Tetrahedron 65 (2009) 6008–6016

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Nucleophilic substitution approach to 4′-substituted thymidines by employing 4′-benzenesulfonyl leaving group

Hisashi Shimada, Satoshi Kikuchi, Saori Okuda, Kazuhiro Haraguchi, Hiromichi Tanaka *

School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

ARTICLE INFO

Article history:
Received 9 April 2009
Received in revised form 26 May 2009
Accepted 27 May 2009
Available online 3 June 2009

Keywords:
Thymidine
Nucleophilic substitution
Benzenesulfonyl leaving group
Organosilicon reagent
Organoaluminum reagent

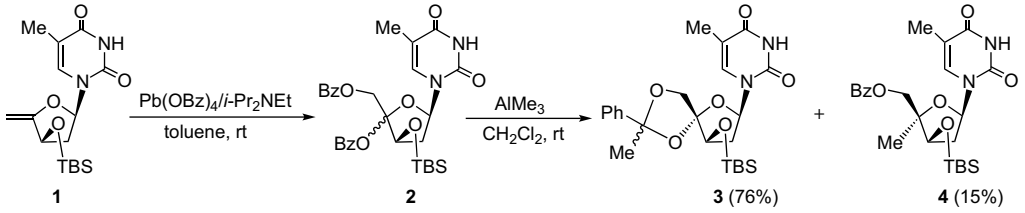
ABSTRACT

Synthesis of 4′-substituted thymidines was investigated based on nucleophilic substitution using organosilicon and organoaluminum reagents. Two substrates having a benzenesulfonyl leaving group at the 4′-position were prepared for this purpose: 1-[4-benzenesulfonyl-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-L-*threo*-pentofuranosyl]thymine (**8α**) and the 4′-(benzenesulfonyl)thymidine derivative (**8β**). The reaction of **8α** with organosilicon reagents ($Me_3SiCH_2CH{=}CH_2$ and Me_3SiN_3) in combination with $SnCl_4$ gave preferentially the 4′-substituted β-D-isomer: the 4′-allyl (**12β**) and 4′-azido (**15β**) derivatives, respectively. The reaction of **8α** with $AlMe_3$, however, gave the 4′-methyl-α-L-isomer (**16α**) as the major product, presumably through an ion pair mechanism. By employing the substrate **8β** in this reaction, the 4′-methylthymidine derivative (**16β**) was obtained exclusively in high yield. The 4′-ethyl (**20β**) and 4′-cyano (**24β**) derivatives were also synthesized by reacting **8β** with the respective organoaluminum reagent.

1. Introduction

Several analogues of thymidine substituted at the 4′-position (azido, cyano, and ethynyl) have been reported to exhibit potent anti-HIV activity.[1] Synthesis of this class of nucleosides has mostly been carried out by manipulating the 4′-hydroxymethyl derivatives of nucleosides or sugars that can be prepared by the well known aldol-Cannizzaro reaction of the corresponding aldehyde,[2,3] although several other newer synthetic methods are also available.[1]

We have developed two different approaches to the 4′-substituted nucleosides: one is ring-opening reaction of 4′,5′- or 3′,4′-epoxysugar nucleosides with organoaluminum or organosilicon reagents,[4,5] and the other is nucleophilic substitution with these reagents by employing 4′-benzoyloxy nucleosides.[6,7] In the latter approach, the 4′-benzoyloxy leaving group was introduced by using unsaturated-sugar nucleosides. One example is shown in Scheme 1 for the preparation of the 4′-benzoyloxy thymine-nucleoside **2** from the 4′,5′-unsaturated derivative **1**.[6]



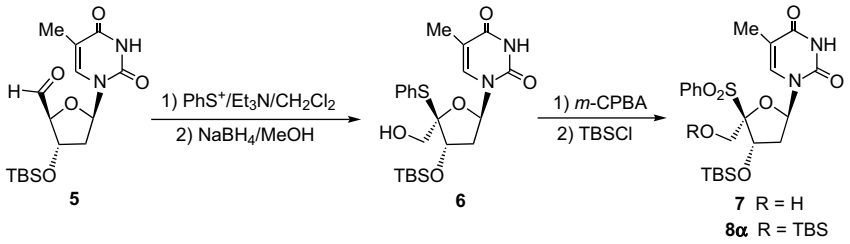
1 **2** **3** (76%) **4** (15%)

Scheme 1.

For the synthesis of 4′-substituted nucleosides, we have learned that nucleophilic substitution is certainly an efficient approach through the studies in Refs. 6 and 7. However, there still remains much room for its improvement. For example, as shown in Scheme 1, the reaction of **2** with $AlMe_3$ resulted in the preponderance formation of the spiro derivative **3**, not the desired **4**.[6] In the present study, we focus on employing substrates having the 3′,5′-bis-*O*-silyl protecting group as well as a different 4′-leaving group from the benzoyloxy group.

* Corresponding author.
E-mail address: hirotnk@pharm.showa-u.ac.jp (H. Tanaka).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.078



Scheme 2.

2. Results and discussion

2.1. Preparation of the 4′-benzenesulfonyl derivatives

Since benzenesulfinic acid is much more acidic (pK_a 1.50) than benzoic acid (pK_a 4.20),[8] one would expect that a benzenesulfonyl group serves as a better leaving group than does benzoyloxy group. In fact, there have been a considerable number of reports for the nucleophilic substitution of a benzenesulfonyl group, especially those at the 2-position of cyclic ethers.[9] We first examined benzenesulfenylation at the 4′-position of thymidine by reacting the 5′-aldehyde (**5**)[10] with several different reagents in the presence of a base (Scheme 2). Compound **5** was prepared in 83% yield by oxidizing 3′-*O*-(*tert*-butyldimethylsilyl)thymidine with 2-iodoxybenzoic acid (IBX)[11] in CH_3CN.

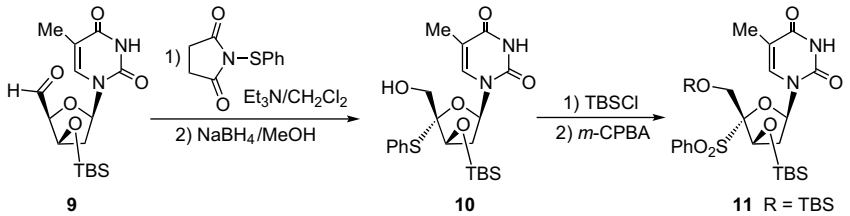
When a mixture of **5** and freshly distilled PhSCl[12] (3 equiv) in CH_2Cl_2 was treated with dropwise addition of Et_3N (6 equiv), the 4′-sulfenylated product was formed. After partial purification by column chromatography, this product was dissolved in MeOH and reacted with $NaBH_4$ to give **6** as the sole product in 69% yield (Scheme 2). The depicted stereochemistry of **6** was confirmed based on NOE experiments: H-5′/H-1′ (1.5%) and H-6/Ph (4.1%). Compound **6** can also be prepared in 60% yield by using PhSCl generated in situ from PhSH/NCS/CH_2Cl_2[13] in the presence of Et_3N.[14] The highest yield of **6** (75%) was obtained when the stable crystalline *N*-(benzenesulfenyl)succinimide (3 equiv) was employed. Although the published method for the preparation of this reagent involves the use of Bu_3SnSPh and NBS,[15] it was prepared in our hands simply by reacting PhSH/Et_3N with NCS in CH_2Cl_2, as described in the Experimental section. Conventional oxidation of **6** with *m*-CPBA led to the benzenesulfonyl derivative **7** in quantitative yield, which was silylated to furnish the substrate **8α** (92% yield).

The stereochemical outcome observed in the above benzenesulfenylation of **5** is assumed to be a reflection of the steric repulsion between the 3′-'down'-*O*-TBS group and the sulfenylating reagents. To confirm this assumption, the 5′-aldehyde **9** having the opposite 3′-configuration was prepared and subjected to the reaction with *N*-(benzenesulfenyl)succinimide followed by $NaBH_4$ as shown in Scheme 3. This resulted in the sole formation of **10** (82%), the stereochemistry of which was evident from its NOE experiment: H-5′b/H-6 (2.0%).[16] Compound **10** was converted to the 4′-benzenesulfonyl derivative **11**.

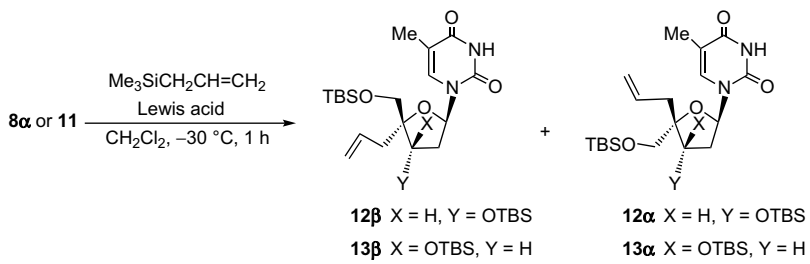
2.2. Reaction of 8α or 11 with organosilicon reagents

To see if the 4′-benzenesulfonyl derivative **8α** is actually a suitable substrate for the introduction of 4′-substituents, its reaction with $Me_3SiCH_2CH{=}CH_2$ was investigated in the presence of several different Lewis acids (Scheme 4). As summarized in Table 1, $BF_3{\cdot}OEt_2$ and Me_3SiOTf did not work at all (entries 1 and 2). In contrast, as shown by entries 3 and 4, both $SnCl_4$ and $MeAlCl_2$ gave a high yield of the 4′-allylated product **12** with a high selectivity for the β-D-isomer (**12β**). When **11,** having the opposite 3′-configuration to **8α**, was reacted under the same reaction conditions as those in entry 3, again the β-D-isomer (**13β**) was formed as the major stereoisomer (entry 5). These results suggested that the 4′-allylation of **8α** and **11** would not be a simple Lewis acid-promoted substitution, but 4′-chlorination of the substrate may possibly be involved as an initial reaction pathway.

