# C-3′-Branched Thymidines as Precursors for the Selective Generation of C-3′-Nucleoside Radicals

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C-3′-nucleoside radicals can be generated via Norrish type I photocleavage of C-3′-acyl nucleoside derivatives. In monomer experiments employing C-3′-acylthymidine derivatives **2** and **3**, a 1:1 mixture of isomers of the H-abstraction products was obtained when the photolysis was carried out in the presence of a hydrogen donor. Derivatives **2** were synthesized by an approach which involves the formation of a silyl-protected cyanohydrin, which is subsequently alkylated with organolithium reagents, followed by hydrolysis. Derivatives **3** could be obtained via a multistep synthesis starting from diol **7**. Several different methods were attempted to oxidize the unprotected diol to the α-hydroxy aldehyde. Finally, a route was chosen which involves a protection−deprotection sequence followed by oxidation of the free primary alcohol. The resulting modified nucleosides should facilitate the study of C-3′-DNA radicals.

## Introduction

The increasing amount of attention focused on the synthesis of nucleosides and analogues is stimulated by a variety of factors. Several sugar-modified nucleosides have been shown to possess the ability to inhibit the growth of various human tumor cells, whereas others have shown antiviral activity.[1] A great deal of energy has also been invested into the design of nucleosides suitable for incorporation into modified oligonucleotides that hybridize with single-stranded RNA.[2] These oligonucleotides are presently under evaluation as novel therapeutic agents (antisense or ribozyme approach). C-3′-Methyl-2′-deoxynucleosides, along with other C-3′-substituted 2′-deoxynucleosides, have shown biological activities on RNA and DNA polymerases.[3]

Modified nucleosides have also found their place in the study of biological processes related to DNA damage. They have been utilized in the investigation of mechanisms involving radical species, which include ionizing radiation and the radical-induced cleavage of DNA by various antitumor agents such as bleomycin[4] and the enediyne antibiotics.[5] Metallointercalators, such as the phenanthrenequinone diimine complexes of rhodium(III), have been postulated to also cleave DNA via a radical-based mechanism similar to that of bleomycin.[6] Whereas the above-mentioned natural products bind to the minor groove of double-stranded DNA and abstract mainly C-4′ and C-5′ H-atoms from the sugar backbone, these metalloorganic compounds intercalate in the major groove of double-stranded DNA and upon photoactivation abstract C-3′ H-atoms from deoxyribose, generating highly reactive DNA radicals that lead to strand fragmentation.

Here, we introduce the synthesis of a new class of C-3′ branched-chain nucleosides and investigate the feasability of their use in the study of the radical-induced DNA cleavage mechanisms postulated to occur from the major groove of DNA. We have demonstrated that 2′-deoxynucleotide-4′-radicals can be selectively and independently generated by photolysis of ketones **1a**−**c**.[7] These modified nucleosides were incorporated into DNA, and the mechanism of cleavage of single- and double-stranded DNA induced by the C-4′ radical has been and continues to be studied.[8] Analogously, C-3′-acyl nucleoside derivatives should generate via photolysis the C-3′-radical intermediate formed in the photoactivated cleavage of DNA with metallointercalators, making it possible to study the mechanisms involved here as well.

Even though considerable attention has been devoted to the synthesis of C-3′-branched nucleosides,[9] only a few examples of C-3′-branched deoxynucleoside analogues

(1) See, for example: (a) Maag, H.; Gutierrez, A.; Prisbe, E.; Rydzweski, R.; Verheyden, J. In *Antibiotics and Antiviral Compounds*; Krohn, K., Kirst, H., Maag, H., Eds.; VCH Verlagsgesellschaft: Weinheim, 1993; pp 421−438. (b) Azuma, A.; Hanaoka, K.; Kurihara, A.; Kobayashi, T.; Miyauchi, S.; Kamo, N.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1995**, *38*, 3391−3397. (c) Drach, J. C. In *Targets for the Design of Antiviral Agents*; De Clercq, E., Walker, R. T., Eds.; Nato Advanced Institutes Series, Series A: Life Sciences; Plenum Press: New York, 1983; Vol. 33, pp 231−257. (d) Hecht, S. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC 1995; 369−388.

(2) (a) Crooke, S. T., Lebleu, B., Eds. *Antisense Research and Applications*; CRC Press: Boca Raton, FL, 1993. (b) Wagner, R. W. *Nature*, **1994**, *372*, 333−335. (c) De Mesmaeker, A.; Häner, R.; Martin, P.; Moser, H. W. *Acc. Chem. Res.* **1995**, *28*, 366−374. (d) Agrawal, S., Ed. *Antisense Therapeutics*; Humana Press: Totowa, NJ, 1996. (e) Akhtar, S.; Agrawal S. *Trends Pharmacol. Sci.* **1997**, *18*, 12−18.

(3) See, for example: (a) Mikhailov, S. N.; Padyukova, N. S.; Lysov, Y. P.; Savochkina, L. R. *Nucleosides Nucleotides* **1991**, *10*, 339−343. (b) Fedorov, I. I.; Kazmina, E. M.; Novicov, N. A.; Gurskaya, G. V.; Bochkarev, A. V.; Jasko, M. V.; Victorova, L. S.; Kukhanova, M. K.; Balzarini, J.; De Clercq, E.; Krayevsky, A. A. *J. Med. Chem.* **1992**, *35*, 4567−4575.

(4) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107−1136. (b) Burger, R. *Chem. Rev.* **1998**, *98*, 1153−1169.

(5) (a) Goldberg, I. H.; Kappen, L. S. *Enediyne Antibiotics as Antitumor Agents*; Marcel Dekker: New York, 1994; pp 327−362. (b) Dedon, P. C.; Goldberg, I. H. *Chem. Res. Tox.* **1992**, *5*, 311−322.

(6) Sitlani, A.; Long, E. C.; Pyle, A. M.; Barton, J. K. *J. Am. Chem. Soc.* **1992**, *114*, 2303−2312. (b) Hudson, B. P.; Barton, J. K. *J. Am. Chem. Soc.* **1998**, *120*, 6877−6888.

(7) Marx, A.; Erdmann, P.; Senn, M.; Körner, S.; Jungo, T.; Petretta, M.; Imwinkelried, P.; Dussy, A.; Kulicke, K.; Macko, L.; Zehnder, M.; Giese, B. *Helv. Chim. Acta* **1996**, *70*, 1980−1994.

(8) (a) Giese, B.; Erdmann, P.; Schaefer, T.; Schwitter, U. *Synthesis* **1994**, 1310−1312. (b) Giese, B.; Dussy, A.; Elie, C.; Erdmann, P.; Schwitter, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1861. (c) Giese, B.; Beyrich-Graf, X.; Erdmann, P.; Petretta, M.; Schwitter, U. *Chem. Biol.* **1995**, *2*, 367. (d) Giese, B.; Dussy, A.; Meggers, E.; Petretta, M. *J. Am. Chem. Soc.* **1997**, *119*, 11130.

