Cekovic, Z.; Lorenc, L. In *Organic Syntheses by Oxidation with Metal Compound*; Mijs, W. J., De Jonge, C. R. H. I., Eds.; Plenum Press: New York and London, 1986; pp 741−815.

(13) Criegee, R.; Dimroth, P.; Noll, K.; Simon, R.; Weis, C. *Chem. Ber*.**1957**, *90*, 1070.

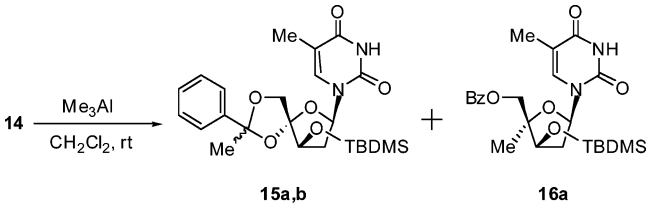
(14) Müller, R.; Plieninger, H. *Chem. Ber*. **1959**, *92*, 3009.

(15) For an example of the reaction of conjugated dienes with $Pb(OAc)_4$, see: Uemura, S.; Tabata, A.; Okano, M. *Chem. Commun.* **1970**, 1630.

(16) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem*. **1974**, *39*, 3573.

(17) The depicted stereochemistry of **12a** was determined by NOE experiment: H-5′b/H-6 (1.7%). Of the two protons at the 5′-position, the one that appears at a higher field is designated as H-5′a, and the other as H-5′b, throughout the text and Experimental Section.

SCHEME 4



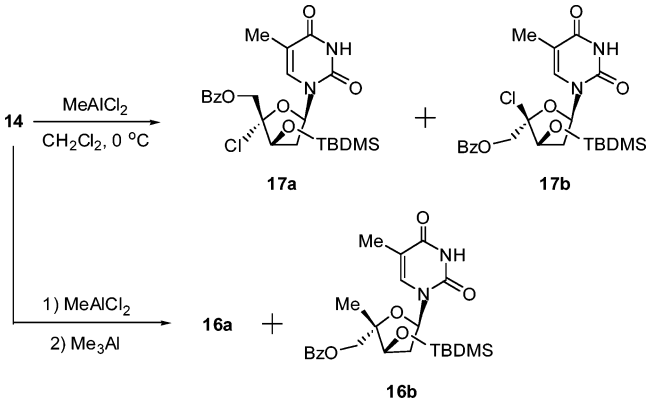
examined by adding bases. After several attempts (imidazole and collidine), the presence of *i*-Pr_2NEt (1.5 equiv) was found to prevent the formation of ***13a*** completely, but the yield of **12** (32%, **12a**/**12b** = 1/0.4) remained unchanged.

Yukawa and Sasaki briefly reported that,[18] although $Pb(OAc)_4$ did not work for vicinal diacetoxylation of styrene, use of lead tetracarboxylate prepared from higher carboxylic acids gave styrene glycol dicarboxylates. When $Pb(OBz)_4$ (1.5 equiv), prepared from $Pb(OAc)_4$ and benzoic acid,[19] was reacted with **3** in the presence of *i*-Pr_2NEt (1.5 equiv) in toluene at room temperature for 14 h, the 4′-benzoyloxy derivative **14** was obtained in 71% yield (**14a**/**14b** = 1/0.8) without forming the aldehyde **13b**. After HPLC separation, the stereochemistry of **14a** and **14b** was confirmed by their NOE experiments: **14a**, H-5′b/H-6 (3.4%) and H-5′a/H-6 (1.4%); **14b**, H-5′b/H-3′ (0.7%).

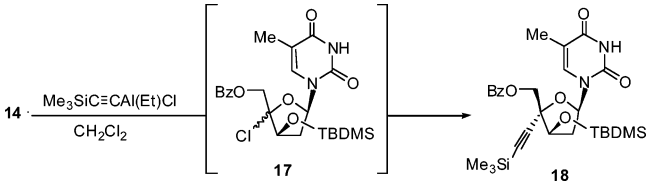
Reaction of the 4′-Benzoyloxy Derivative (14) with Organoaluminum Reagents. Reaction of the 4′-benzoyloxy derivative (**14**) with a commercially available hexane solution of Me_3Al was first carried out as a model experiment. As shown in Scheme 4, three isomeric products [*m*/*z* 475 ($M^+ + H$)] were formed upon reacting **14** with 4.0 equiv of Me_3Al. The minor product was the expected 4′-methyl derivative **16a** (15%),[20] which underwent debenzoylation by treatment with NaOMe in MeOH. Silica gel column chromatography gave other two products as a mixture of two diastereomers (76%, **15a**/**15b** = 1/1). Their spiro structure was assumed based on the fact that they did not undergo debenzoylation with NaOMe in MeOH. HPLC separation of the mixture followed by NOE experiment[21] led us to propose the depicted 4′-configuration for both diastereomers.