Although such a 4′-chlorinated intermediate was assumed to be quite unstable, we were able to isolate the 4′-chloro derivative **14**



Scheme 3.



Scheme 4.

Table 1
Reaction of **8** or **11** with allyltrimethylsilane by changing Lewis acid[a]

Entry	Substrate	Lewis acid	Yield (%) of **12** or **13**	Ratio of β-D/α-L[b]
1	**8α**	$BF_3{\cdot}OEt_2$[c]	—	—
2	**8α**	Me_3SiOTf[d]	0	—
3	**8α**	$SnCl_4$	95	9/1
4	**8α**	$MeAlCl_2$	94	20/1
5	**11**	$SnCl_4$	62	5/1

[a] All reactions were carried out by adding the respective Lewis acid (4 equiv) to a mixture of **8α** or **11** and allyltrimethylsilane (10 equiv) in CH_2Cl_2.
[b] The ratio was determined based on ^{1}H NMR spectroscopy.
[c] A complex mixture of products was observed by TLC (hexane/EtOAc=1/1) analysis.
[d] Compound **8α** remained intact as evidenced by TLC analysis.

(Fig. 1) in 73% yield upon reacting **8α** with $MeAlCl_2$ alone in CH_2Cl_2 followed by HPLC purification (hexane/EtOAc=1/1, t_R 8.1 min). The MS spectrum of **14** thus isolated supported the structure: M^++H *m/z* 505 (^{35}Cl) and 507 (^{37}Cl); M^+−Cl *m/z* 465. The ^{1}H and ^{13}C NMR spectra of **14** measured in CD_2Cl_2 showed that it was contaminated with an unknown product (ca. 8%, the 4′-epimer?), but allowed us to assign all the proton and carbon signals corresponding to the depicted structure.[17] Its NOE experiment led to the confirmation of the α-L-stereochemistry: H-5′a/H-1′ (0.4%). It should be mentioned that, when the above NMR sample in CD_2Cl_2 was measured again after 6 h, some additional signals derived from decomposed product(s) appeared.

When the above isolated 4′-chloro derivative (**14**) was dissolved in CH_2Cl_2 and treated with $Me_3SiCH_2CH{=}CH_2$, no reaction took place. However, addition of $MeAlCl_2$ (3 equiv) to the solution gave **12** in 99% yield with exactly the same diastereomer ratio as that of entry 4.

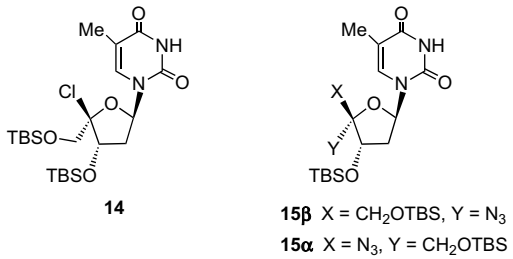


Figure 1.

Attempts to introduce a cyano group to the 4′-position of **8α** by reacting with Me_3SiCN under the conditions of either entry 3 or 4 failed. In contrast, the use of Me_3SiN_3 in the presence of $SnCl_4$ gave the 4′-azido derivative **15** (Fig. 1) in 99% yield in favor of the β-D-isomer (**15β**/**15α**=2/1).

2.3. Reaction of 8α or 11 with $AlMe_3$

We next examined the reaction of **8α** with $AlMe_3$ (Scheme 5). When **8α** was reacted with $AlMe_3$ (8 equiv) in CH_2Cl_2 for 1 h, the 4′-methylated product (**16**) was obtained in 92% yield as a mixture of two diastereomers (**16β**/**16α**=1/5.3). However, NOE experiment of the major isomer showed that it has the wrong 4′-stereochemistry: H-5′b/H-1′ (1.1%). The use of **11** in this reaction gave the corresponding 4′-methyl-β-D-isomer (**17β**) as the major product (**17β**/**17α**=ca. 20/1, combined yield: 95%). Also observed in these reactions is the formation of variable amounts of methyl phenyl sulfoxide, which had presumably been formed through the reaction of $Me_2AlOSOPh$ with $AlMe_3$.[18]

The above fact that both reactions proceeded mostly with retention of configuration at the 4′-position suggests an ion pair mechanism (S_Ni mechanism) as reported recently from our laboratory.[19] In fact, when the above reaction of **8α** was carried out in the less polar solvent CCl_4, an increase of the ratio of **16α** was observed (**16β**/**16α**=1/7.1, combined yield: 93%).

These results clearly suggest that, for the stereoselective entry to 4′-substituted thymidines through the reaction with organoaluminum reagents, the 4′-benzenesulfonyl substrate having a β-D-configuration was needed.

2.4. Inversion of the 4′-benzenesulfenyl group

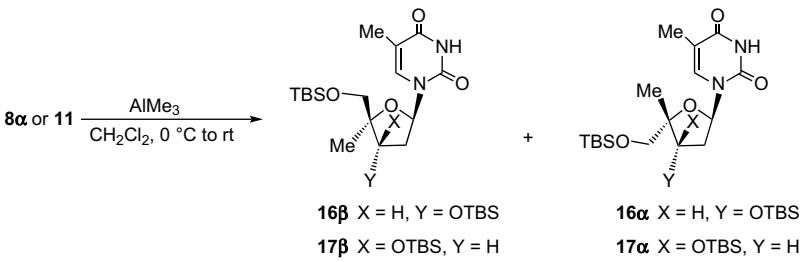
An attempt to invert the 4′-configuration was made first by reacting the 4′-benzenesulfonyl derivative **8α** with Me_3SiSPh in the presence of $MeAlCl_2$ in CH_2Cl_2. However, this reaction gave an equal amount of **18β** and **18α** at −78 °C for 1 h, as evidenced by ^{1}H NMR spectroscopy. We, therefore, turned to the use of the 4′-benzenesulfenyl derivative **18α** which was prepared by silylation of **6**.

Although no inversion took place upon reacting **18α** with Me_3SiSPh in the presence of $SnCl_4$ (CH_2Cl_2, −30 °C),[20] treatment with $Hg(OAc)_2$/AcOH in CH_2Cl_2 at rt for 0.5 h gave the 4′-acetoxy derivative **19** (**19β**/**19α**=1/0.61) in almost quantitative yield (Scheme 6). Reaction of **19** with Me_3SiSPh in the presence of $SnCl_4$ at −30 °C for 1 h gave the 4′-sulfenylated β-D-isomer **18β** as the major product (**18β**/**18α**=20/1, combined yield: 78%) together with the 5′-*O*-desilylated products (**6** and its β-D-*erythro*-isomer,[21] ca. 20% yield). After oxidation of **18** with *m*-CPBA, the desired 4′-sulfone having β-D-*erythro*-configuration (**8β**) was isolated by HPLC separation (Fig. 2).

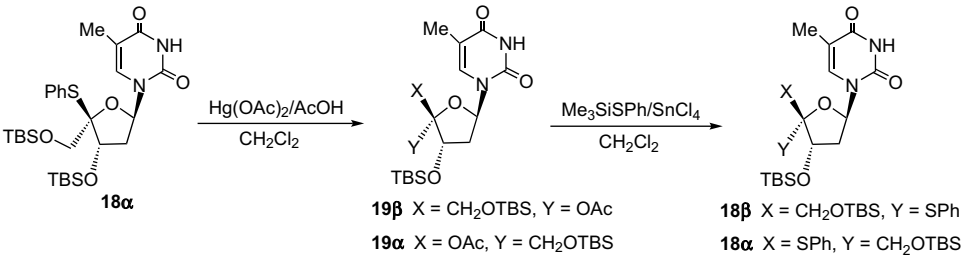
2.5. Reaction of 8β with organoaluminum reagents

When the above prepared **8β** was reacted with $AlMe_3$ in a manner similar to the case of **8α** (in CH_2Cl_2, 0 °C to rt), the 4′-methylated product **16β** was obtained exclusively in 93% yield (Scheme 7), which was formed as a result of retention of the 4′-configuration. This fact certainly strengthens our recently proposed ion pair mechanism[19] in that, even the 4′-leaving group and the neighboring 3′-silyloxy substituent occupy the same face, the aluminate $[Me_3AlOSOPh]^-$ formed after coordination to the leaving group remains on the side it departed, from which nucleophilic transfer of a methyl ligand inevitably takes place from the same face.

The high β-D-selectivity observed in the reaction with $AlMe_3$ was also the case for $AlEt_3$ to give the 4′-ethyl derivatives **20β** and



Scheme 5.



Scheme 6.

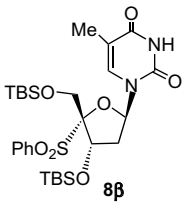
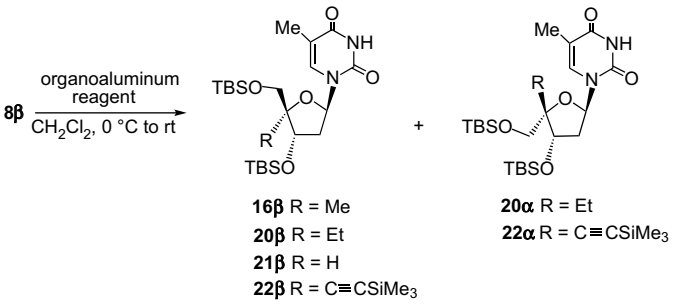


Figure 2.



Scheme 7.