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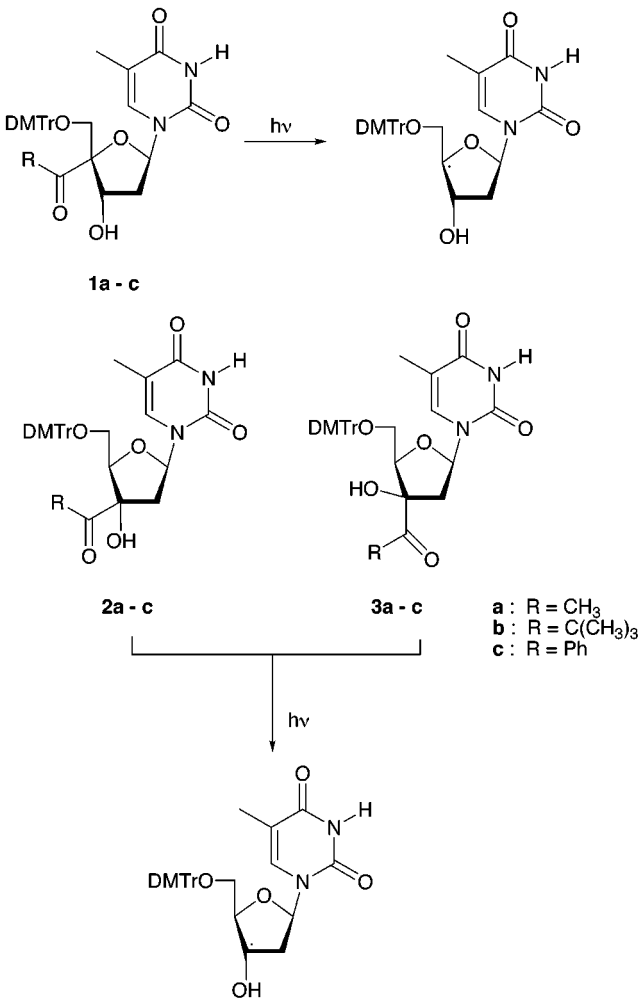
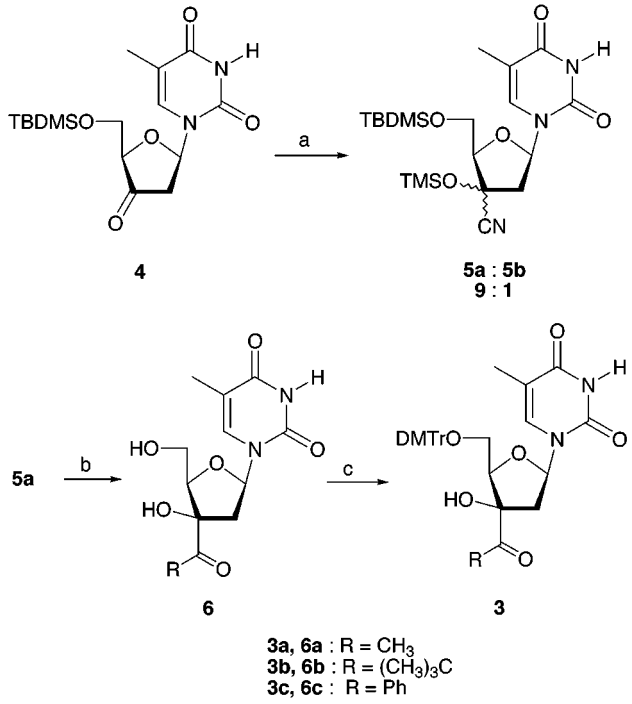



**Figure 1.**

with both a 3′-α-hydroxy group and a 3′-*β*-carbon substituent can be found in the literature.[10] Via the most obvious method for the generation of these derivatives, the addition of a carbon nucleophile to a 3′-ketonucleoside, it has been observed that mainly the *threo*-configured nucleoside analogues are obtained.[11] Wengel et al.[10c] used this preference for α attack to generate nucleoside derivatives with a hydroxymethyl substituent by bishydroxylation of the corresponding C-3′-methylidene nucleoside derivatives. This very useful diol was chosen as a starting point for our synthesis of *erythro* C-3′-acyl-substituted 2′-deoxynucleosides.

**Scheme 1**[a]




[a]Reagents: (a) TMSCN, KCN, 18-crown-6, $CH_2Cl_2$, 63%; (b) 1. RLi, CuI, THF, 2. 1N HCl; (c) DMTrCl, DMAP, pyridine

## Results and Discussion

To investigate the relationship between the diastereoselectivity of product formation in the reduction of the C-3′ radical and the stereochemistry of the starting nucleoside, both the *threo* and *erythro* modified nucleosides were synthesized. Taking advantage of the fact that 3′-keto-2′-deoxynucleosides show a preference for nucleophilic attack from the α face, we used this method to synthesize *threo*-configured C-3′-acyl-substituted 2′-deoxynucleosides **3a**−**c**. Our approach involved the formation of a trimethylsilyl-protected cyanohydrin that could then be alkylated and hydrolyzed to give the desired ketones. Because of the extreme sensitivity of 3′-keto-2′-deoxynucleosides to acid and base, care was necessary in the selection of the proper conditions for the nucleophilic addition of $CN^-$ to this ketone. Greenlee et al.[12] reported the addition of trimethylsilyl cyanide to α-substituted ketones by means of potassium cyanide and 18-crown-6 as catalyst. This method was found to be quite useful for the synthesis of cyanohydrins from acid-sensitive ketones. With this method, ketone **4**[13] was converted to the protected cyanohydrins **5a** and **5b**, which were isolated as a 9:1 *threo*:*erythro* mixture of isomers in 63% yield (Scheme 1). The isomers were separated by repeated flash chromatography. Cyanohydrin **5a** was then subjected to nucleophilic addition of PhLi, MeLi, and *t*-BuLi (3−5 equiv of the organolithium reagent and 0.01 equiv of CuI) followed by acid hydrolysis with 1 M HCl to give the desired ketones **6a**−**c** in high yield. The absolute configuration of these ketones was unambiguously established by $^1$H NOE difference experiments employing ketone **6b**. These experiments revealed a

(9) See, for example: (a) Nutt, R. F.; Dickinson, M. J.; Holly, F. W.; Walton, E. *J. Org. Chem.* **1968**, *33*, 1789−1795. (b) Auguste, S. P.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 395−404. (c) Jung, P. M. J.; Burger, A.; Biellmann, J.-F. *Tetrahedron Lett.* **1995**, *36*, 1031−1034.