On the other hand, when **14** was reacted with a hexane solution of $MeAlCl_2$ (4.0 equiv) in CH_2Cl_2 for 2 h at 0 °C (Scheme 5), the 4′-methyl derivative was not detected, but instead two isomeric 4′-chlorinated products (**17a**, 53%; **17b**, 14%)[22] were formed. These compounds are rather unstable (decomposed during TLC analysis), but they can be isolated by HPLC. Independent treatment of the isolated **17a** or **17b** with $MeAlCl_2$ in CH_2Cl_2 again resulted in a mixture of both compounds, showing that they are interconvertible in the presence of $MeAlCl_2$. It was found that further treatment of the above reaction mixture containing **17** with Me_3Al (6.0 equiv, at room temperature for 23 h) gave the 4′-methyl derivatives (**16a**, 14%; **16b**, 19%) in one-pot manner. Although the yield

SCHEME 5



SCHEME 6



of **16** was not high, formation of the spiro derivative **15** was suppressed to a trace amount.

With these experimental results in hand, introduction of an ethynyl group to the 4′-position of **14** was investigated. One-pot treatment of **14** with $MeAlCl_2$ followed by triethynylaluminum, previously employed for epoxide ring-opening,[8] did not allow the introduction of an ethynyl group. On the other hand, the use of ethyl[trimethylsilyl(ethynyl)]aluminum chloride $Me_3SiC{\equiv}CAl(Et)Cl$[23] in this one-pot reaction, in place of triethynylaluminum, furnished the 4′-ethynyl derivative **18** as a single isomer in 51% yield.[24] During this ethynylation reaction of **14**, we noticed that the ethynylaluminum reagent itself was capable of chlorinating **14**, and that the 4′-ethynylation gradually took place afterward. Thus, when **14** was reacted with 8.0 equiv of $Me_3SiC{\equiv}CAl(Et)Cl$ in CH_2Cl_2 at room temperature overnight (Scheme 6), **18** was formed stereoselectively and isolated in 62% yield by silica gel column chromatography. This ethynylation can be performed in several-10 g scale. To ascertain that both isomers of the 4′-chloro intermediate (**17**) lead to the formation of **18**, the reaction of $Me_3SiC{\equiv}CAl(Et)Cl$ with the two isomers was independently carried out. As a result, both **17a** and **17b** gave **18** exclusively in 71% and 50% yields, respectively.

It is not clear why **17** furnished the desired 4′-α-ethynyl derivative **18** exclusively while it gave two isomeric 4′-methyl derivatives (**16a** and **16b**, Scheme 5) upon reacting with Me_3Al.[25] However, it is certainly true that the 3′-*β*-*O*-TBDMS group had played an important role in the above ethynylation, since the 4′-benzoyloxy derivative **19**[9] with the opposite 3′-configu-

(18) Yukawa, Y.; Sakai, M. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 761.

(19) For the preparation of $Pb(OBz)_4$, see: Bachman, G. B.; Wittmann, J. W. *J. Org. Chem.* **1963**, *28*, 65.

(20) The depicted stereochemistry of **16a** was determined by NOE experiment: H-6/H-5′a (1.8%), H-6/H-5′b (3.6%), H-1′/CH_3-4′ (1.4%), and H-3′/CH_3-4′ (3.6%).

(21) NOE data for **15a** (less polar) and **15b** (more polar) are as follows: **15a**, H-5′a/H-6 (2.5%); **15b**, H-5′b/H-6 (3.3%).

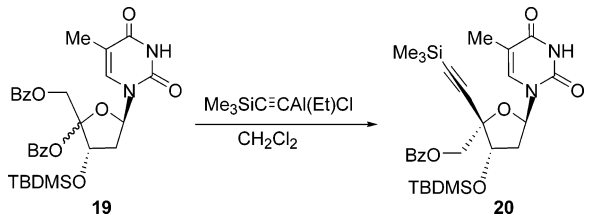
(22) NOE data for **17a** and **17b** are as follows: **17a**, H-5′b/H-6 (1.3%) and H-5′a/H-6 (1.1%); **17b**, H-3′/H-5′a (1.4%).

(23) This reagent has been successfully used for the introduction of the trimethylsilylethynyl group to the anomeric position of uracil nucleoside, see: Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem.* **1995**, *60*, 656.

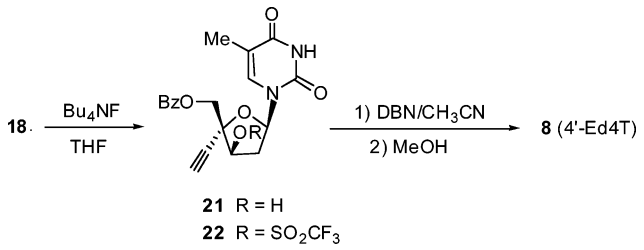
(24) The depicted stereochemistry of **18** was determined by NOE experiment: H-5′a,b/H-6 (6.5%).

(25) The bulkiness of aluminum reagent working in this reaction is certainly one important determinant for the observed stereochemical outcome, but it is difficult to know its actual structure.