20α in a ratio of 14/1 (combined yield: ca. 79%) together with a small amount of the reduction product **21β** (ca. 10%): retention (**20β** plus **21β**)/inversion (**20α**)=ca. 84/5. We also examined introduction of an ethynyl group through the reaction between **8β** and $EtAl(C{\equiv}CSiMe_3)_2$. The reagent was prepared by reacting $EtAlCl_2$/toluene with lithium (trimethylsilyl)acetylide (2 equiv)/hexane. However, this reaction gave the 4′-ethynylthymidine derivative (**22β**) only in 9% yield.[22] Other products were the 4′-ethyl (**20β**, 58%), 3′,5′-bis-*O*-TBS-thymidine (**21β**, 13%), and the 4′-ethynyl-α-L-nucleoside (**22α**, 13%): retention (**22β** plus **20β** plus **21β**)/inversion (**22α**)=80/13.[23]

In contrast to the above cases, when $AlPh_3$ was employed for this reaction (in CH_2Cl_2 at rt for 3 h), **8β** remained intact as evidenced by TLC analysis (hexane/EtOAc=1/1). By performing the reaction under reflux for 4 h, most **8β** (R_f 0.5) was converted to one less polar product (R_f 0.6). However, this product was found to be **23** (93%, stereochemistry not known), which was formed through an elimination pathway (Fig. 3). At the present time, we do not have a clear explanation for this result, but one might assume that this aluminum reagent formed a complex with THF during its preparation[24] and, therefore, acts simply as a base rather than coordinating to the 4′-benzenesulfonyl group.

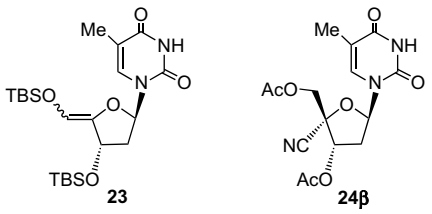


Figure 3.

Finally, we examined the synthesis of 4′-cyanothymidine which was not obtained from **8α** by reacting with Me_3SiCN as mentioned previously. Compound **8β** was reacted with Et_2AlCN in refluxing toluene for 4 h.[25] Since separation of the resulting mixture of products failed even by HPLC,[26] the mixture was desilylated with Bu_4NF/THF and then acetylated. HPLC separation ($CHCl_3$/MeOH=100/2) of the acetylated mixture enabled us to isolate 3′,5′-di-*O*-acetyl-4′-cyanothymidine (**24β**) in 45% yield (Fig. 3).

3. Conclusion

A nucleophilic substitution approach to the 4′-substituted analogues of thymidine was investigated by using the substrates **8α** and **8β** having a benzenesulfonyl leaving group. In the reaction of the α-L-*threo*-isomer **8α** with organosilicon reagents, Lewis acids used such as $SnCl_4$ and $MeAlCl_2$ serve as a chlorinating agent to generate the 4′-chloro intermediate (**14**). Organosilicon nucleophiles then react with **14** presumably through the S_N2 mechanism to give the 4′-allyl (**12β**) and 4′-azido (**15β**) analogues. In contrast to this, organoaluminum reagents seem to react with **8α** mostly through an S_Ni mechanism, which results in retention of configuration at the 4′-position to afford the 4′-substituted α-L-nucleosides. Compound **8β** having β-D-*erythro*-configuration was, therefore, prepared from **18α**. Its reaction with organoaluminum reagents allowed to synthesize the 4′-methyl (**16β**), 4′-ethyl (**20β**), and 4′-cyano (**24β**) analogues of thymidine.

4. Experimental section

4.1. General

NMR spectra were recorded either at 400 MHz (JNM-GX 400) or at 500 MHz (JNM-LA 500). Chemical sifts are reported relative to Me_4Si. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix on a JNS-SX 102A. UV spectra were measured on a JASCO Ubest-55 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). High performance liquid chromatography (HPLC) was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H) KIT column (2×25 cm).

4.2. 3′-*O*-(*tert*-Butyldimethylsilyl)thymidine-5′-aldehyde (5)

An CH_3CN (17 mL) solution containing IBX (980 mg, 3.5 mmol) and 3′-*O*-(*tert*-butyldimethylsilyl)thymidine (1.04 g, 2.92 mmol) was refluxed with vigorous stirring for 1 h. The reaction mixture was filtered through a Celite pad. The resulting filtrate was

evaporated and then partitioned between EtOAc and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc=1/2) of the organic layer gave **5** (859 mg, 83%) as a foam.

4.3. Preparation of *N*-(benzenesulfenyl)succinimide

To a CH_2Cl_2 (15 mL) solution of NCS (1.01 g, 7.53 mmol) were added PhSH (0.77 mL, 7.53 mmol) and then Et_3N (1.05 mL, 7.53 mmol) dropwise at 0 °C. The reaction mixture was stirred for 18 h at rt. After the reaction mixture being partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl, column chromatography ($CHCl_3$) of the organic layer gave *N*-(benzenesulfenyl)succinimide (1.34 g, 86%), which was crystallized from CH_2Cl_2/Et_2O: mp 116 °C (identical with that reported in Ref. 15).

4.4. 1-[4-Benzenesulfenyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-L-*threo*-pentofuranosyl]thymine (6)

A mixture of *N*-(benzenesulfenyl)succinimide (354 mg, 1.71 mmol) and Et_3N (0.48 mL, 3.42 mmol) in CH_2Cl_2 (4 mL) was stirred for 1 h at rt. To this solution was added a CH_2Cl_2 (5 mL) solution of **5** (200 mg, 0.57 mmol). After stirring for 24 h, the reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. Column chromatography (hexane/EtOAc=6/1) of the organic layer gave the product (203 mg), which was dissolved in MeOH (5 mL) and reacted with $NaBH_4$ (33.3 mg, 0.88 mmol) at rt for 0.5 h. The reaction mixture was evaporated, partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. Purification of the organic layer by column chromatography (hexane/EtOAc=3/1) gave **6** (198 mg, 75%) as a foam: UV (MeOH) λ_{max} 261 nm (ε 11,800), λ_{min} 237 nm (ε 4800); ^{1}H NMR ($CDCl_3$) δ 0.117 and 0.119 (6H, each as s), 0.91 (9H, s), 1.92 (3H, d, J=1.2 Hz), 2.42 (1H, ddd, J=2.7, 6.3 and 13.7 Hz), 2.48–2.55 (2H, m, J=5.4, 6.8, 7.8 and 13.7 Hz), 3.72 (2H, d, J=6.8 Hz), 4.51 (1H, dd, J=2.7 and 5.4 Hz), 6.63 (1H, dd, J=6.3 and 7.8 Hz), 7.32–7.57 (5H, m), 7.73 (1H, d, J=1.2 Hz), 9.23(1H, br); NOE experiment H-5′/H-1′ (1.5%); ^{13}C NMR ($CDCl_3$) δ −5.22, −4.90, 12.58, 17.93, 25.60, 40.46, 62.86, 77.61, 86.69, 99.92, 111.59, 129.19, 129.25, 129. 69, 134.70, 136.04, 150.42, 163.72; FABMS (*m*/*z*) 465 (M^++H). Anal. Calcd for $C_{22}H_{32}N_2O_5SSi$: C, 56.87; H, 6.94; N, 6.03. Found: C, 57.01; H, 6.99; N, 6.00.

4.5. 1-[4-Benzenesulfonyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-L-*threo*-pentofuranosyl]thymine (7)

A mixture of **6** (105 mg, 0.23 mmol) and *m*-CPBA (126 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) was stirred for 24 h at rt. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Purification of the organic layer by column chromatography (hexane/EtOAc=3/1) gave **7** (112 mg, 100%) as a foam: UV (MeOH) λ_{max} 266 nm (ε 10,400), λ_{min} 238 nm (ε 4100); ^{1}H NMR ($CDCl_3$) δ 0.22 and 0.24 (6H, each as s), 0.95 (9H, s), 2.05 (3H, d, J=1.2 Hz), 2.38 (1H, ddd, J=1.2, 6.1 and 13.7 Hz), 2.67 (1H, ddd, J=6.3, 9.5 and 13.7 Hz), 3.64 (1H, d, J=12.4 Hz), 4.04 (1H, d, J=12.4 Hz), 5.33 (1H, dd, J=1.2 and 6.3 Hz), 6.76 (1H, dd, J=6.1 and 9.5 Hz), 7.55–7.82 (5H, m), 7.89 (1H, d, J=1.2 Hz), 8.87 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.24, −4.96, 12.69, 17.96, 25.62, 40.84, 62.16, 73.80, 86.20, 102.38, 112.50, 129.26, 129.93, 134.70, 135.25, 150.40, 163.34; FABMS (*m*/*z*) 497 (M^++H). Anal. Calcd for $C_{22}H_{32}N_2O_7SSi$: C, 53.20; H, 6.49; N, 5.64. Found: C, 53.28; H, 6.52; N, 5.54.

4.6. 1-[4-Benzenesulfonyl-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-L-*threo*-pentofuranosyl]thymine (8α)

A mixture of **7** (2.25 g, 4.53 mmol), TBSCl (1.37 g, 9.08 mmol), and imidazole (1.55 g, 22.7 mmol) in DMF (30 mL) was stirred for 15 h at rt. The reaction mixture was partitioned between EtOAc and H_2O. Purification of the organic layer by column chromatography (hexane/EtOAc=5/1) gave **8α** (2.56 g, 92%) as a foam: UV (MeOH) λ_{max} 266 nm (ε 10,400), λ_{min} 237 nm (ε 3400); ^{1}H NMR ($CDCl_3$) δ −0.32, −0.13, 0.18 and 0.20 (12H, each as s), 0.72 and 0.93 (18H, each as s), 2.05 (3H, d, J=1.2 Hz), 2.39 (1H, ddd, J=3.2, 6.8 and 13.4 Hz), 2.61 (1H, ddd, J=7.3, 7.6 and 13.4 Hz), 3.95 (1H, d, J=11.7 Hz), 4.15 (1H, d, J=11.7 Hz), 5.23 (1H, dd, J=3.2 and 7.3 Hz), 6.67 (1H, dd, J=7.6 and 6.8 Hz), 7.48–7.82 (5H, m), 7.86 (1H, d, J=1.2 Hz), 9.19 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.99, −5.83, −5.21, −5.00, 12.65, 17.94, 18.33, 25.57, 25.67, 40.73, 62.43, 72.41, 85.51, 103.57, 112.28, 128.64, 129.89, 133.80, 135.60, 137.63, 150.40, 163.70; FABMS (*m*/*z*) 611 (M^++H). Anal. Calcd for $C_{28}H_{46}N_2O_7SSi_2$: C, 55.05; H, 7.59; N, 4.59. Found: C, 55.34; H, 7.74; N, 4.54.