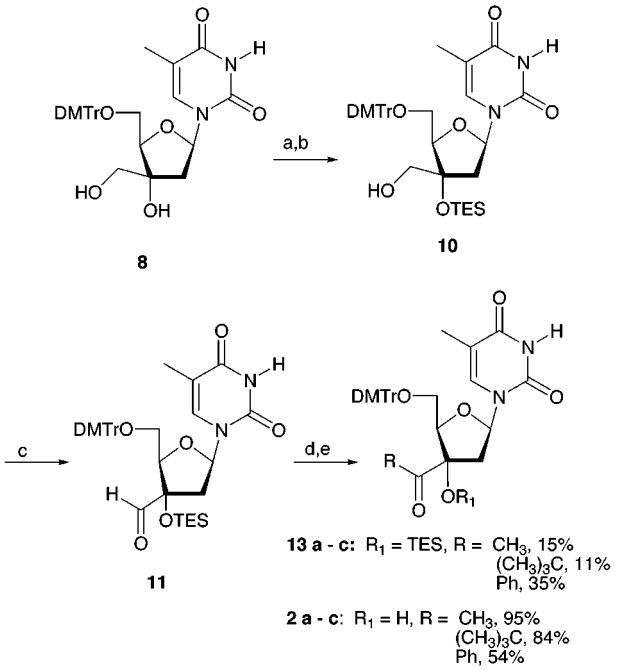
(10) (a) Jorgensen, P. N.; Stein, P. C.; Wengel, J. *J. Am. Chem. Soc.* **1994**, *116*, 2231−2232. (b) Svendsen, M. L.; Wengel, J.; Dahl, O.; Kirpekar, F.; Roepstorff, R. *Tetrahedron* **1993**, *49*, 11341−11352. (c) Jorgensen, P. N. Svendsen, M. L.; Scheuer- Larsen, C.; Wengel, J. *Tetrahedron*, **1995**, *51*, 2155−2164. (d) Jung, P. M. J.; Burger, A.; Biellmann, J.-F. *J. Org. Chem.* **1997**, *62*, 8309−8314. (e) Jorgensen, P. N.; Sorensen, U. S.; Pfundheller, H. M.; Olsen, C. E.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3275−3284. (f) Nielsen, P.; Pfundheller, H. M.; Wengel, *J. Chem. Commun.* **1997**, 825−826. (g) Ichikawa, S.; Shuto, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 1368−1375.

(11) Weeb, T. R. *Tetrahedron Lett.* **1988**, *29*, 3769−3772. (b) Bender, S. L.; Moffett, K. K. *J. Org. Chem.* **1992**, *57*, 1646−1647. (c) Hayakawa, H.; Tanaka, J.; Itoh, N.; Nakajimia, M.; Miyuasak, K.; Yamaguchi, Y.; Iitaka, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2605. (d) Koole, L. H.; Buck, H. M.; Vial, J.-M.; Chattopadhyaya, J. *Acta Chem. Scand.* **1989**, *43*, 665−669.

(12) Greenlee, W. J.; Hangauer, D. G. *Tetrahedron Lett.* **1983**, *24*, 4559−4560.

(13) Robins, M. J.; Samano, V. *J. Org. Chem.* **1990**, *55*, 5186−5188. Jørgensen et al. *Nucleosides Nucleotides* **1995**, *14*, 1465.

**Scheme 2**[a]




[a] Reagents: (a) TESCl, imidazole, DMF, 72%; (b) HF-pyridine, THF, 77%; (c) TPAP, NMO, $CH_2Cl_2$, 98%; (d) RLi, $CeCl_3$, THF; (e) Dess-Martin Reagent, $CH_2Cl_2$; (f) TBAF, THF

strong NOE effect between the 2′-$\beta$-H of the sugar and the 3′-OH. The 2′-$\beta$-H was identified by the NOE effect observed between this proton and H-6 of the nucleoside base. These modified nucleosides were then tritylated by means of standard methods.

When cyanohydrin **5b** was subjected to the same reaction conditions as mentioned above, no ketone could be isolated. It seems that in this case primarily trimethylsilyl cleavage occurs and the cyanohydrin then reverts to the starting ketone. Under these reaction conditions, this ketone then undergoes base elimination. We then turned our attention to a different method utilizing diol **8**, which was first synthesized by Wengel et al.[10c] Attempts were made to oxidize the primary hydroxy group to an aldehyde moiety without protection of the tertiary hydroxy group by employing the Dess−Martin reagent, TPAP-catalyzed oxidation with NMO, and NIS/tetrabutylammonium iodide. All of these methods led to ring fragmentation. The diol was then doubly protected by employing triethylsilyl chloride in the presence of 1*H*-imidazole in DMF. Bissilyl ether **9** was isolated in 72% yield. After selective deprotection of the primary triethylsilyl ether with HF−pyridine complex in THF, alcohol **10** was obtained in 82% yield (Scheme 2). Through TPAP-catalyzed oxidation of **10** with NMO in the presence of 4 Å molecular sieve powder in $CH_2Cl_2$, aldehyde **11** could be isolated in 98% yield.[14] The next step was the alkylation of the aldehyde followed by oxidation to give the desired ketones. When the alkylation was attempted using organolithium or Grignard reagents, primarily silyl migration was observed from the tertiary 3′-O of the sugar to the newly formed secondary OH group of the side chain. When the alkylation was carried out with organolithium reagents in the presence of $CeCl_3$, satisfactory results could be obtained.[15] Reaction of MeLi (10 equiv), PhLi (10 equiv), and *t*-BuLi (14 equiv) along with an equimolar amount of $CeCl_3$ with **11** in THF delivered the corresponding alcohols, which were used in the next step without further purification. Dess−Martin oxidation of **12a**−**c** in $CH_2Cl_2$ and subsequent deprotection of the 3′-hydroxy substituent with TBAF in THF afforded radical precursors **2a**−**c**.

**Scheme 3**

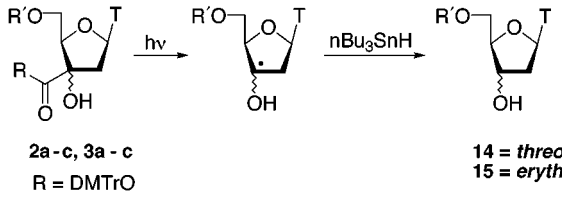



**Table 1. Irradiation of C-3′-Branched Ketones 2 and 3**

| | length of irradiation | yield (%) | ratio of products **14**:**15** |
|---|---|---|---|
| R = $CH_3$ (**2a**) | 3 h | 20 | 1:1 |
| R = $CH_3$ (**3a**) | 3 h | 65 | 1:1 |
| R = Ph (**2c**) | 2 h | 35 | 1:1 |
| R = Ph (**3c**) | 2 h | 33 | 1:1 |
| R = $(CH_3)_3C$ (**2b**) | 1 h | 79 | 1:1 |
| R = $(CH_3)_3C$ (**3b**) | 1 h | 92 | 1:1 |

The structural assignment of ketones **2a**−**c** was done by comparison of the coupling constants of the H-1′ of these ketones to the same proton of ketones **3a**−**c**. The H-1′ signal of ketones **3a**−**c** appears as a doublet of doublets with a coupling constant of $J_{1'-2'\beta} \approx 3.0$ Hz, whereas in the case of **2a**−**c**, this coupling is ≈ 5.5 Hz.

With these radical precursors in hand, we then looked at the selective generation of C-3′-nucleoside radicals by irradiation of ketones **2** and **3**. To probe the efficiency of radical formation, these ketones were irradiated in the presence of a hydrogen donor.