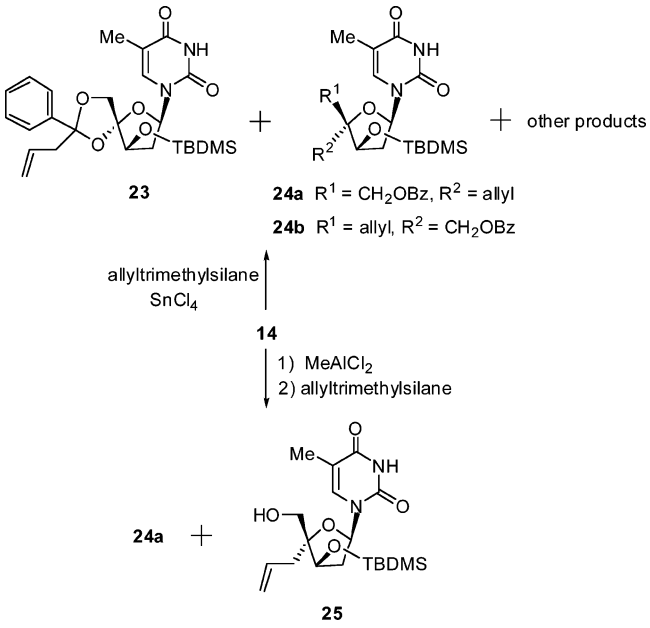
SCHEME 7



SCHEME 8



SCHEME 9

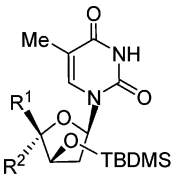


ration gave solely the 4′-*β*-ethynylated product **20**[26] in 31% yield (Scheme 7).

Preparation of 4′-Ed4T (8). The above-prepared **18** was converted to 4′-Ed4T (**8**) by a conventional reaction sequence (Scheme 8). Thus, desilylation of **18** with Bu_4NF in THF gave the 3′-hydroxy derivative **21** (97%), which was sulfonylated with $(CF_3SO_2)O$ in the presence of pyridine in THF. The resulting 3′-triflate **22** was not isolated, instead extracted with $CHCl_3$, and subjected to *β*-elimination with DBN/CH_3CN. Removal of the 5′-*O*-benzoyl group was carried out in a one-pot manner by adding MeOH to the elimination mixture. This procedure allowed preparation of the title compound 4′-Ed4T (**8**) in 69% overall yield from **21**.

Synthesis of the 4′-Allyl and 4′-Cyano Derivatives. To demonstrate the utility of the 4′-benzoyloxy derivative (**14**), preparation of other 4′-carbon-substituted analogues was examined by using organosilicon reagents. As shown in Scheme 9, when allyltrimethylsilane (5 equiv) was reacted with **14** in the presence of $SnCl_4$ (3 equiv) in CH_2Cl_2, many products were formed, from which the spiro derivative **23** (14%, obtained as a single isomer, stereochemistry of the newly formed ketal carbon is not known) and the two isomeric 4′-allyl derivatives (**24a**, 9.4%; **24b**, 14%) were isolated. The observed formation of the spiro derivative (**23**) in a considerable amount was certainly reminiscent of the reaction with Me_3Al shown in Scheme 4.

We, therefore, pretreated **17** with $MeAlCl_2$ (5.0 equiv) and then reacted with allyltrimethylsilane (6.0 equiv) in a one-pot manner. This reaction suppressed the formation of **23** to a trace amount and gave stereoselectively the 4′-α-allyl derivative **24a** (31%) and its 5′-*O*-debenzoylated product **25** (11%) without forming **24b**. In contrast to this, the 4′-cyanation carried out under similar reaction conditions by using cyanotrimethylsilane produced the 4′-α-cyano (**26a**, 29%) as well as the 4′-*β*-cyano (**26b**, 23%) derivatives.



26a $R^1 = CH_2OBz$, $R^2 = CN$

26b $R^1 = CN$, $R^2 = CH_2OBz$

Conclusion

As an alternative method for the synthesis of 4′-Ed4T (**8**), a nucleophilic substitution approach was investigated. The first step, introduction of a leaving group to the 4′-position, was accomplished by vicinal diacyloxylation of the 4′,5′-unsaturated thymine-nucleoside **3** with $Pb(OBz)_4$ in the presence of *i*-Pr_2-NEt. The formation of the 4′-benzoloxy derivative (**14**) in this reaction constitutes the first example of the introduction of a leaving group to the 4′-position of nucleosides.

Nucleophilic ethynylation of the 4′-benzoyloxy group of **14** was successfully carried out by using $Me_3SiC{\equiv}CAl(Et)Cl$ as a nucleophile to give the desired 4′-"down"-ethynyl derivative **18** exclusively. It was found that this ethynylation proceeds through the 4′-chloro intermediate (**17**), and the presence of the 3′-*O*-silyl group of **14** is crucial for the stereochemical outcome.

Allylation and cyanation of **14** were also examined briefly by using allyltrimethylsilane and cyanotrimethylsilane, respectively. In these instances, pretreatment of **14** with $MeAlCl_2$ was necessary.

Experimental Section

Reaction of $Pb(OBz)_4$ with 3 in the Presence of *i*-Pr_2NEt: Preparation of 1-[5-*O*-Benzoyl-4-benzoyloxy-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-*threo*-pentofuranosyl]thymine (14a) and 1-[5-*O*-Benzoyl-4-benzoyloxy-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-L-*erythro*-pentofuranosyl]thymine (14b). To a toluene (70 mL) solution of **3** (3.98 g, 11.76 mmol) were added *i*-Pr_2NEt (5.1 mL, 29.4 mmol) and $Pb(OBz)_4$ (20.33 g, 29.4 mmol) at 0 °C under Ar atmosphere. The mixture was stirred at room temperature for 4 h, quenched with saturated aq $NaHCO_3$, and filtered through a Celite pad. The filtrate was partitioned between $CHCl_3$/saturated aq $NaHCO_3$. Column chromatography (hexane/EtOAc = 3/1) of the organic layer gave a mixture of **14a** and **14b** (4.84 g, 71%,

(26) The depicted stereochemistry of **20** was determined by its NOE data [*tert*-butyl/H-5′a,b (0.3%); $SiMe_3$/H-6 (0.8%)] as well as by the fact that its H-5′ resonance appeared as a singlet.