4.7. The aldehyde (9) derived from 1-[3-*O*-(*tert*-butyl-dimethylsilyl)-2-deoxy-β-D-*threo*-pentofuranosyl]thymine

This compound was prepared as a foam in 94% yield from 1-[3-*O*-(*tert*-butyl-dimethylsilyl)-2-deoxy-β-D-*threo*-pentofuranosyl]-thymine by the procedure described for the preparation of **5**. Physical data for **9**: ^{1}H NMR ($CDCl_3$) δ 0.03 and 0.08 (6H, each as s), 0.82 (9H, s), 1.94 (3H, d, J=1.2 Hz), 2.15 (1H, ddd, J=1.0, 2.2 and 14.6 Hz), 2.62 (1H, ddd, J=5.1, 7.8 and 14.6 Hz), 4.52 (1H, d, J=4.4 Hz), 4.84 (1H, ddd, J=1.0, 4.4 and 5.1 Hz), 6.32 (1H, dd, J=2.2 and 7.8 Hz), 7.86 (1H, d, J=1.2 Hz), 9.58 (1H, br), 9.72 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.49, −4.99, 12.59, 17.76, 25.31, 41.88, 72.50, 86.04, 88.74, 110.28, 136.31, 150.58, 164.09, 197.20; FABMS (*m*/*z*) 355 (M^++H). FAB-high resolution MS (*m*/*z*) calcd for $C_{16}H_{27}N_2O_5Si$: 355.1689, found: 355.1668 (M^++H).

4.8. 1-[4-Benzenesulfenyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-*threo*-pentofuranosyl]thymine (10)

A mixture of **9** (276.5 mg, 0.78 mmol), *N*-(benzenesulfenyl)succinimide (485 mg, 2.34 mmol), and Et_3N (0.65 mL, 4.68 mmol) in CH_2Cl_2 (7.0 mL) was stirred for 24 h at rt. The reaction mixture was evaporated and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc=4/1) of the organic layer gave the 4′-sulfenylated aldehyde (314.5 mg), which was dissolved in MeOH (8.0 mL) and treated with portionwise addition of $NaBH_4$ (51.4 mg, 1.36 mmol). The reaction mixture was stirred for 20 min at rt and then partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. Column chromatography (hexane/EtOAc=3/1) of the organic layer gave **10** (298.1 mg, 82%) as a foam: UV (MeOH) λ_{max} 264 nm (ε 11,900), λ_{min} 238 nm (ε 4200); ^{1}H NMR ($CDCl_3$) δ 0.12 and 0.17 (6H, each as s), 0.92 (9H, s), 1.90 (3H, d, J=1.0 Hz), 1.95 (1H, ddd, J=2.2, 4.1 and 14.1 Hz), 2.63 (1H, dd, J=3.2 and 10.5 Hz), 3.08 (1H, ddd, J=6.1, 7.8 and 14.1 Hz), 3.69 (1H, dd, J=3.2 and 12.0 Hz), 3.80 (1H, dd, J=10.5 and 12.0 Hz), 4.39 (1H, dd, J=2.2 and 6.1 Hz), 6.59 (1H, dd, J=4.1 and 7.8 Hz), 7.33–7.57 (5H, m), 7.64 (1H, d, J=1.0 Hz), 9.27 (1H, br); NOE experiment H-5′b/H-6 (2.0%); ^{13}C NMR ($CDCl_3$) δ −5.19, −5.05, 12.52, 17.95, 25.60, 41.56, 62.12, 83.85, 99.98, 111.43, 128.52, 129.12, 129.49, 136.12, 136.21, 150.46, 163.76; FABMS (*m*/*z*) 465 (M^++H). Anal. Calcd for $C_{22}H_{32}N_2O_5SSi$: C, 56.87; H, 6.94; N, 6.03. Found: C, 57.08; H, 6.97; N, 6.19.

4.9. 1-[4-Benzenesulfonyl-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-*threo*-pentofuranosyl]thymine (11)

This compound was prepared as a foam in 96% yield from **10** by the procedure described for the preparation of **8α** from **6**. Physical data for **11**: UV (MeOH) λ_{max} 266 nm (ε 10,400), λ_{min} 237 nm (ε 3900); ^{1}H NMR ($CDCl_3$) δ −0.30, −0.14, 0.20 and 0.23 (12H, each as s), 0.70 and 0.95 (18H, each as s), 1.90 (3H, d, J=1.0 Hz), 2.01 (1H, ddd, J=3.4, 4.9 and 14.1 Hz), 3.25 (1H, ddd, J=7.1, 7.8 and 14.1 Hz),

4.16 (2H, s), 5.15 (1H, dd, *J*=3.4 and 7.1 Hz), 6.77 (1H, dd, *J*=4.9 and 7.8 Hz), 7.50–7.91 (6H, m), 9.48 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.88, −5.75, −5.11, 12.38, 17.94, 18.49, 25.60, 25.68, 41.81, 62.78, 72.72, 85.73, 104.91, 111.81, 128.59, 130.27, 133.78, 135.80, 136.98, 150.44, 163.76; FABMS (*m*/*z*) 611 (M^++H). Anal. Calcd for $C_{28}H_{46}N_2O_7S_0Si_2$: C, 55.05; H, 7.59; N, 4.59. Found: C, 55.27; H, 7.66; N, 4.42.

4.10. Reaction between 8α and allyltrimethylsilane in the presence of $MeAlCl_2$: preparation of 4′-ally-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)thymidine (12β) and its 4′-epimer (12α) as a typical procedure for the reactions listed in Table 1

To a solution of **8α** (100.6 mg, 0.16 mmol) in CH_2Cl_2 (3.0 mL), were added allyltrimethylsilane (0.25 mL, 1.60 mmol) and then $MeAlCl_2$ (1.0 M hexane solution, 0.64 mL, 0.64 mmol) at below −30 °C under positive pressure of dry Ar. The reaction mixture was stirred for 1 h at −30 °C, and quenched by adding saturated aqueous NH_4Cl. The mixture was filtered through a Celite pad and the resulting filtrate was extracted with CH_2Cl_2. Column chromatography (hexane/EtOAc=6/1) of the extract gave **12** (79.3 mg, 94%, **12β**/**12α**=20/1). HPLC separation (hexane/EtOAc=2/1) of **12** led to the isolation of **12β** (t_R 12.2 min) and **12α** (t_R 13.2 min).

Physical data for **12β**: UV (MeOH) λ_{max} 267 nm (ε 9700), λ_{min} 234 nm (ε 1900); ^{1}H NMR ($CDCl_3$) δ 0.087, 0.094 and 0.10 (12H, each as s), 0.91 and 0.93 (18H, each as s), 1.92 (3H, d, *J*=1.2 Hz), 2.13–2.20 (2H, m, *J*=6.3, 6.8, 7.1, 13.4 and 14.4 Hz), 2.30 (1H, ddd, *J*=3.7, 6.3 and 13.4 Hz), 2.48–2.54 (1H, m, *J*=6.1 and 14.4 Hz), 3.55 (1H, d, *J*=10.7 Hz), 3.69 (1H, d, *J*=10.7 Hz), 4.46 (1H, dd, *J*=3.7 and 6.3 Hz), 5.08 (1H, s), 5.12 (1H, d, *J*=4.9 Hz), 5.82–5.92 (2H, m, *J*=4.9, 6.1 and 6.8 Hz), 6.28 (1H, dd, *J*=6.3 and 7.1 Hz), 7.49 (1H, d, *J*=1.2 Hz), 9.19 (1H, br); NOE experiment H-5′b/H-6 (2.3%); ^{13}C NMR ($CDCl_3$) δ −5.46, −5.41, −5.10, −4.60, 12.55, 17.98, 18.35, 25.71, 25.90, 36.78, 41.57, 66.15, 72.55, 83.60, 88.76, 110.68, 118.18, 133.62, 135.51, 150.35, 163.96; FABMS (*m*/*z*) 511 (M^++H). Anal. Calcd for $C_{25}H_{46}N_2O_5Si_2$: C, 58.78; H, 9.08; N, 5.48. Found: C, 59.00; H, 9.27; N, 5.40.

Physical data for **12α**: ^{1}H NMR ($CDCl_3$) δ 0.077, 0.083 and 0.09 (12H, each as s), 0.90 and 0.92 (18H, each as s), 1.93 (3H, d, *J*=1.2 Hz), 2.10 (1H, ddd, *J*=5.1, 7.6 and 13.4 Hz), 2.35–2.37 (2H, m), 2.54 (1H, ddd, *J*=6.1, 7.1 and 13.4 Hz), 3.59 (1H, d, *J*=10.7 Hz), 3.82 (1H, d, *J*=10.7 Hz), 4.29 (1H, dd, *J*=6.1 and 7.6 Hz), 5.14–5.20 (2H, m), 5.80–5.91 (1H, m), 6.26 (1H, dd, *J*=5.1 and 7.1 Hz), 7.22 (1H, d, *J*=1.2 Hz), 7.98 (1H, br); NOE experiment H-5′b/H-1′ (1.4%); ^{13}C NMR ($CDCl_3$) δ −5.54, −5.49, −5.03, −4.49, 12.61, 17.89, 18.25, 25.66, 25.93, 38.98, 41.07, 65.17, 73.59, 84.79, 88.16, 110.55, 119.13, 133.08, 135.86, 149.83, 163.38; FABMS (*m*/*z*) 511 (M^++H). FAB-high resolution MS (*m*/*z*) calcd for $C_{25}H_{47}N_2O_5Si_2$: 511.3024, found: 511.3035 (M^++H).