The photolysis of ketones **2a**−**c** and **3a**−**c** ($\lambda_{max} \geq 320$ nm) was carried out in the presence of an excess of $n$Bu$_3$SnH in $CH_3CN$ (Scheme 3). When the crude reaction mixture of the photolysis was analyzed directly by reversed phase HPLC, the reduction products were detected as a 1:1 mixture of α and $\beta$-5′-*O*-tritylated thymidine (Table 1). As expected, *tert*-butyl ketones **2b** and **3b** underwent a clean and efficient Norrish type I cleavage, giving the best results with high yields and only trace amounts of side products. Methyl ketone **3a** also performs well as a radical precursor; however, in the case of ketone **2a**, side products were detected which caused a much lower yield. These side products are likely the result of Norrish type II reaction of the methyl ketone. In the case of benzoyl ketones **2c** and **3c**, the reduction products **14** and **15** were also obtained, however, in low yield (35% and 33%, respectively). This was not surprising because of the known complications involved in the use of aryl ketones as radical precursors.[16] The stereochemistry at the 3′-C position of the starting ketone seems to have no influence on the photocleavage process or the diastereoselectivity of the reduction, which implies that the reduction takes place via a free radical process.

(14) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13−19.

(15) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(16) Greenberg, M. M.; Barvian, M. R.; Cook, G. P.; Goodman, B. K. Matray, T. J.; Tronche, C.; Venkatesan, H. *J. Am. Chem. Soc.* **1997**, *119*, 1828−183.

## Conclusion

We have described the synthesis of a new class of C-3′-α- and β-branched nucleosides. These ketones undergo Norrish type I photocleavage to give the desired C-3′ radical. This radical is easily reduced in the presence of a hydrogen donor via a free radical process. The *tert*-butyl ketones undergo the most efficient cleavage, delivering the highest yield of reduction products. These nucleosides shall be incorporated into oligonucleotides by means of standard DNA synthesis techniques. The synthesis of these modified nucleotides will facilitate the study of the cleavage of DNA by C-3′ radicals. This work is currently in progress.

## Experimental Section

**Material and Methods.** All quoted temperatures are uncorrected. All reagents were commercially available and were used without further purification. Fast atom bombardment (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol as matrix. Combustion analyses were performed by the Mikroanalytisches Labor, University of Basel. Analytical HPLC was performed on a Kontron instrument using a Merck Lichrospher 100 column, RP 18 (5 mm), 250 mm × 4. The solvents were purified and dried according to standard procedures. Anhydrous cerium chloride was prepared as described by Imamoto et al.[15]: cerium chloride heptahydrate was pulverized and heated to 100 °C for 4 h in vacuo with occasional swirling. A stir bar was then placed in the flask, and the temperature was raised to 140 °C. After 3 h at this temperature, the solid was cooled to 0 °C and THF was added. The suspension was then left to stir under argon at least overnight. The reactions were carried out in carefully dried apparatus and under an inert atmosphere.

**General Procedure for the Synthesis of Trimethylsilyl-Protected Cyanohydrins 5a and 5b.** After 18-crown-6 (10 mg, 0.03 mmol), KCN (10 mg, 0.20 mmol), and ketone **4** (4.50 g, 12.21 mmol) were coevaporated twice with $CH_2Cl_2$, the mixture was dissolved in 100 mL of $CH_2Cl_2$. To the solution was slowly added, over 10 min, TMSCN (3.05 mL, 24.4 mmol) at room temperature. After 5 h of stirring, the reaction was quenched by the addition of $H_2O$ (100 mL), and the mixture was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic phases were washed with brine and dried over $MgSO_4$, and the solvent was evaporated. Flash chromatography (AcOEt/pentane, 1:3) gave 3.47 g (63%) of **5a** and **5b** as a mixture of diastereoisomers (*xylo*:*ribo* 9:1).

**1-(5-*O*-(*tert*-Butyldimethylsilyl)-3-*O*-(trimethylsilyl)-3-*C*-cyano-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (5a).** $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 6 H), 0.28 (s, 9 H), 0.94 (s, 9 H), 1.92 (s, 3 H), 2.24 (dd, $J$ = 2.4 Hz, 14.9 Hz, 1 H), 2.95 (dd, $J$ = 7.8 Hz, 14.9 Hz, 1 H), 3.97 (m, 2 H), 4.08 (m, 1 H), 6.29 (dd, $J$ = 2.4 Hz, 7.2 Hz, 1 H), 7.31 (d, $J$ = 1.2 Hz, 1 H), 9.32 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ −5.2, 0.9, 12.6, 18.3, 25.8, 47.8, 59.2, 70.0, 83.8, 87.1, 110.5, 117.8, 135.3, 150.2, 163.7; FAB−MS 454 (18, $[M + 1]^+$). Anal. Calcd for $C_{20}H_{35}N_3O_5Si_2$ (453.69): C 52.95, H 7.78, N 9.26. Found C 52.88, H 7.57, N 9.10.

**1-(5-*O*-(*tert*-Butyldimethylsilyl)-3-*O*-(trimethylsilyl)-3-*C*-cyano-2-deoxy-β-D-*erythro*-pentofuranosyl)thymine (5b).** $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 6 H), 0.31 (s, 9 H), 0.94 (s, 9 H), 1.94 (s, 3 H), 2.40 (dd, $J$ = 9 Hz, 12.8 Hz, 1 H), 2.67 (dd, $J$ = 4.8 Hz, 12.8 Hz, 1 H), 4.00 (ddd, $J$ = 2.4 Hz, 11.7 Hz, 19.2 Hz, 2 H), 4.15 (dd, $J$ = 2.4 Hz, 12.6 Hz, 1 H), 6.29 (dd, $J$ = 5.1 Hz, 9.0 Hz, 1 H), 7.52 (d, $J$ = 1.2 Hz, 1 H), 8.85 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ −5.6, 1.0, 12.5, 18.3, 25.7, 45.7, 62.7, 73.8, 84.1, 88.9, 111.2, 118.0, 134.9, 150.2, 163.8; FAB−MS 454 (17, $[M + 1]^+$). Anal. Calcd for $C_{20}H_{35}N_3O_5Si_2$ (453.69): C 52.95, H 7.78, N 9.26. Found C 53.17, H 7.67, N 9.11.

**General Procedure for the Alkylation of Cyanohydrin 5a with Lithium Reagents.** After coevaporation twice with toluene, nitrile **5b** and CuI (0.01 equiv) were dissolved in THF and cooled to −78 °C. To the solution was then slowly added the lithium reagent (3−5 equiv). After 5 h of stirring at this temperature, the reaction was hydrolyzed over 24−72 h at 25 °C with 1 N HCl (20 mL). The reaction mixture was then extracted with AcOEt and dried over $MgSO_4$, and the solvent was removed. After flash chromatography, the products were isolated as white solids.

**1-(3-*C*-Acetyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6a).** The alkylation of **5a** (700 mg, 1.54 mmol) was performed using 3 equiv of a 5% solution of MeLi in diethyl ether (4.62 mmol). The intermediate was hydrolyzed over 24 h with 1 N HCl, and ketone **6a** was isolated in 78% yield (342 mg) after FC (AcOEt/pentane 2:1 to AcOEt): $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.94 (d, $J$ = 1.2 Hz, 3 H), 2.23 (dd, $J$ = 3.6 Hz, 14.6 Hz, 1 H), 2.42 (s, 3 H), 2.84 (dd, $J$ = 8.4 Hz, 14.6 Hz, 1 H), 3.97 (m, 2 H), 4.25 (dd, $J$ = 4.2 Hz, 5.7 Hz, 1 H), 6.26 (dd, $J$ = 3.3 Hz, 8.4 Hz, 1 H), 7.82 (d, $J$ = 1.2 Hz, 1 H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) δ 12.4, 26.4, 44.0, 58.3, 83.2, 83.9, 86.0, 108.8, 136.7, 150.4, 163.8, 210.5; FAB−MS 285 (38, $[M + 1]^+$). Anal. Calcd for $C_{12}H_{16}N_2O_6$ (284.27): C 50.70, H 5.67, N 9.85, O 33.77. Found C 50.41, H 5.83, N 9.90, O 33.45.