14a/**14b** = 1/0.8). Compounds **14a** (foam, t_R 13.7 min) and **14b** (foam, t_R 15.2 min) were separated by HPLC (CH_2Cl_2/EtOAc = 5/1).

Physical data for **14a**: UV (MeOH) λ_{max} 266 nm (ϵ 11600), λ_{min} 250 nm (ϵ 9300); ^{1}H NMR ($CDCl_3$) δ 0.15 and 0.20 (6H, each as s), 0.93 (9H, s), 1.91 (3H, d, J = 1.0 Hz), 1.98 (1H, dt, J = 8.2 and 2.8 Hz), 2.94−3.01 (1H, m), 4.95 (1H, t, J = 2.8 Hz), 5.11 (1H, d, J = 12.0 Hz), 5.19 (1H, d, J = 12.0 Hz), 6.65 (1H, dd, J = 8.2 and 3.0 Hz), 7.35 (2H, dd, J = 10.7 and 4.9 Hz), 7.45−7.54 (3H, m), 7.61 (2H, ddd, J = 10.5, 5.8, and 2.1 Hz), 7.93 (2H, dd, J = 8.3 and 1.1 Hz), 8.03 (2H, dd, J = 8.3 and 1.1 Hz), 8.57 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.9, 12.5, 17.9, 25.6, 39.9, 62.0, 74.2, 85.4, 111.5, 111.9, 128.4, 128.6, 129.4, 129.5, 129.6, 129.8, 133.2, 133.7, 135.9, 150.2, 163.4, 164.6, 165.7. FAB-MS (*m*/*z*) 581 $[M + H]^+$. Anal. Calcd for $C_{30}H_{36}N_2O_8Si$: C, 62.05; H, 6.25; N, 4.82. Found: C, 62.00; H, 6.26; N, 4.75.

Physical data for **14b**: UV (MeOH) λ_{max} 268 nm (ϵ 10800), λ_{min} 251 nm (ϵ 8300); ^{1}H NMR ($CDCl_3$) δ 0.02 and 0.06 (6H, each as s), 0.75 (9H, s), 1.69 (3H, d, J = 0.7 Hz), 2.33−2.40 (1H, m), 2.76−2.82 (1H, m), 4.73 (1H, t, J = 6.6 Hz), 4.91 (1H, d, J = 11.7 Hz), 5.08 (1H, d, J = 11.7 Hz), 6.35 (1H, t, J = 6.3 Hz), 7.45−7.52 (4H, m), 7.58−7.66 (3H, m), 8.02−8.04 (2H, m), 8.10−8.13 (2H, m), 8.53 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.3, −4.8, 12.3, 17.7, 25.4, 39.0, 63.3, 72.1, 84.1, 109.0, 111.0, 128.6, 128.7, 129.3, 129.7, 129.8, 129.8, 133.5, 135.6, 150.2, 163.4, 163.9, 165.6. FAB-MS (*m*/*z*) 581 $[M + H]^+$. Anal. Calcd for $C_{30}H_{36}N_2O_8Si$: C, 62.05; H, 6.25; N, 4.82. Found: C, 62.05; H, 6.28; N, 4.77.

Reaction of 14 with $MeAlCl_2$: Formation of 1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-chloro-2-deoxy-*β*-D-*threo*-pentofuranosyl]thymine (17a) and 1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-chloro-2-deoxy-α-L-*erythro*-pentofuranosyl]thymine (17b). To a CH_2Cl_2 (7 mL) solution of **14** (300 mg, 0.52 mmol) was added $MeAlCl_2$ (1.0 M hexane solution, 2.6 mL, 2.6 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 2 h at 0 °C, quenched with saturated aq $NaHCO_3$, and filtered through a Celite pad. The filtrate was partitioned between CH_2Cl_2/saturated aq $NaHCO_3$. HPLC purification (hexane/EtOAc = 7/3) of the organic layer gave **17a** (foam, 135 mg, 53%, t_R 11 min) and **17b** (foam, 35 mg, 14%, t_R 13 min).

Physical data for **17a**: ^{1}H NMR ($CDCl_3$) δ 0.12 (6H, s), 0.90 (9H, s), 1.87 (1H, t, J = 2.9 Hz), 1.91 (3H, d, J = 1.4 Hz), 3.17−3.24 (1H, m), 4.72 (1H, d, J = 5.1 Hz), 4.77 (1H, d, J = 12.0 Hz), 4.85 (1H, d, J = 12.0 Hz), 6.70 (1H, dd, J = 8.8 and 2.9 Hz), 7.45−7.52 (3H, m), 7.59−7.61 (1H, m), 8.07−8.10 (2H, m), 8.82 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.9, 12.4, 17.8, 25.5, 39.1, 65.0, 78.6, 85.5, 108.7, 112.0, 128.4, 129.2, 129.7, 133.4, 135.6, 150.4, 163.8, 165.6. FAB-MS (*m*/*z*) 459 ($M^+ - {}^{35}Cl$). High-resolution FAB-MS (*m*/*z*) calcd for $C_{23}H_{32}ClN_2O_6Si$: 495.1718 $[M + H]^+$. Found: 495.1740.