4.11. 1-[4-Allyl-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-*threo*-pentofuranosyl]-thymine (13β) and its 4′-epimer (13α)

These compounds were prepared by the procedure described for the preparation of **12**. The following amounts of reagents and **11** (100.6 mg, 0.16 mmol) were employed: allyltrimethylsilane (0.26 mL, 1.65 mmol) and $SnCl_4$ (1.0 M CH_2Cl_2 solution, 0.66 mL, 0.66 mmol). After workup of the reaction mixture, the CH_2Cl_2 extract was purified by column chromatography (hexane/EtOAc=5/1). This gave **13** (50.8 mg, 62%, foam, **13β**/**13α**=5/1). HPLC separation (hexane/EtOAc=2/1) of **13** led to the isolation of **13β** (t_R 14.3 min) and **13α** (t_R 12.6 min).

Physical data for **13β**: UV (MeOH) λ_{max} 268 nm (ε 9500), λ_{min} 235 nm (ε 1700); ^{1}H NMR ($CDCl_3$) δ 0.04, 0.08 and 0.09 (12H, each as s), 0.87 and 0.92 (18H, each as s), 1.92 (3H, d, *J*=1.2 Hz), 1.97 (1H, ddd, *J*=2.9, 3.4 and 14.4 Hz), 2.27 (1H, dd, *J*=7.3 and 14.1 Hz), 2.36 (1H, dd, *J*=7.1 and 14.1 Hz), 2.77 (1H, ddd, *J*=5.6, 7.6 and 14.4 Hz), 3.81 (2H, s), 4.20 (1H, dd, *J*=2.9 and 5.6), 5.11–5.16 (2H, m), 5.75–5.85 (1H, m, *J*=7.1 and 7.3 Hz), 6.15 (1H, dd, *J*=3.4 and 7.6 Hz), 7.65 (1H, d, *J*=1.2 Hz), 8.83 (1H, br); NOE experiment H-6/H-5′ (1.9%); ^{13}C NMR ($CDCl_3$) δ −5.42, −5.31, −5.15, −4.81, 12.57, 17.92, 18.33, 25.60, 26.00, 38.31, 41.69, 63.52, 73.58, 84.20, 90.18, 109.99, 118.95, 132.88, 136.49, 150.37, 163.88; FABMS (*m*/*z*) 511 (M^++H). Anal. Calcd for $C_{25}H_{46}N_2O_5Si_2$: C, 58.78; H, 9.08; N, 5.48. Found: C, 58.75; H, 9.28; N, 5.31.

Physical data for **13α**: UV (MeOH) λ_{max} 268 nm (ε 9600), λ_{min} 234 nm (ε 1700); ^{1}H NMR ($CDCl_3$) δ 0.057, 0.061 and 0.10 (12H, each as s), 0.89 and 0.91 (18H, each as s), 1.88–1.93 (4H, m, *J*=1.2, 1.5, 2.7 and 14.4 Hz), 2.42 (1H, dd, *J*=8.3 and 14.6 Hz), 2.64 (1H, dd, *J*=6.1 and 14.6 Hz), 2.83 (1H, ddd, *J*=5.6, 7.8 and 14.4 Hz), 3.28 (1H, d, *J*=10.2 Hz), 3.53 (1H, d, *J*=10.2 Hz), 4.38 (1H, dd, *J*=1.5 and 5.6 Hz), 5.13–5.17 (2H, m), 5.83–5.94 (1H, m, *J*=6.1 and 8.3 Hz), 6.21 (1H, dd, *J*=2.7 and 7.8 Hz), 7.63 (1H, d, *J*=1.2 Hz), 8.95 (1H, br); NOE experiment H-5′a/H-1′ (3.3%); ^{13}C NMR ($CDCl_3$) δ −5.66, −5.61, −5.14, −4.88, 12.61, 17.97, 18.07, 25.64, 25.75, 35.78, 42.07, 64.77, 73.02, 84.89, 90.64, 110.15, 118.39, 133.58, 136.68, 150.44, 163.95; FABMS (*m*/*z*) 511 (M^++H). Anal. Calcd for $C_{25}H_{46}N_2O_5Si_2$: C, 58.78; H, 9.08; N, 5.48. Found: C, 58.82; H, 9.28; N, 5.32.

4.12. 1-[3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-4-chloro-2-deoxy-α-L-*threo*-pentofuranosyl]thymine (14)

To a solution of **8** (200.5 mg, 0.33 mmol) in CH_2Cl_2 (6.0 mL) was added $MeAlCl_2$ (1.0 M hexane solution, 2.64 mL, 2.64 mmol) at below −30 °C under positive pressure of dry Ar. The reaction mixture was stirred for 1 h at −30 °C, quenched by adding saturated aqueous NH_4Cl, and filtered through a Celite pad. The filtrate was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. HPLC purification (hexane/EtOAc=1/1) of the organic layer gave **14** (t_R 8.1 min, 119.6 mg, 73%, containing ca. 8% of unknown product); ^{1}H NMR (CD_2Cl_2) δ 0.126, 0.130 and 0.15 (12H, each as s), 0.92 and 0.93 (18H, each as s), 1.92 (3H, d, *J*=1.2 Hz), 2.31 (1H, dd, *J*=5.9 and 13.4 Hz), 2.57 (1H, ddd, *J*=3.7, 9.5 and 13.4 Hz), 3.90 (1H, d, *J*=11.2 Hz), 4.10 (1H, d, *J*=11.2 Hz), 4.65 (1H, d, *J*=3.7 Hz), 6.64 (1H, dd, *J*=5.9 and 9.5 Hz), 7.65 (1H, d, *J*=1.2 Hz), 8.91 (1H, br); NOE experiment H-5′a/H-1′ (0.4%), H-5′b/H-1′ (0.6%); ^{13}C NMR (CD_2Cl_2) δ −5.84, −5.81, −5.68, −5.44, 12.04, 17.51, 18.08, 25.09, 25.38, 37.69, 64.53, 78.45, 87.32, 111.33, 113.45, 135.43, 150.31, 163.70; FABMS (*m*/*z*) 505 (M^++H) and 505 (M^++H), 496 (M^+−Cl). FAB-high resolution MS (*m*/*z*) calcd for $C_{22}H_{42}ClN_2O_5Si_2$: 505.2321, found: 505.2289 (M^++H).

4.13. 4′-Azido-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-thymidine (15β) and its 4′-epimer (15α)

These compounds were prepared by the procedure described for the preparation of **12**. The following amounts of reagents and **8α** (107.7 mg, 0.18 mmol), were employed: Me_3SiN_3 (0.24 mL, 1.80 mmol) and $SnCl_4$ (1.0 M CH_2Cl_2 solution, 0.72 mL, 0.72 mmol). Column chromatography (hexane/EtOAc=5/1) of the CH_2Cl_2 extract gave **15** (88.9 mg, 99%, foam, **15β**/**15α**=2/1). HPLC separation (hexane/EtOAc=2/1) of **15** led to the isolation of **15β** (t_R 11.7 min) and **15α** (t_R 14.0 min).

Physical data for **15β**: IR (neat) 2116 cm^{-1} (N_3); UV (MeOH) λ_{max} 265 nm (ε 9800), λ_{min} 234 nm (ε 2500); ^{1}H NMR ($CDCl_3$) δ 0.13 and 0.15 (12H, each as s), 0.93 and 0.94 (18H, each as s), 1.93 (3H, d, *J*=1.2 Hz), 2.23 (1H, ddd, *J*=6.3, 6.6 and 13.2 Hz), 2.44 (1H, ddd, *J*=4.6, 6.6 and 13.2 Hz), 3.64 (1H, d, *J*=11.0 Hz), 3.83 (1H, d, *J*=11.0 Hz), 4.54 (1H, dd, *J*=4.6 and 6.3 Hz), 6.49 (1H, t, *J*=6.6 Hz), 7.39 (1H, d, *J*=1.2 Hz), 8.32 (1H, br); NOE experiment H-5′b/H-6 (1.2%); ^{13}C NMR ($CDCl_3$) δ −5.52, −5.48, −5.08, −5.01, 12.53, 18.10, 18.30, 25.60, 25.78, 39.99, 64.50, 73.62, 84.60, 99.79, 111.28, 134.99, 150.23, 163.95; FABMS (*m*/*z*) 512 (M^++H). Anal. Calcd for $C_{22}H_{41}N_5O_5Si_2$: C, 51.63; H, 8.08; N, 13.68. Found: C, 51.53; H, 8.18; N, 13.82.

Physical data for **15α**: IR (neat) 2113 cm^{-1} (N_3); UV (MeOH) λ_{max} 265 nm (ε 9400), λ_{min} 234 nm (ε 2900); ^{1}H NMR ($CDCl_3$) δ 0.11, 0.12

and 0.13 (12H, each as s), 0.91 and 0.93 (18H, each as s), 1.97 (3H, d, J=1.2 Hz), 2.27–2.30 (2H, m, J=1.7, 3.2, 6.6 and 8.3 Hz), 3.96 (1H, d, J=10.7 Hz), 4.00 (1H, d, J=10.7 Hz), 4.19 (1H, dd, J=1.7 and 3.2 Hz), 6.57 (1H, dd, J=6.6 and 8.3 Hz), 7.34 (1H, d, J=1.2 Hz), 8.43 (1H, br); NOE experiment H-5′a/H-1′ (0.8%); ^{13}C NMR ($CDCl_3$) δ −5.73, −5.59, −5.22, −4.76, 12.67, 17.85, 18.28, 25.55, 25.78, 39.12, 64.57, 75.49, 86.04, 101.54, 111.99, 134.88, 150.61, 163.84; FABMS (m/z) 512 (M^++H). Anal. Calcd for $C_{22}H_{41}N_5O_5Si_2$: C, 51.63; H, 8.08; N, 13.68. Found: C, 51.68; H, 8.14; N, 13.68.