**1-(3-*C*-(1,1-Dimethylpropanoyl)-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6b).** The alkylation of **5a** (1.00 g, 2.20 mmol) was performed using 6 equiv of a 1.5 M solution of *t*-BuLi in pentane (13.20 mmol). The intermediate was hydrolyzed over 72 h with 1 N HCl, and ketone **6b** was isolated in 56% yield (405 mg) after FC (AcOEt/pentane 2:1 to AcOEt). $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 1.20 (s, 9 H), 1.79 (d, $J$ = 1.2 Hz, 3 H), 2.22 (dd, $J$ = 4.1, 14.3 Hz, 1 H), 2.56 (dd, $J$ = 7.9, 14.3 Hz, 1 H), 3.64 (m, 2 H), 4.14 (dd, $J$ = 5.4, 4.9 Hz, 1 H), 4.98 (t, $J$ = 5.5 Hz, 1 H), 5.88 (s, 1 H), 6.00 (dd, $J$ = 4.0, 7.9 Hz, 1 H), 7.69 (d, $J$ = 1.2 Hz, 1 H), 11.32 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 12.5, 26.4, 45.2, 46.7, 60.8, 83.8, 84.7, 88.2, 110.8, 138.4, 150.5, 164.1, 216.4; FAB−MS 327 (46, $[M + 1]^+$). Anal. Calcd for $C_{15}H_{22}N_2O_6$ (326.35): C 55.21, H 6.80, N 8.58. Found C 55.28, H 6.68, N 8.48.

**1-(3-*C*-Benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6c).** The alkylation of **5a** (700 mg, 1.54 mmol) was performed using 3 equiv of a 2 M solution of PhLi in cyclohexane/ether (7.95 mmol). The intermediate was hydrolyzed over 36 h with 1 N HCl, and ketone **6c** was isolated in 61% yield (560 mg) after FC (AcOEt/pentane 2:1 to AcOEt): $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.81 (s, 3 H), 2.41 (dd, $J$ = 4.1 Hz, 14.3 Hz, 1 H), 2.88 (dd, $J$ = 8.4 Hz, 14.3 Hz, 1 H), 3.73 (m, 2 H), 4.33 (dd, $J$ = 4.2 Hz, 6.3 Hz, 1 H), 4.89 (t, $J$ = 5.7 Hz, 1 H), 6.14 (dd, $J$ = 3.9, 8.1 Hz, 1 H), 6.41 (s, 1 H), 7.56 (m, H), 7.84 (s, 1 H), 8.05 (m, H), 11.31 (s, 1 H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) δ 12.5, 44.5, 59.7, 83.1, 84.0, 85.6, 109.1, 128.2, 129.8, 132.8, 135.3, 136.8, 150.6, 163.9, 200.8; FAB−MS 347 (8, $[M + 1]^+$). Anal. Calcd for $C_{17}H_{18}N_2O_6$ (346.35): C 58.95, H 5.24, N 8.09, O 27.72. Found C 58.73, H 5.43, N 7.88, O 27.73.

**General Procedure for the Preparation of 3′-*C*-Acyl-5′-*O*-(4,4′-dimethoxy-trityl)thymidines 3.** To a solution of **6** in pyridine (40 mL/mmol) at 25 °C was added 4,4′-dimethoxytrityl chloride (3 equiv) and DMAP (0.025 equiv). After 15 h of stirring, the reaction was complete. MeOH was added, and the reaction mixture was left to stir for 30 min. The solvent was removed and the residue was dissolved in $CH_2Cl_2$ and washed with $NaHCO_3$ and $H_2O$. The organic phase was collected and dried over $MgSO_4$, and the solvent was removed. FC gave **3** as pale yellow foams.

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*C*-acetyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (3a).** Compound **6a** (178 mg, 0.56 mmol) was converted to **3a** and after FC was isolated in 83% yield (272 mg): $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.84 (d, $J$ = 1.2 Hz, 3 H), 2.19 (dd, $J$ = 2.7 Hz, 14.7 Hz, 1 H), 2.31 (s, 3 H), 2.86 (dd, $J$ = 8.4 Hz, 14.7 Hz, 1 H), 3.48 (m, 2 H), 3.79 (s, 6 H), 4.28 (dd, $J$ = 4.8 Hz, 6.6 Hz, 1 H), 4.79 (s, 1 H), 6.26 (dd, $J$ = 2.7 Hz, 8.4 Hz, 1 H), 6.84 (m, 4 H), 7.30 (m, 9 H), 7.59 (d, $J$ = 1.2 Hz, 1 H), 9.38 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) δ 12.5, 25.6, 44.6, 55.2, 60.3, 83.8, 84.4, 84.7, 87.4, 110.5, 113.2, 127.0, 127.9, 127.9, 129.9, 135.2, 136.9, 144.0, 150.6, 158.6, 163.9, 208.4; FAB−MS 587 (2, $[M + 1]^+$). Anal. Calcd for

$C_{33}H_{34}N_2O_8 \cdot 2H_2O$ (622.64): C 63.60, H 6.15, N 4.49. Found C 63.20 H 6.15 N 4.31. HRMS calcd for $C_{33}H_{34}N_2O_8$ 586.2315, found 586.2315.

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*C*-(1,1-dimethylpropanoyl)-2-deoxy-*β*-D-*threo*-pentofuranosyl)thymine (3b).** Compound **6b** (142 mg, 0.40 mmol) was converted to **3b** and after FC was isolated in 88% yield (221 mg): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.15 (s, 9 H), 1.92 (d, $J$ = 1.1 Hz, 3 H), 2.37 (dd, $J$ = 3.0 Hz, 14.3 Hz, 1 H), 2.69 (dd, $J$ = 8.5 Hz, 14.3 Hz, 1 H), 3.24 (dd, $J$ = 2.5 Hz, 11.3 Hz, 2 H), 3.80 (s, 6 H), 4.45 (m, 1 H), 6.26 (dd, $J$ = 2.9 Hz, 8.5 Hz, 1 H), 6.84 (m, 4 H), 7.24−7.41 (m, 9 H), 8.02 (d, $J$ = 1.1 Hz, 1 H), 9.31 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 12.6, 26.3, 45.0, 47.6, 51.8, 55.1, 55.2, 61.6, 83.8, 84.4, 87.6, 110.7, 113.0, 113.1, 113.4, 113.4, 126.6, 127.2, 127.7, 127.7, 128.1, 128.2, 129.1, 129.8, 130.0, 134.4, 134.8, 137.1, 150.5, 158.7, 158.8, 163.9, 215.8; FAB−MS 629 (1, $[M + 1]^+$). HRMS calcd for $C_{36}H_{40}N_2O_8$ 628.2786, found 628.2786.