Physical data for **17b**: ^{1}H NMR ($CDCl_3$) δ 0.11 (6H, s), 0.92 (9H, s), 1.97 (3H, d, J = 1.2 Hz), 2.32−2.36 (1H, m), 2.62−2.68 (1H, m), 4.51 (1H, d, J = 12.2 Hz), 4.60 (1H, dd, J = 10.9 and 6.5 Hz), 4.92 (1H, d, J = 12.2 Hz), 6.38 (1H, dd, J = 9.5 and 6.1 Hz), 7.46−7.50 (3H, m), 7.58−7.64 (1H, m), 7.71 (1H, d, J = 1.2 Hz), 8.01−8.03 (2H, m), 8.30 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.7, 12.7, 17.9, 25.5, 25.5, 25.6, 36.5, 63.9, 71.0, 83.6, 108.9, 112.1, 128.6, 129.0, 129.7, 133.6, 135.5, 150.5, 163.3, 165.2. FAB-MS (*m*/*z*) 459 ($M^+ - {}^{35}Cl$). High-resolution FAB-MS $[M + H]^+$ calcd for $C_{23}H_{32}N_2O_6Si$: 460.2030 ($M^+ - Cl + H$). Found: 460.2004.

Reaction of 14 with $MeAlCl_2$ Followed by Me_3Al in a One-Pot Manner: Formation of 16a and 1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4-*C*-methyl-α-L-*erythro*-pentofuranosyl]thymine (16b). To a CH_2Cl_2 (5 mL) solution of **14** (100 mg, 0.17 mmol) was added $MeAlCl_2$ (1.0 M hexane solution, 0.86 mL, 0.86 mmol) at 0 °C under Ar atmosphere. After the mixture was stirred for 2 h at 0 °C, Me_3Al (1 M hexane solution, 1.03 mL, 1.03 mmol) was added, and it was kept stirring at room temperature for 20 h.

The reaction mixture was quenched with saturated aq $NaHCO_3$ and filtered through a Celite pad. The filtrate was partitioned between CH_2Cl_2/saturated aq $NaHCO_3$. Column chromatography (hexane/EtOAc = 5/1−3/1) of the organic layer followed by separation by HPLC (hexane/EtOAc = 11/9) gave **16a** (syrup, 11.6 mg, 11%, t_R 15.8 min) and **16b** (syrup, 15.3 mg, 19%, t_R 12.5 min).

Physical data for **16b**: UV (MeOH) λ_{max} 267 nm (ϵ 11100), λ_{min} 247 nm (ϵ 6900); ^{1}H NMR ($CDCl_3$) δ 0.07 and 0.11 (6H, each as s), 0.90 (9H, s), 1.51 (3H, s), 1.94 (3H, d, J = 1.2 Hz), 2.01 (1H, dd, J = 15.0 and 2.7 Hz), 2.94 (1H, ddd, J = 15.0, 7.8, and 5.7 Hz), 4.18 (1H, d, J = 11.5 Hz), 4.24−4.29 (2H, m), 6.34 (1H, dd, J = 7.8 and 2.7 Hz), 7.46−7.50 (2H, m), 7.60−7.62 (2H, m), 8.02−8.05 (2H, m), 8.52 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.9, 12.6, 18.0, 18.7, 25.6, 68.0, 73.3, 84.9, 88.2, 110.4, 128.6, 129.4, 129.6, 130.1, 133.5, 136.4, 150.2, 163.5, 166.0. FAB-MS $[M + H]^+$ 475 ($M^+ + H$). Anal. Calcd for $C_{24}H_{34}N_2O_6Si$: C, 60.73; H, 7.22; N, 5.90. Found: C, 61.01; H, 7.36; N, 5.64.

1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4-*C*-(trimethylsilyl)ethynyl-*β*-D-*threo*-pentofuranosyl]thymine (18). To a toluene (15 mL)/hexane (100 mL) solution of TMSC≡CAl(Et)-Cl[23] (68.88 mmol) was added a CH_2Cl_2 (45 mL) solution of **14** (5.0 g, 8.61 mmol) at 0 °C under Ar atmosphere. The mixture was stirred at room temperature overnight, quenched with saturated aq $NaHCO_3$, and filtered through a Celite pad. The filtrate was partitioned between $CHCl_3$/saturated aq $NaHCO_3$. Column chromatography (hexane/EtOAc = 3/1) of the organic layer gave **18** (foam, 3.0 g, 62%): UV (MeOH) λ_{max} 266 nm (ϵ 10900), λ_{min} 247 nm (ϵ 6000); ^{1}H NMR ($CDCl_3$) δ 0.09 and 0.13 (6H, each as s), 0.12 (9H, s), 0.89 (9H, s), 1.90 (3H, d, J = 1.2 Hz), 1.95 (1H, ddd, J = 2.8, 1.2, and 14.6 Hz), 3.01 (1H, ddd, J = 8.2, 5.2, and 14.6 Hz), 4.50 (1H, dd, J = 1.2 and 5.2 Hz), 4.64 (1H, d, J = 10.8 Hz), 4.68 (1H, d, J = 10.8 Hz), 6.40 (1H, dd, J = 2.8 and 8.2 Hz), 7.44−7.48, 7.57−7.61, and 8.07−8.10 (6H, each as m), 8.24 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.9, 0.5, 12.5, 17.9, 18.0, 25.5, 25.57, 25.6. 41.5, 64.8, 76.4, 83.2, 84.4, 93.3, 101.1, 110.8, 128.29, 128.35, 128.37, 129.5, 129.72, 129.7, 133.2, 136.2, 150.4, 163.8, 166.0. FAB-MS $[M + H]^+$ 557 ($M^+ + H$). Anal. Calcd for $C_{29}H_{36}N_2O_6Si$: C, 60.40; H, 7.24; N, 5.03. Found: C, 60.36; H, 7.38; N, 4.79.