4.14. 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-methylthymidine (16β) and its 4′-epimer (16α)

To a solution of **8α** (102.0 mg, 0.17 mmol) in CH_2Cl_2 (3.0 mL) cooled at 0 °C was added $AlMe_3$ (1.08 M hexane solution, 1.26 mL, 1.36 mmol). The reaction mixture was then stirred at rt for 1 h, quenched by adding saturated aqueous NH_4Cl, and filtered through a Celite pad. The filtrate was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. Column chromatography of the organic layer gave **16** (74.3 mg, 92%, **16β**/**16α**=ca. 1/5.3). HPLC separation (hexane/EtOAc=3/1) of **16** led to the isolation of **16β** (t_R 12.2 min) and **16α** (t_R 13.6 min).

Physical data for **16β**: UV (MeOH) λ_{max} 267 nm (ε 9700), λ_{min} 234 nm (ε 2000); ^{1}H NMR ($CDCl_3$) δ 0.07, 0.08 and 0.11 (12H, each as s), 0.91 and 0.93 (18H, each as s), 1.14 (3H, s), 1.92 (3H, d, J=1.2 Hz), 2.16 (1H, ddd, J=6.3, 6.6 and 13.4 Hz), 2.29 (1H, ddd, J=3.7, 6.3 and 13.4 Hz), 3.54 (1H, d, J=11.0 Hz), 3.69 (1H, J=11.0 Hz), 4.37 (1H, dd, J=3.7 and 6.3 Hz), 6.27 (1H, dd, J=6.3 and 6.6 Hz), 7.53 (1H, d, J=1.2 Hz), 9.15 (1H, br); NOE experiment H-5′b/H-6 (1.9%); ^{13}C NMR ($CDCl_3$) δ −5.45, −5.41, −5.13, −4.69, 12.55, 18.00, 18.21, 18.39, 25.69, 25.92, 41.61, 67.74, 72.35, 83.45, 87.95, 110.62, 135.57, 150.37, 163.96; FABMS (m/z) 485 (M^++H). Anal. Calcd for $C_{23}H_{44}N_2O_5Si_2$: C, 56.98; H, 9.15; N, 5.78. Found: C, 57.02; H, 9.36; N, 5.69.

Physical data for **16α**: UV (MeOH) λ_{max} 268 nm (ε 9900), λ_{min} 234 nm (ε 2000); ^{1}H NMR ($CDCl_3$) δ 0.079 and 0.084 (12H, each as s), 0.90 and 0.92 (18H, each as s), 1.29 (3H, s), 1.94 (3H, d, J=1.2 Hz), 2.16 (1H, ddd, J=5.1, 6.8 and 13.2 Hz), 2.56 (1H, ddd, J=6.3, 6.8 and 13.2 Hz), 3.60 (1H, d, J=10.5 Hz), 3.77 (1H, d, J=10.5 Hz), 4.16 (1H, dd, J=6.3 and 6.8 Hz), 6.19 (1H, dd, J=5.1 and 6.8 Hz), 7.19 (1H, d, J=1.2 Hz), 9.12 (1H, br); NOE experiment H-5′b/H-1′ (1.1%); ^{13}C NMR ($CDCl_3$) δ −5.51, −5.11, −4.68, 12.69, 17.91, 18.29 22.09, 25.64, 25.92, 41.26, 66.14, 76.35, 85.73, 87.08, 110.42, 135.71, 150.08, 164.04; FABMS (m/z) 485 (M^++H). Anal. Calcd for $C_{23}H_{44}N_2O_5Si_2$: C, 56.98; H, 9.15; N, 5.78. Found: C, 57.15; H, 9.35; N, 5.72.

4.15. 1-[3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4-methyl-β-D-*threo*-pentofuranosyl]thymine (17β) and its 4′-epimer (17α)

These compounds were prepared from **11** (101.5 mg, 0.17 mmol) in 95% yield (**17β**/**17α**=ca. 20/1) by the procedure described for the preparation of **16** from **8α**. HPLC separation (hexane/EtOAc=2/1) of **17** led to the isolation of **17β** (t_R 18.0 min) and **17α** (t_R 14.3 min).

Physical data for **17β**: UV (MeOH) λ_{max} 268 nm (ε 9400), λ_{min} 235 nm (ε 1900); ^{1}H NMR ($CDCl_3$) δ 0.05, 0.09 and 0.10 (12H, each as s), 0.88 and 0.92 (18H, each as s), 1.20 (3H, s), 1.92–1.96 (4H, m, J=1.2, 1.7, 2.9 and 14.6 Hz), 2.81 (1H, ddd, J=5.1, 7.6 and 14.6 Hz), 3.74 (1H, d, J=10.2 Hz), 3.88 (1H, d, J=10.2 Hz), 4.09 (1H, dd, J=1.7 and 5.1 Hz), 6.20 (1H, dd, J=2.9 and 7.6 Hz), 7.65 (1H, d, J=1.2 Hz), 9.27 (1H, br); NOE experiment H-5′a/H-6 (3.3%); ^{13}C NMR ($CDCl_3$) δ −5.40, −5.28, −5.20, −4.93, 12.58, 17.96, 18.42, 21.30, 25.60, 25.98, 41.69, 65.07, 75.18, 83.90, 88.60, 109.96, 136.67, 150.54, 164.08; FABMS (m/z) 485 (M^++H). Anal. Calcd for $C_{23}H_{44}N_2O_5Si_2$: C, 56.98; H, 9.15; N, 5.78. Found: C, 57.13; H, 9.19; N, 5.78.

Physical data for **17α**: ^{1}H NMR ($CDCl_3$) δ 0.06, 0.07 and 0.09 (12H, each as s), 0.90 and 0.91 (18H, each as s), 1.33 (3H, s), 1.88–1.93 (4H, m, J=1.2, 2.0 and 14.0 Hz), 2.88 (1H, ddd, J=5.6, 8.0 and 14.0 Hz), 3.41 (1H, d, J=10.2 Hz), 3.42 (1H, d, J=10.2 Hz), 4.29 (1H, d, J=5.6 Hz), 6.24 (1H, dd, J=2.0 and 8.0 Hz), 7.65 (1H, d, J=1.2 Hz), 8.35 (1H, br); NOE experiment H-5′/H-1′ (3.9%), H-6/4′-CH_3 (2.2%); ^{13}C NMR ($CDCl_3$) δ −5.66, −5.56, −5.15, −5.01, 12.60, 17.99, 18.12, 18.17, 25.60, 25.78, 42.43, 68.05, 73.05, 84.89, 90.11, 110.18, 136.84, 150.54, 164.04; FABMS (m/z) 485 (M^++H). FAB-high resolution MS (m/z) calcd for $C_{23}H_{45}N_2O_5Si_2$: 485.2867, found: 485.2893 (M^++H).

4.16. 1-[4-Benzenesulfenyl-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-L-*threo*-pentofuranosyl]thymine (18α)

This compound (solid, mp 199 °C) was prepared from **6** in 91% yield by the procedure described for the preparation of **8α**. Physical data for **18α**: UV (MeOH) λ_{max} 260 nm (ε 11,900), λ_{min} 236 nm (ε 4300); ^{1}H NMR ($CDCl_3$) δ −0.09, −0.03, 0.10 and 0.12 (12H, each as s), 0.87 and 0.92 (18H, each as s), 1.85 (3H, d, J=1.2 Hz), 2.31 (1H, ddd, J=5.1, 6.3 and 13.2 Hz), 2.56 (1H, ddd, J=6.1, 6.8 and 13.2 Hz), 3.67 (1H, d, J=10.7 Hz), 3.92 (1H, d, J=10.7 Hz), 4.37 (1H, dd, J=6.1 and 6.3 Hz), 6.47 (1H, dd, J=5.1 and 6.8 Hz), 7.28–7.58 (6H, m, J=1.2 Hz), 9.07 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.76, −5.50, −4.86, −4.68, 12.65, 17.94, 18.21 25.65, 25.87, 40.69, 63.51, 75.65, 86.27, 99.09, 110.99, 128.43, 128.87, 131.07, 134.10, 136.27, 150.28, 163.88; FABMS (m/z) 579 (M^++H). Anal. Calcd for $C_{28}H_{46}N_2O_5SSi_2$: C, 58.09; H, 8.01; N, 4.84. Found: C, 58.35; H, 8.13; N, 4.82.

4.17. 4′-Acetoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-thymidine (19β) and its 4′-epimer (19α)

A mixture of **18α** (500.4 mg, 0.86 mmol), $Hg(OAc)_2$ (602.3 mg, 1.89 mmol), and AcOH (0.49 mL, 8.60 mmol) in CH_2Cl_2 (7.0 mL) was stirred at rt for 0.5 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer separated was washed with 5% aqueous NaCN and then purified by column chromatography (hexane/EtOAc=3/1). This gave **19** (448.9 mg, 98%, foam, **19β**/**19α**=1.0/0.61). HPLC separation (hexane/EtOAc=2/1) of **19** led to the isolation of **19β** (t_R 6.8 min) and **19α** (t_R 11.0 min).