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*C*-(benzoyl-2-deoxy-*β*-D-*threo*-pentofuranosyl)thymine (3c).** Compound **6c** (106 mg, 0.28 mmol) was converted to **3c** (for **3c** and **2c**, no accurate combustion analysis or HRMS could be obtained) and after FC was isolated in 81% yield (148 mg): IR (KBr) 3386, 3058, 2932, 1686, 1607, 1578, 1560, 1542, 1509, 1466, 1448, 1375, 1251, 1177, 1153, 1074, 1033. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.90 (d, $J$ = 1.2 Hz, 3 H), 2.46 (dd, $J$ = 3.3 Hz, 14.9 Hz, 1 H), 3.03 (dd, $J$ = 8.7 Hz, 15.2 Hz, 1 H), 3.66 (m, 2 H), 3.72 (s, 6 H), 4.72 (dd, $J$ = 4.2 Hz, 5.4 Hz, 1 H), 5.05 (s, 1 H), 6.40 (dd, $J$ = 3.0 Hz, 8.4 Hz, 1 H), 6.75 (m, 4 H), 7.22 (m, 10 H), 7.46 (m, 2 H), 7.60 (m, 1 H), 7.82 (d, $J$ = 1.2 Hz, 1 H), 8.02 (m, 2 H), 8.62 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 12.6, 46.4, 55.2, 61.4, 83.4, 83.9, 85.0, 87.6, 111.0, 113.3, 127.1, 127.8, 128.0, 128.4, 129.8, 130.1, 133.4, 134.2, 134.8, 134.9, 143.9, 136.7, 150.5, 158.7, 163.7, 199.3. FAB−MS: 649 (1, $[M + 1]^+$).

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*O*-(triethylsilyl)-3-*C*-(triethylsilyl-oxymethyl)-2-deoxy-*β*-D-*erythro*-pentofuranosyl)thymine (9).** A solution of diol **8**[10c] (945 mg, 1.64 mmol) and imidazole (535 mg, 7.78 mmol) in DMF (8 mL) was stirred at 25 °C for 5 min, after which TESCl (0.66 mL, 3.94 mmol) was added. After 24 h of stirring, the mixture was poured onto saturated $NaHCO_3$, extracted with $CH_2Cl_2$ (3 × 100 mL), and dried ($MgSO_4$), and the solvent was evaporated. After FC (AcOEt/pentane 1:2), **9** was isolated as a colorless foam in 72% yield (946 mg): IR (KBr) 3412, 3186, 3058, 2955, 2911, 2875, 2836, 1698, 1608, 1582, 1509, 1464, 1414, 1375, 1252, 1209, 1176, 1150, 1112, 1034; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.49 (q, 6 H), 0.61 (t, 6 H), 0.90 (m, 18 H), 1.44 (d, $J$ = 1.2 Hz, 1 H), 2.08 (dd, $J$ = 8.7 Hz, 12.9 Hz, 1 H), 2.41 (dd, $J$ = 5.7 Hz, 12.9 Hz, 1 H), 3.17 (dd, $J$ = 4.5 Hz, 10.8 Hz, 1 H), 3.41 (d, $J$ = 10.2 Hz, 1 H), 3.53 (dd, $J$ = 3.6 Hz, 10.8 Hz, 1 H), 3.60 (d, $J$ = 10.2 Hz, 1 H), 3.80 (s, 6 H), 4.10 (m, 1 H), 6.36 (dd, $J$ = 5.7 Hz, 8.7 Hz, 1 H), 6.83 (m, 4 H), 7.34 (m, 9 H), 7.67 (d, $J$ = 1.2 Hz, 1 H), 7.90 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 4.1, 6.3, 6.8, 7.0, 11.7, 42.8, 55.2, 62.3, 65.6, 77.2, 83.7, 84.2, 87.0, 87.7, 110.8, 113.2, 113.2, 127.1, 127.9, 128.3, 130.2, 135.3, 135.4, 144.1, 135.9, 150.0, 158.7, 163.4; FAB−MS 804 (0.5, $[M + 1]^+$). Anal. Calcd for $C_{44}H_{62}N_2O_8Si_2$ (803.15): C 65.80, H 7.78, N 3.49. Found C 65.87, H 7.77, N 3.39. HRMS calcd for $C_{44}H_{62}O_8N_2Si_2$ 802.4045, found 802.4042.

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*O*-(triethylsilyl)-3-*C*-(hydroxymethyl)-2-deoxy-*β*-D-*erythro*-pentofuranosyl)thymine (10).** A solution of **9** (150 mg, 0.19 mmol) in THF (4 mL) and pyridine (0.2 mL) was cooled to 0 °C and HF−pyridine (0.3 mL, 0.95 mmol) was added dropwise. After 7 h of stirring, the reaction mixture was placed directly on a column of silica gel and eluted with AcOEt/pentane 2:1 to AcOEt. Alcohol **10** was isolated in 77% yield (98 mg) as a colorless foam: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.60 (q, 6 H), 0.93 (t, 9 H), 1.60 (s, 3 H), 2.18 (dd, $J$ = 8.6 Hz, 13.4 Hz, 1 H), 2.36 (dd, $J$ = 6.0 Hz, 13.4 Hz, 1 H), 3.25 (dd, $J$ = 2.6 Hz, 10.8 Hz, 1 H), 3.54 (m, 2 H), 3.79 (s, 6 H), 4.07 (dd, $J$ = 2.5 Hz, 4.7 Hz, 1 H), 6.40 (dd, $J$ = 6.0 Hz, 8.5 Hz, 1 H), 6.85 (m, 4 H), 7.33 (m, 9 H), 7.70 (s, 1 H), 8.62 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 6.6, 7.2, 12.3, 42.5, 55.5, 62.0, 65.9, 83.6, 83,7, 86.8, 87.9, 111.4, 113.6, 124.0, 127.5, 128.3, 128.4, 130.3, 134.9, 135.3, 136.2, 144.0, 149.8, 136.4, 150.9, 159.1, 164.3; FAB−MS 689 (0.8, $[M + 1]^+$). Anal. Calcd for $C_{38}H_{48}N_2O_8Si$ (688.90): C 66.25, H 7.02, N 4.07. Found C 66.28, H 7.18, N 4.23.

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*O*-(triethylsilyl)-3-*C*-formyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)thymine (11).** To a mixture of **10** (200 mg, 0.30 mmol), NMO (520 mg, 0.45 mmol), and 4 Å molecular sieve powder (150 mg) in $CH_2Cl_2$ (4 mL) was added TPAP (0.02 mmol, 7.0 mg). After 1 h of stirring, the reaction mixture was placed directly on a column of silica gel and eluted with 0.5 L of AcOEt/pentane 2:1 followed by pure AcOEt. Compound **11** was isolated in 98% yield (196 mg) as a colorless foam: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.58 (q, 6 H), 0.90 (t, 9 H), 1.79 (s, 3 H), 2.33 (dd, $J$ = 6.9 Hz, 13.9 Hz, 1 H), 2.60 (dd, $J$ = 6.9 Hz, 13.8 Hz, 1 H), 3.27 (dd, $J$ = 2.4 Hz, 11.1 Hz, 1 H), 3.49 (dd, $J$ = 4.5 Hz, 10.9 Hz, 1 H), 3.79 (s, 6 H), 4.03 (m, 1 H), 6.38 (t, $J$ = 6.9 Hz, 1 H), 6.83 (m, 4 H), 7.31 (m, 9 H), 7.60 (d, $J$ = 1.2 Hz, 1 H), 9.47 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 6.1, 6.5, 6.6, 12.3, 14.1, 21.0, 40.3, 55.1, 59.7, 60.3, 83.0, 84.9., 87.3, 111.1, 113.0, 113.1, 126.9, 127.8, 127.9, 129.9, 135.0, 13.1, 135.6, 144.0, 150.5, 18.6, 163.8, 199.3; FAB−MS 687 (1, $[M + 1]^+$). Anal. Calcd for $C_{38}H_{46}N_2O_8Si \cdot 0.5H_2O$ (695.89): C 65.52, H 6.81, N 4.02. Found C 65.65, H 6.96, N 3.88.