1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4-*C*-(trimethylsilyl)ethynyl-α-L-*threo*-pentofuranosyl]thymine (20). This compound was obtained in 31% yield (foam, 30 mg) from **19** (100 mg, 0.17 mmmol) by the procedure described above for the preparation of **18**. Physical data for **20**: UV (MeOH) λ_{max} 228 nm (ϵ 15100) and 267 nm (ϵ 10700), λ_{min} 247 nm (ϵ 6800); ^{1}H NMR ($CDCl_3$) δ 0.11, 0.13, and 0.14 (15H, each as s), 0.91 (9H, s), 1.96 (3H, d, J = 1.0 Hz), 2.36−2.42 (1H, m), 2.49 (1H, ddd, J = 13.5, 5.7, and 2.0 Hz), 4.58 (2H, s), 4.57−4.59 (1H, m), 6.46 (1H, dd, J = 8.0 and 5.7 Hz), 7.46 (2H, t), 7.57−7.60 (1H, m), 7.67 (1H, d, J = 1.0 Hz), 8.07 (2H, dd, J = 8.3 and 1.2 Hz), 8.74 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.7, −0.41, −0.03, 12.8, 17.9, 25.6, 41.5, 65.0, 83.3, 86.6, 94.6, 102.8, 110.9, 128.4, 129.7, 129.9, 133.1, 135.8, 150.1, 163.6, 165.8. FAB-MS (*m*/*z*) 557 $[M + H]^+$. Anal. Calcd for $C_{29}H_{36}N_2O_6Si$: C, 60.40; H, 7.24; N, 5.03. Found: C, 60.53; H, 7.35; N. 4.99.

1-[5-*O*-Benzoyl-2-deoxy-4-*C*-ethynyl-*β*-D-*threo*-pentofuranosyl]thymine (21). To a THF (17 mL) solution of **18** (2.99 g, 5.368 mmol) was added $Bu_4NF{\cdot}3H_2O$ (2.81 g, 10.74 mmol) at 0 °C, and the mixture was stirred for 1.5 h. Evaporation of the solvent followed by column chromatography (2% MeOH in CH_2Cl_2) of the residue gave **21** (foam, 1.93 g, 97%): UV (MeOH) λ_{max} 266 nm (ϵ 10000), λ_{min} 247 nm (ϵ 6500); ^{1}H NMR ($CDCl_3$, after addition of D_2O) δ 1.94 (3H, d, J = 1.2 Hz), 2.15 (1H, dd, J = 15.0 and 3.2 Hz), 2.60 (1H, s), 3.01 (1H, ddd, J = 15.0, 9.0, and 5.2 Hz), 4.34 (1H, d, J = 5.2 Hz), 4.40 (1H, d, J = 11.2 Hz), 4.96 (1H, d, J = 11.2 Hz), 6.34 (1H, d, J = 9.0 and 3.2 Hz), 7.46−7.51, 7.61−7.65, and 8.09−8.11 (5H, each as m), 7.70 (1H, d, J = 1.2 Hz), 8.47 (1H, br); ^{13}C NMR ($CDCl_3$) δ 12.5, 38.8, 63.4, 74.6, 76.4, 80.0, 82.3, 84.9, 111.5, 128.4, 128.6, 129.0, 130.0, 130.1, 133.3,

133.8, 137.9, 150.6, 163.7, 167.4. FAB-MS (*m*/*z*) 371 $[M + H]^+$. Anal. Calcd for $C_{19}H_{19}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.31; H, 4.88; N, 7.35.

2′,3′-Didehydro-3′-deoxy-4′-*C*-ethynylthymidine (8: 4′-Ed4T). To a THF (50 mL) solution of **21** (5.0 g, 13.5 mmol) were added pyridine (8.1 mL, 101.3 mmol) and $(CF_3SO_2)_2O$ (7.5 mL, 44.6 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred at room temperature overnight and then partitioned between $CHCl_3/H_2O$. The organic layer containing **22** was dried (Na_2SO_4) and evaporated. The resulting syrup was dissolved in CH_3CN (20 mL) and reacted with DBN (5.0 mL, 40.5 mmol) at room temperature for 4 h, after which MeOH (40 mL) was added and stirring was continued further for 2 h. Evaporation of the reaction mixture followed by column chromatography (4% MeOH in $CHCl_3$) gave **8** (solid, 2.3 g, 69%). For physical data of this compound, see ref 8.