Physical data for **19β**: UV (MeOH) λ_{max} 266 nm (ε 9500), λ_{min} 233 nm (ε 1900); ^{1}H NMR ($CDCl_3$) δ 0.09, 0.10, 0.128 and 0.129 (12H, each as s), 0.90 and 0.94 (18H, each as s), 1.92 (3H, d, J=1.2 Hz), 2.06 (3H, s), 2.26 (1H, ddd, J=5.4, 8.0 and 13.4 Hz), 2.55 (1H, ddd, J=5.6, 7.3 and 13.4 Hz), 3.96 (1H, d, J=10.7 Hz), 4.02 (1H, d, J=10.7 Hz), 4.74 (1H, dd, J=5.6 and 8.0 Hz), 6.50 (1H, dd, J=5.4 and 7.3 Hz), 7.33 (1H, d, J=1.2 Hz), 9.64 (1H, br); NOE experiment H-5′b/H-6 (1.1%); ^{13}C NMR ($CDCl_3$) δ −5.36, −5.05, −4.79, 12.51, 17.79, 18.42, 21.72, 25.53, 25.87, 40.43, 63.61, 71.34, 86.10, 109.70, 110.95, 135.99, 150.21, 164.06, 168.73; FABMS (m/z) 529 (M^++H). Anal. Calcd for $C_{24}H_{44}N_2O_7Si_2$: C, 54.51; H, 8.39; N, 5.30. Found: C, 54.55; H, 8.49; N, 5.26.

Physical data for **19α**: UV (MeOH) λ_{max} 265 nm (ε 9300), λ_{min} 232 nm (ε 2000); ^{1}H NMR ($CDCl_3$) δ 0.059, 0.062, 0.13 and 0.14 (12H, each as s), 0.89 and 0.91 (18H, each as s), 1.92 (3H, d, J=1.2 Hz), 2.09 (3H, s), 2.14 (1H, ddd, J=4.1, 8.5 and 13.4 Hz), 2.43 (1H, dd, J=5.9 and 13.4 Hz), 4.18 (1H, d, J=11.0 Hz), 4.24 (1H, d, J=11.0 Hz), 4.60 (1H, d, J=4.1 Hz), 6.48 (1H, dd, J=5.9 and 8.5 Hz), 7.37 (1H, d, J=1.2 Hz), 9.44 (1H, br); NOE experiment H-5′/H-1′ (1.3%); ^{13}C NMR ($CDCl_3$) δ −5.69, −5.43, −5.17, −4.80, 12.69, 17.85, 18.16, 21.81, 25.57, 25.74, 39.29, 60.14, 74.85, 87.11, 111.08, 113.01, 135.17, 150.34, 163.90, 168.75; FABMS (m/z) 529 (M^++H). Anal. Calcd for $C_{24}H_{44}N_2O_7Si_2$: C, 54.51; H, 8.39; N, 5.30. Found: C, 54.24; H, 8.48; N, 5.21.

4.18. Preparation of a mixture of 18β and 18α from 19

To a solution of **19** (422.8 mg, 0.80 mmol, **19β**/**19α**=1.0/0.61) in CH_2Cl_2 (7.0 mL) were added Me_3SiSPh (1.51 mL, 8.00 mmol) and then $SnCl_4$ (1.0 M CH_2Cl_2 solution, 3.20 mL, 3.20 mmol) at below −78 °C under positive pressure of dry Ar. Immediately after addition of these reagents, the reaction mixture was warmed to −30 °C and stirred for 1 h. The mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc=5/1) of the organic layer gave **18** (356.5 mg, 78%, foam, **18β**/**18α**=20/1).

4.19. 4′-Benzenesulfonyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-thymidine (8β) and its 4′-epimer (8α)

To a solution of **18** (354.9 mg, 0.61 mmol, **18β**/**18α**=20/1) in CH_2Cl_2 (7.0 mL) was added *m*-CPBA (330.3 mg, 1.34 mmol) at 0 °C. The reaction mixture was stirred for 5 h at rt, and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc=3/1) of the organic layer gave **8** (355.4 mg, 95%, foam, **8β**/**8α**=20/1). HPLC separation (hexane/EtOAc=1/1) of **8** led to the isolation of **8β** (t_R 10.2 min) and **8α** (t_R 8.8 min).

Physical data for **8β**: UV (MeOH) λ_{max} 266 nm (ε 10,500), λ_{min} 235 nm (ε 3300); ^{1}H NMR ($CDCl_3$) δ 0.02, 0.03, 0.16 and 0.18 (12H, each as s), 0.85 and 0.98 (18H, each as s), 1.89 (3H, d, J=1.2 Hz), 2.27 (1H, ddd, J=4.1, 8.8 and 13.4 Hz), 3.02 (1H, ddd, J=8.0, 8.3 and 13.4 Hz), 3.64 (1H, d, J=11.2 Hz), 4.27 (1H, d, J=11.2 Hz), 5.14 (1H, dd, J=8.0 and 8.8 Hz), 6.80 (1H, dd, J=4.1 and 8.3 Hz), 7.06 (1H, d, J=1.2 Hz), 7.54–7.91 (5H, m), 9.16 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.52, −5.47, −5.01, −4.69, 12.70, 18.01, 18.38, 25.57, 25.78, 39.46, 60.68, 71.55, 84.90, 101.98, 111.89, 128.85, 129.90, 133.90, 134.91, 137.20, 150.05, 163.52; FABMS (m/z) 611 (M^++H). Anal. Calcd for $C_{28}H_{46}N_2O_7SSi_2$: C, 55.05; H, 7.59; N, 4.59. Found: C, 55.13; H, 7.70; N, 4.50.

4.20. 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4-ethylthymidine (20β) and its 4′-epimer (20α)

These compounds and **21β** were prepared from **8β** by using $AlEt_3$ (0.96 M hexane solution) by the procedure for the preparation of **16** from **8α**. After column chromatography of the reaction mixture, a mixture of the three products (74.5 mg, combined yield: 89%, **20β**/**20α**/**21β**=1/0.07/0.13) was obtained. Compounds **20β** and **20α** were separated by HPLC (hexane/EtOAc=2/1): **20β** t_R 11.1 min; **20α** t_R 13.1 min.

Physical data for **20β**: UV (MeOH) λ_{max} 267 nm (ε 9600), λ_{min} 235 nm (ε 1900); ^{1}H NMR ($CDCl_3$) δ 0.07, 0.08 and 0.11 (12H, each as s), 0.90 (9H, s), 0.92–0.96 (12H, m, J=7.6 Hz), 1.41–1.50 (1H, m, J=7.6 and 14.9 Hz), 1.69–1.78 (1H, m, J=7.6 and 14.9 Hz), 1.93 (3H, d, J=1.2 Hz), 2.15 (1H, ddd, J=6.3, 7.1 and 13.4 Hz), 2.28 (1H, ddd, J=3.7, 6.3 and 13.4 Hz), 3.56 (1H, d, J=10.7 Hz), 3.73 (1H, d, J=10.7 Hz), 4.44 (1H, dd, J=3.7 and 6.3 Hz), 6.25 (1H, dd, J=6.3 and 7.1 Hz), 7.51 (1H, d, J=1.2 Hz), 9.41 (1H, br); NOE experiment H-5′b/H-6 (2.0%); ^{13}C NMR ($CDCl_3$) δ −5.49, −5.42, −5.16, −4.64, 8.08, 12.55, 17.95, 18.33, 24.48, 25.68, 25.89, 41.69, 65.74, 72.72, 83.52, 89.40, 110.64, 135.53, 150.45, 164.09; FABMS (m/z) 499 (M^++H). Anal. Calcd for $C_{24}H_{46}N_2O_5Si_2$: C, 57.79; H, 9.30; N, 5.62. Found: C, 58.17; H, 9.59; N, 5.62.

Physical data for **20α**: UV (MeOH) λ_{max} 267 nm (ε 9600), λ_{min} 234 nm (ε 1700); ^{1}H NMR ($CDCl_3$) δ 0.079, 0.082 and 0.085 (12H, each as s), 0.90 and 0.92 (18H, each as s), 0.97 (3H, t, J=7.6 Hz), 1.57–1.73 (2H, m, J=7.6 Hz), 1.94 (3H, d, J=1.2 Hz), 2.13 (1H, ddd, J=5.1, 7.6 and 12.9 Hz), 2.54 (1H, ddd, J=6.1, 7.3 and 12.9 Hz), 3.62 (1H, d, J=10.7 Hz), 3.81 (1H, d, J=10.7 Hz), 4.25 (1H, dd, J=6.1 and 7.6 Hz), 6.23 (1H, dd, J=5.1 and 7.3 Hz), 7.17 (1H, d, J=1.2 Hz), 8.98 (1H, br); NOE experiment H-5′b/H-1′ (1.5%); ^{13}C NMR ($CDCl_3$) δ −5.55, −5.52, −5.11, −4.49, 8.34, 12.71, 17.89, 18.23, 25.67, 25.92, 27.89, 41.33, 64.28, 74.37, 85.16, 88.99, 110.50, 135.83, 150.10, 163.95; FABMS (m/z) 499 (M^++H). Anal. Calcd for $C_{24}H_{46}N_2O_5Si_2$: C, 57.79; H, 9.30; N, 5.62. Found: C, 58.00; H, 9.58; N, 5.57.

4.21. Reaction of 8β with EtAl(C≡CSiMe$_3$)$_2$: formation of 22β, 22α, 20β, and 21β

The aluminum reagent was prepared as follows. To a solution of $Me_3SiC{\equiv}CH$ (1.42 ml, 10.24 mmol) in toluene (5.5 mL) was added BuLi (1.65 M in hexane, 6.20 mL, 10.24 mmol) at 0 °C under positive pressure of dry Ar. After the above mixture being stirred for 0.5 h at 0 °C, $EtAlCl_2$ (1.04 M in hexane, 4.92 mL, 5.12 mmol) was added and the whole mixture was stirred at 0 °C for 0.5 h.