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*O*-(triethylsilyl)-3-*C*-(1-hydroxyethyl)-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-thymine (12a).** To a suspension of dry $CeCl_3$ (8.6 mL, 2.60 mmol) and aldehyde **11** (180 mg, 0.26 mmol) in THF at −10 °C was slowly added a 3 M solution of MeMgBr (0.86 mL, 2.6 mmol) in diethyl ether. The reaction stirred at this temperature for 3 h, after which it was quenched by the addition of aqueous $NH_4Cl$ and allowed to warm to room temperature. The product was then extracted with $CH_2Cl_2$ (3 × 25 mL), the organic layer was dried over $MgSO_4$, and the solvent was removed. The mixture of diastereoisomers, which were neither separated nor further characterized, were used in the next step without further purification.

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*O*-(triethylsilyl)-3-*C*-(1-hydroxy-2,2-dimethylpropyl)-2-deoxy-*β*-D-*erythro*-pentofuranosyl)thymine (12b).** To a suspension of dry $CeCl_3$ (13.3 mL, 3.92 mmol) in THF at −78 °C was slowly added a 1.6 M solution of *t*-butyllithium (2.45 mL, 3.92 mmol) in pentane. This was allowed to stir for 1.5 h before a solution of **11** (190 mg, 0.28 mmol) in THF (5 mL) was added dropwise at the same temperature. The reaction stirred at this temperature for 3 h, after which it was quenched by the addition of aqueous $NH_4Cl$. The product was then extracted with $CH_2Cl_2$ (12 × 25 mL), the organic layer was dried over $MgSO_4$, and the solvent was removed. As a result, 197 mg (93%) of **12b** was isolated as a single diastereoisomer, which was used in the next step without further purification: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.63 (m, 6 H), 0.88 (t, 9 H), 0.90 (s, 9 H), 1.92 (s, 3 H), 2.22 (dd, $J$ = 7.2, 14.3, 1 H), 2.88 (dd, $J$ = 2.7, 14.3, 1 H), 3.15 (d, $J$ = 5.1, 1 H), 3.26 (dd, $J$ = 2.7, 10.5, 1 H), 3.47 (d, $J$ = 5.1, 1 H), 3.71 (dd, $J$ = 5.1, 10.7, 1 H), 3.80 (s, 6 H), 3.95 (dd, $J$ = 2.7, 4.8, 1 H), 6.33 (t, $J$ = 7.2, 1 H), 6.85 (m, 4 H), 7.35 (m, 9 H), 7.84 (s, 1 H), 7.95 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 6.4, 6.9, 12.6, 28.2, 36.1, 40.9, 55.2, 60.3, 78.0, 82.5, 85.4, 87.3, 87.9, 111.1, 113.4, 127.1, 127.9, 128.1, 129.9, 134.8, 135.0, 136.7, 143.8, 150.6, 158.7, 163.9; FAB−MS 745 (0.4, $[M + 1]^+$).

**1-(5-*O*-(4,4′-Dimethoxytrityl)-3-*O*-(triethylsilyl)-3-*C*-(1-hydroxy-1-phenylmethyl)-2-deoxy-*β*-D-*erythro*-pentofuranosyl)thymine (12c).** To a suspension of dry $CeCl_3$ (8.6 mL, 2.6 mmol) and aldehyde **11** (180 mg, 0.26 mmol) in THF at −10 °C was slowly added a 1 M solution of PhMgBr (0.86 mL, 2.6 mmol) in THF. The reaction mixture stirred at this temperature for 3 h, after which it was quenched by the addition of aqueous $NH_4Cl$. The product was then extracted with $CH_2Cl_2$, the organic layer was dried over $MgSO_4$, and the solvent was removed. As a result, 62 mg (31%) of **12c** was isolated as a mixture of diastereoisomers, which were neither separated nor further characterized and were used in the next step without further purification.

**General Procedure for the Synthesis of Ketones 13.** To a solution of the alcohol in $CH_2Cl_2$ and pyridine at room temperature was added the Dess−Martin reagent in one

portion. After 2 h of stirring, the reaction was quenched by the addition of a solution of $Na_2S_2O_3$. The mixture was diluted with ether and washed with $NaHCO_3$. The organic layer was collected and dried over $MgSO_4$, and the solvent was removed. The residue was then chromatographed on silica gel with AcOEt:pentane 1:2 as eluent.

**5′-*O*-(4,4′-Dimethoxytrityl)-3′-*O*-(triethylsilyl)-3′-*C*-(acetyl)thymidine (13a).** Alcohol **12a** was converted to **13a** and isolated as an off-white foam in 15% yield (25 mg): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.66 (q, 6 H), 0.95 (t, 9 H), 1.67 (s, 3 H), 1.96 (s, 3 H), 2.37 (dd, $J$ = 6.6 Hz, 14.1 Hz, 1 H), 2.68 (dd, $J$ = 7.8 Hz, 14.1 Hz, 1 H), 3.22 (dd, $J$ = 4.2 Hz, 10.8 Hz, 1 H), 3.34 (dd, $J$ = 4.2 Hz, 10.7 Hz, 1 H), 3.79 (s, 6 H), 4.05 (m, 1 H), 6.38 (m, 1 H), 6.80 (m, 4 H), 7.10 (m, 9 H), 7.72 (s, 1 H), 8.21 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 6.2, 6.9, 12.1, 26.7, 42.1, 55.2, 61.4, 82.9, 87.2, 87.5, 111.0, 113.1, 127.1, 127.9, 128.3, 130.1, 130.2, 135.1, 135.1, 136.3, 143.8, 150.4, 158.7, 163.4, 163.4, 208.9. Anal. Calcd for $C_{39}H_{48}N_2O_8Si$ (700.91): C 66.83, H 6.09, N 4.00. Found C 66.68, H 7.17, N 3.75.