Reaction of 14 with Allyltrimethylsilane in the Presence of $SnCl_4$. To a CH_2Cl_2 (5 mL) solution of **14** (116.1 mg, 0.2 mmol) were added allyltrimethylsilane (0.16 mL, 1.0 mmol) and $SnCl_4$ (0.6 mL, 0.6 mmol) at 0 °C under Ar atmosphere. After being stirred for 20 h at room temperature, the reaction mixture was partitioned between $CHCl_3$/saturated aq $NaHCO_3$. Column chromatography (hexane/EtOAc = 3/1−1/1) of the organic layer gave a mixture of **23**, **24a**, and **24b**. These products were separated by preparative TLC (hexane/EtOAc = 2/1) to give **23** (13.6 mg, 14%, syrup), **24a** (9.4 mg, 9%, syrup), and **24b** (14.1 mg, 14%, syrup).

Physical data for **23**: ^{1}H NMR ($CDCl_3$) δ −0.28 and −0.21 (6H, each as s), 0.77 (9H, s), 1.86 (1H, ddd, J = 14.6, 7.3, and 2.0 Hz), 1.89 (3H, d, J = 1.2 Hz), 2.72−2.74 (2H, m), 2.99 (1H, ddd, J = 14.6, 8.3, and 5.1 Hz), 3.97−4.01(2H, m),4.25 (1H, d, J = 9.9 Hz), 5.01−5.08 (2H, m), 5.69−5.78 (1H, m), 6.44 (1H, dd, J = 8.3 and 2.0 Hz), 7.29−7.46 (5H, m), 7.47 (1H, d, J = 1.2 Hz), 8.60 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.1, 12.6, 17.8, 25.5, 29.7, 40.0, 45.4, 69.2, 74.9, 84.0, 110.5, 112.6, 114.7, 118.6, 125.4, 128.2, 128.3, 131.7, 136.4, 141.2, 150.1, 163.4. NOE experiment: H-6/H-5′b (1.4%). FAB-MS (*m*/*z*) 501 ($M^+ + H$). High-resolution FAB-MS $[M + H]^+$ calcd for $C_{26}H_{37}N_2O_6Si$: 501.2421 ($M^+ + H$). Found: 501.2419.

Physical data for **24a**: ^{1}H NMR ($CDCl_3$) δ 0.05 and 0.07 (6H, each as s), 0.86 (9H, s), 1.84 (3H, d, J = 1.0 Hz), 2.23−2.58 (3H, m), 2.84 (1H, ddd, J = 14.3, 7.3, and 6.0 Hz), 4.45(1H, d, J = 11.7 Hz), 4.64 (1H, t, J = 12.6 Hz), 5.09−5.25 (3H, m), 5.81−5.88 (1H, m), 6.22−6.26 (1H, m), 7.45−7.49 (2H, m), 7.57−7.64 (2H, m), 8.03−8.05 (1H, m), 8.78 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.3, −4.8, −0.03, 12.4, 17.8, 25.5, 39.3, 41.5, 65.0, 74.0, 84.0, 88.1, 110.8, 120.0, 128.5, 129.5, 131.8, 133.3, 136.0, 150.3, 163.6, 166.1. NOE experiment: H-6/H-5′a (1.1%), H-6/H-5′b (3.6%), and H-2′/H-5′b (1.2%). FAB-MS (*m*/*z*) 501 ($M^+ + H$). High-resolution FAB-MS $[M + H]^+$ calcd for $C_{26}H_{37}N_2O_6Si$: 501.2421 ($M^+ + H$). Found: 501.2416.

Physical data for **24b**: ^{1}H NMR ($CDCl_3$) δ 0.10 and 0.11 (6H, each as s), 0.92 (9H, s), 1.91 (3H, d, J = 1.2 Hz), 2.23 (1H, m), 2.36−2.46 (2H, m), 2.62−2.66 (1H, m), 4.31(1H, d, J = 12.1 Hz),4.52 (1H, d, J = 12.1 Hz), 4.55 (1H, dd, J = 4.0 and 3.5 Hz), 5.18−5.22 (2H, m), 5.90−5.98 (1H, m), 6.23 (1H, t, J = 6.3 Hz), 7.45−7.50, 7.58−7.63, 8.01−8.03 (6H, each as m), 8.26 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.6, 12.2, 18.0, 25.7, 36.6, 41.1, 66.1, 72.5, 84.0, 87.2, 111.0, 119.3, 128.7, 129.4, 129.5, 132.7, 133.6, 134.9, 150.0, 163.4, 166.0. NOE experiment: H-3′/H-5′a (2.1%) and *tert*-Bu/CH_2CH=CH_2 (0.2%). FAB-MS (*m*/*z*) 501 $[M + H]^+$. High-resolution FAB-MS (*m*/*z*) calcd for $C_{26}H_{37}N_2O_6Si$: 501.2421 ($M^+ + H$). Found: 501.2443.

Reaction of 14 with $MeAlCl_2$ Followed by Allyltrimethylsilane in a One-Pot Manner. To a CH_2Cl_2 (4 mL) solution of **14** (58.1 mg, 0.1 mmol) was added $MeAlCl_2$ (1 M hexane solution, 0.5 mL, 0.5 mmol) at 0 °C under Ar atmosphere, and the mixture was stirred for 2 h. The resulting mixture containing **17** was further reacted with allyltrimethylsilane (0.20 mL, 1.72 mmol) at room temperature for 16 h. The reaction mixture was partitioned between $CHCl_3$/saturated aq $NaHCO_3$. Preparative TLC (hexane/EtOAc = 1/1) of the organic layer gave **24a** (15.3 mg, 31%) and **25** (4.5 mg, 11%, syrup).