**5′-*O*-(4,4′-Dimethoxytrityl)-3′-*O*-(triethylsilyl)-3′-*C*-(1,1-dimethylpropanoyl)thymidine (13b).** Alcohol **12b** was converted to **13b** and isolated as an off-white foam in 94% yield (20 mg): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.77 (q, 6 H), 0.96 (s, 9H), 0.98 (t, 9 H), 1.77 (s, 3 H), 2.47 (d, $J$ = 7.5 Hz, 2 H), 2.93 (dd, $J$ = 1.5 Hz, 10.5 Hz, 1 H), 3.16 (dd, $J$ = 7.5 Hz, 10.5 Hz, 1 H), 4.22 (dd, $J$ = 1.5 Hz, 7.2 Hz, 1 H), 6.44 (m, 1 H), 6.81 (m, 4 H), 7.29 (m, 9 H), 7.76 (s, 1 H), 8.79 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 6.2, 6.8, 12.2, 27.0, 28.9, 45.0, 55.0, 63.9, 82.9, 88.8, 89.8, 111.9, 113.2, 127.1, 127.9, 128.3, 130.1, 135.1, 135.2, 136.3, 144.1, 150.2, 158.4, 164.0, 216.0. Anal. Calcd for $C_{42}H_{54}N_2O_8Si\cdot H_2O$ (760.99): C 66.21, H 7.42, N 3.68. Found C 65.81, H 7.73, N 3.92.

**5′-*O*-(4,4′-Dimethoxytrityl)-3′-*O*-(Triethylsilyl)-3′-*C*-(benzoyl)thymidine (13c).** Alcohol **12c** (62.2 mg, 0.08 mmol) was converted to **13c** and isolated as an off-white foam in 35% yield (60 mg): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.51 (tq, 6 H), 0.84 (t, 9 H), 1.19 (s, 3 H), 2.47 (dd, $J$ = 4.8 Hz, 13.8 Hz, 1 H), 3.07 (dd, $J$ = 2.4 Hz, 11.0 Hz, 1 H), 3.18 (dd, $J$ = 10.2 Hz, 13.8 Hz, 1 H), 3.45 (dd, $J$ = 3.0 Hz, 11.0 Hz, 1 H), 3.75 (s, 6 H), 4.55 (m, 1 H), 6.59 (dd, $J$ = 4.8 Hz, 10.4 Hz, 1 H), 6.68 (m, 4 H), 7.06 (m, 4 H), 7.32 (m, 8 H), 7.76 (d, $J$ = 0.9 Hz), 7.80 (m, 2 H), 8.37 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 6.0, 6.8, 11.2, 42.1, 55.2, 62.1, 83.3, 87.5, 89.1, 89.3, 111.5, 112.9, 113.0, 127.2, 127.8, 128.2, 128.5, 130.3, 130.5, 133.1, 133.8, 134.3, 134.6, 136.1, 143.5, 150.4, 158.6, 163.6, 195.3; HRMS calcd for $C_{44}H_{50}N_2O_8Si$ 762.3334, found 762.3334.

**General Procedure for the Preparation of 3′-*C*-Acyl-5′-*O*-(4,4′-dimethoxytrityl)thymidines 2.** To a solution of the protected alcohol in THF at O °C was added dropwise TBAF (1.5 equiv). The solution was then allowed to warm to room temperature and was stirred at this temperature for 15 min. The reaction mixture was placed directly on a column of silica gel and was chromatographed with 2:1 AcOEt:Pentane to AcOEt as eluent.

**5′-*O*-(4,4′-Dimethoxytrityl)-3′-*C*-(acetyl)thymidine (2a).** Compound **13a** (15.9 mg, 0.02 mmol) was converted to 11.1 mg (95%) of **2a**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.69 (s, 3 H), 2.12 (s, 3 H), 2.36 (dd, $J$ = 6.0 Hz, 13.8 Hz, 1 H), 2.53 (dd, $J$ = 8.4 Hz, 13.8 Hz, 1 H), 3.29 (dd, $J$ = 6.6 Hz, 10.7 Hz, 1 H), 3.38 (dd, $J$ = 4.4 Hz, 10.7 Hz, 1 H), 3.80 (s, 6 H), 4.06 (dd, $J$ = 4.5 Hz, 6.7 Hz, 1 H), 6.37 (dd, $J$ = 6.3 Hz, 8.4 Hz, 1 H), 6.84 (m, 4 H), 7.30 (m, 9 H), 7.52 (d, $J$ = 0.9 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 12.2, 15.3, 26.8, 42.7, 55.2, 61.9, 65.8, 83.6, 85.4, 86.4, 87.6, 111.5, 113.3, 127.2, 127.9, 128.0, 128.1, 129.9, 130.0, 130.1, 134.9, 135.6, 143.8, 150.1, 158.8, 163.2, 208.2; HRMS calcd for $C_{33}H_{34}N_2O_8$ 586.2135, found 586.2135.

**5′-*O*-(4,4′-Dimethoxytrityl)-3′-*C*-(2,2-dimethylpropanoyl)-thymidine 2b.** Compound **13b** (20 mg, 0.03 mmol) was converted to 16 mg (84%) **2b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.01 (s, 9 H), 2.17, (s, 3 H), 2.33 (dd, $J$ = 5.0 Hz, 13.5 Hz, 1 H), 2.74 (dd, $J$ = 9.9 Hz, 13.5 Hz, 1 H), 3.07 (dd, $J$ = 5.2 Hz, 10.8 Hz, 1 H), 3.19 (dd, $J$ = 3.3 Hz, 10.8 Hz, 1 H), 3.78 (s, 6 H), 4.25 (m, 1 H), 6.50 (dd, 5.2 Hz, 9.5 Hz, 1 H), 6.82 (m, 4 H), 7.32 (m, 9 H), 7.63 (s, 1 H), 8.01 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) d 11.8, 26.9, 44.5, 55.3, 76.6, 76.8, 87.2, 87.4, 88.4, 111.1, 113.2, 127.2, 127.9, 128.6, 130.4, 135.9, 150.6, 158.8, 202.6; HRMS calcd for $C_{36}H_{40}O_8N_2$ 628.2786, found 628.2786.

**5′-*O*-(4,4′-Dimethoxytrityl)-3′-*C*-(benzoyl)thymidine 2c.** Compound **13c** (55 mg, 0.07 mmol) was converted to 25 mg (54%) of **2c**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.20 (s, 3 H), 2.43 (dd, $J$ = 4.8 Hz, 13.7 Hz, 1 H), 2.63 (m, 1 H), 3.12 (m, 1 H), 3.49 (dd, $J$ = 2.8 Hz, 7.1 Hz, 1 H), 3.75 (s, 6 H), 4.50 (m, 1 H), 6.63 (dd, $J$ = 5.1 Hz, 9.9 Hz, 1 H), 6.68 (m, 4 H), 7.05 (m, 4 H), 7.15 (m, 4 H), 7.28 (m, 3 H), 7.46 (m, 1 H), 7.71 (s, 1 H), 7.85 (m, 2 H), 8.68 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 11.3, 42.9, 55.2, 62.1, 83.2, 86.7, 87.2, 87.6, 111.9, 113.0, 127.2, 127.8, 128.3, 128.5, 130.2, 130.3, 130.4, 133.0, 134.2, 134.4, 134.6, 136.1, 143.5, 150.7, 158.6, 158.7, 163.6, 195.9.

**General Photolysis Conditions.** Photolyses were carried out in quartz glass cells (1 cm path length) in 2 mL of acetonitrile in the presence of 3 equiv of $n$Bu$_3$SnH. A 500 W Hg high-pressure lamp with a 320 nm cut-off filter was employed. The cells were maintained at 20 °C. After photolysis, the solutions were analyzed, and the yields were determined by reverse-phase HPLC. Products were identified by comparison with authentic samples.

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**Supporting Information Available:** NMR spectra of compounds **2c** and **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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