Physical data of **25**: ^{1}H NMR ($CDCl_3$) δ 0.09 and 0.13 (6H, each as s), 0.90 (9H, s), 1.93 (3H, d, J = 1.2 Hz), 1.93−2.04 (1H, m), 2.46 (1H, dd, J = 9.8 and 3.9 Hz), 2.68−2.75 (1H, m), 3.72 (1H, dd, J = 12.2 and 9.8 Hz), 3.86 (1H, dd, J = 12.2 and 3.9 Hz), 4.36 (1H, dd, $J_{2'a,3'} = J_{2'b,3'}$ = 6.4 Hz, H-3′), 5.13−5.21 (2H, m), 5.75−5.86 (1H, m), 6.17 (1H, t, J = 6.6 Hz), 7.88 (1H, d, J = 1.2 Hz), 8.33 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.7, 12.6, 17.8, 25.6, 39.4, 41.8, 66.0, 75.2, 82.5, 87.8, 111.0, 119.6, 132.2, 136.1, 150.4, 163.6. NOE experiment: H-6/H-5′a (0.8%), H-6/H-5′b (0.5%), H-1′/CH_2–CH=CH_2 (1%), H-1′/CH_2–CH=CH_2 (0.9%), and H-3′/CH_2–CH=CH_2 (2.4%). High-resolution FAB-MS (*m*/*z*) calcd for $C_{19}H_{33}N_2O_5Si$: 397.2159 $[M + H]^+$. Found: 397.2167.

1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-*C*-cyano-2-deoxy-β-D-*threo*-pentofuranosyl]thymine (26a) and 1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-*C*-cyano-2-deoxy-α-L-*erythro*-pentofuranosyl]thymine (26b). Compounds **26a** and **26b** were obtained in 29% and 23% yields, respectively, from **14** (50 mg, 0.086 mmol) and cyanotrimethylsilane (0.07 mL, 0.69 mmol) by the procedure employed for the preparation of **24**. HPLC (hexane/EtOAc = 11/9) separation gave analytically pure samples (**26a**, foam, t_R 12.8 min; **26b**, foam, t_R 20.6 min).

Physical data for **26a**: UV (MeOH) λ_{max} 266 nm (ϵ 10000), λ_{min} 248 nm (ϵ 6900); ^{1}H NMR ($CDCl_3$) δ 0.13 and 0.15 (6H, each as s), 0.91 (9H, s), 1.93 (3H, d, J = 1.0 Hz), 2.15 (1H, dd, J = 15.2 and 2.8 Hz), 3.04−3.09 (1H, m), 4.64 (1H, d, J = 11.5 Hz), 4.77 (1H, d, $J_{2'b,3'}$ = 4.1 Hz, H-3′), 4.84 (1H, d, J = 11.5 Hz), 6.57 (1H, dd, J = 8.3 and 2.8 Hz), 7.46−7.50 (3H, m), 7.61−7.63 (1H, m), 8.08−8.10 (2H, m), 9.49 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.9, 12.5, 18.0, 25.5, 40.7, 62.8, 75.2, 82.4, 85.12, 111.6, 116.6, 125.7, 128.6, 129.9, 133.8, 135.2, 150.0, 163.1, 165.5. NOE experiment: H-6/H-5′a (0.9%), H-6/H-5′b (2.1%); IR (neat) 2240 cm^{-1} (CN). FAB-MS (*m*/*z*) 486 $[M + H]^+$. Anal. Calcd for $C_{24}H_{31}N_3O_6Si$: C, 59.36; H, 6.43; N, 8.65. Found: C, 59.03; H, 6.44; N, 8.34.

Physical data for **26b**: UV (MeOH) λ_{max} 266 nm (ϵ 10000), λ_{min} 248 nm (ϵ 7000); ^{1}H NMR ($CDCl_3$) δ 0.11 and 0.17 (6H, each as s), 0.91 (9H, s), 1.98 (3H, d, J = 1.0 Hz), 2.27 (1H, dt, J = 14.3 and 4.6 Hz), 2.81 (1H, dd, J = 14.3 and 6.4 Hz), 4.51−4.55 (3H, m), 6.40 (1H, dd, J = 6.4 and 4.6 Hz), 7.47−7.51 (2H, m), 7.57 (1H, d, J = 1.0 Hz), 7.62−7.64 (1H, m), 8.06−8.08 (2H, m), 8.81 (1H, br); IR (neat) 2252 cm^{-1} (CN); ^{13}C NMR ($CDCl_3$) δ −5.1, −5.0, 12.7, 17.9, 25.4, 40.0, 64.0, 73.3, 85.2, 86.1, 111.6, 115.7, 128.5, 128.7, 129.9, 134.0, 135.2, 150.1, 163.2, 165.4. NOE experiment: CH_2-5′/H-2′b (1.3%). FAB-MS (*m*/*z*) 486 $[M + H]^+$. Anal. Calcd for $C_{24}H_{31}N_3O_6Si \cdot {}^1/_2\ H_2O$: C, 58.92; H, 6.47; N, 8.59. Found: C, 58.93; H, 6.43; N, 8.28.

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Supporting Information Available: General experimental procedures, details of the preparation of **3**, **10**−**13**, **15**−**16**, and **19**, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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