To a solution of **8β** (99.7 mg, 0.16 mmol) was added the above prepared reagent (4.51 mL, containing 1.28 mmol of the aluminum reagent) at 0 °C under positive pressure of dry Ar. The reaction mixture was stirred for 1 h at rt, and quenched by adding saturated aqueous NH_4Cl. Filtration of the reaction mixture through a Celite pad was followed by partition between CH_2Cl_2 and saturated NH_4Cl. Column chromatography (hexane/EtOAc=2/1) of the organic layer gave a mixture of **22β**, **22α**, **20β**, and **21β** (78.5 mg, combined yield: 93%, **22β**/**22α**/**20β**/**21β**=1/1.4/6.2/1.4). Small portions of pure **22β** and **22α** were obtained by repeating HPLC separation (hexane/EtOAc=2/1).

Physical data for **22β**: ^{1}H NMR ($CDCl_3$) δ 0.09, 0.10, 0.12 and 0.13 (12H, each as s), 0.17 (9H, s), 0.92 and 0.94 (18H, each as s), 1.91 (3H, d, J=1.2 Hz), 2.10 (1H, ddd, J=6.6, 6.8 and 12.9 Hz), 2.42 (1H, ddd, J=5.4, 6.3 and 12.9 Hz), 3.76 (1H, d, J=11.2 Hz), 3.91 (1H, d, J=11.2 Hz), 4.45 (1H, dd, J=5.4 and 6.8 Hz), 6.37 (1H, dd, J=6.3 and 6.6 Hz), 7.41 (1H, d, J=1.2 Hz), 8.54 (1H, br); NOE experiment H-5′b/H-6 (1.4%); ^{13}C NMR ($CDCl_3$) δ −5.38, −5.34, −4.87, −4.67, −0.17, 12.54, 18.07, 18.41, 25.69, 25.91, 40.55, 65.61, 71.15, 83.68, 85.44, 93.51, 100.72, 110.83, 135.47, 150.02, 163.53; FABMS (m/z) 567 (M^++H). FAB-high resolution MS (m/z) calcd for $C_{27}H_{51}N_2O_5Si_3$: 567.3106, found: 567.3126 (M^++H).

Physical data for **22α**: UV (MeOH) λ_{max} 268 nm (ε 9700), λ_{min} 235 nm (ε 2100); ^{1}H NMR ($CDCl_3$) δ 0.11, 0.128 and 0.131 (12H, each as s), 0.20 (9H, s), 0.91 and 0.92 (18H, each as s), 1.96 (3H, d, J=1.2 Hz), 2.31 (1H, ddd, J=4.1, 7.8 and 13.2 Hz), 2.44 (1H, ddd, J=2.2, 5.6 and 13.2 Hz), 3.76 (1H, d, J=9.8 Hz), 3.88 (1H, d, J=9.8 Hz), 4.45 (1H, dd, J=2.2 and 4.1 Hz), 6.36 (1H, dd, J=5.6 and 7.8 Hz), 7.67 (1H, d, J=1.2 Hz), 8.91 (1H, br); NOE experiment H-5′b/H-1′ (1.0%); ^{13}C NMR ($CDCl_3$) δ −5.25, −5.20, −5.06, −4.82, −0.18, 12.76, 17.98, 18.42, 25.64, 25.95, 41.51, 63.89, 76.68, 85.16, 86.48, 93.08, 105.06, 110.65, 135.98, 150.21, 163.88; FABMS (m/z) 567 (M^++H). Anal. Calcd for $C_{27}H_{50}N_2O_5Si_3$: C, 57.20; H, 8.89; N, 4.94. Found: C, 57.60; H, 8.99; N, 4.83.

4.22. Reaction of 8β with AlPh$_3$: formation of 23

To a suspension of $AlCl_3$ (1.00 g, 7.50 mmol) in CH_2Cl_2 (9.4 mL) was added a THF solution of PhMgBr (1.09 M, 20.6 mL, 22.5 mmol) at 0 °C under positive pressure of dry Ar. The resulting yellow solution was stirred at rt for 10 h. A solution of **8β** (97.7 mg, 0.16 mmol) in CH_2Cl_2 (1.0 mL) was reacted with the above prepared $AlPh_3$ (5.12 mL, 1.28 mmol) at rt for 3 h, and then at refluxing temperature for 4 h. The reaction mixture was treated with aqueous NH_4Cl and filtered through a Celite pad. The resulting filtrate was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. Column chromatography (hexane/EtOAc=3/1) of the organic layer gave **23** (69.6 mg, 93%).

Physical data for **23**: ^{1}H NMR ($CDCl_3$) δ 0.067, 0.071 and 0.15 (12H, each as s), 0.86 and 0.92 (18H, each as s), 1.90 (3H, d, J=1.2 Hz), 2.02 (1H, ddd, J=5.4, 7.6 and 13.4 Hz), 2.42 (1H, ddd, J=2.0, 5.9 and 13.4 Hz), 4.68 (1H, dd, J=2.0 and 5.4 Hz), 5.78 (1H, s), 6.56 (1H, dd, J=5.9 and 7.6 Hz), 7.06 (1H, d, J=1.2 Hz), 9.51 (1H, br);

^{13}C NMR ($CDCl_3$) δ −5.43, −5.22, −4.72, −4.64, 12.55, 17.95, 18.43, 25.63, 41.81, 69.53, 86.00, 111.37, 119.44, 134.52, 142.43, 150.17, 163.92; FABMS (*m*/*z*) 469 (M^++H). FAB-high resolution MS (*m*/*z*) calcd for $C_{22}H_{41}N_2O_5Si_2$: 469.2554, found: 469.2549 (M^++H).

4.23. 3′,5′-Di-*O*-acetyl-4′-cyanothymidine (24β)

To a solution of **8β** (130.2 mg, 0.21 mmol) in toluene (3.0 mL) was added Et_2AlCN (1.0 M in toluene, 1.68 mL, 1.68 mmol). The reaction mixture was heated at reflux for 4 h, and then treated with saturated aqueous NH_4Cl. Filtration of the reaction mixture through a Celite pad was followed by partition of the filtrate between CH_2Cl_2 and saturated aqueous NH_4Cl. Column chromatography (hexane/EtOAc=3/1) of the organic layer gave a mixture of products and **8β**, which was reacted with Bu_4NF (1.0 M in THF, 0.42 mL, 0.42 mmol) in THF (3.0 mL) at rt for 1 h. The resulting solution was then reacted with Ac_2O (0.20 mL, 2.10 mmol) for 17 h at rt. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc=1/1) of the organic layer gave a mixture of products (57.0 mg), HPLC separation ($CHCl_3$/MeOH=100/2) of which gave **24β** (33.1 mg, 45%, t_R 11.5 min).

Physical data for **24β**: IR (neat) 2254 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ 1.94 (3H, d, *J*=1.2 Hz), 2.17 and 2.22 (6H, each as s), 2.58 (1H, ddd, *J*=4.9, 6.8 and 14.4 Hz), 2.64 (1H, ddd, *J*=7.1, 7.3 and 14.4 Hz), 4.50 (1H, d, *J*=12.0 Hz), 4.52 (1H, d, *J*=12.0 Hz), 5.56 (1H, dd, *J*=4.9 and 7.3 Hz), 6.31 (1H, dd, *J*=6.8 and 7.1 Hz), 7.08 (1H, d, *J*=1.2 Hz), 9.71 (1H, br); NOE experiment H-5′/H-3′ (10.3%); ^{13}C NMR ($CDCl_3$) δ 12.48, 20.53, 20.70, 35.52, 64.17, 72.79, 81.47, 86.96, 112.13, 114.48, 135.62, 149.94, 163.60, 169.62, 169.63; FABMS (*m*/*z*) 352 (M^++H). FAB-high resolution MS (*m*/*z*) calcd for $C_{15}H_{18}N_3O_7$: 352.1145, found: 352.1163 (M^++H).

Acknowledgements

Financial support from Showa University Research Grant for Young Researchers (to H.S.) is gratefully acknowledged. The authors thank Ms. K. Shiohara, S. Matsubayashi, and Y. Odanaka (Center for Instrumental Analysis, Showa University) for technical assistance with NMR, MS, and elemental analyses.

References and notes

1. For an excellent review, see: Hayakawa, H.; Kohgo, S.; Kitano, K.; Ashida, N.; Kodama, E.; Mitsuya, H.; Ohrui, H. *Antiviral Chem. Chemother.* **2004**, *15*, 169.
2. Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. *J. Med. Chem.* **1999**, *42*, 2901.
3. Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. *J. Med. Chem.* **2000**, *43*, 4516.
4. (a) Haraguchi, K.; Takeda, S.; Tanaka, H. *Org. Lett.* **2003**, *5*, 1399; (b) Haraguchi, K.; Takeda, S.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3775.
5. Kubota, Y.; Haraguchi, K.; Kunikata, M.; Hayashi, M.; Ohkawa, M.; Tanaka, H. *J. Org. Chem.* **2006**, *71*, 1099.
6. Haraguchi, K.; Sumino, M.; Tanaka, H. *J. Org. Chem.* **2006**, *71*, 4433.
7. Kubota, Y.; Kunikata, M.; Ishizaki, N.; Haraguchi, K.; Odanaka, Y.; Tanaka, H. *Tetrahedron* **2008**, *64*, 2391.
8. Data taken from: *Lange's Handbook of Chemistry*, 15th ed.; Dean, J. H., Ed.; McGraw-Hill: New York, NY, 1999.
9. For typical examples, see: (a) Brown, D. S.; Ley, S. V.; Bruno, M. *Heterocycles* **1989**, *28*, 773; (b) Lee, S.; Oh, S. *Tetrahedron Lett.* **2002**, *43*, 2891.
10. Giese, B.; Erdmann, P.; Giraud, J.; Göbel, T.; Peyretta, M.; Schäfer, T.; von Raumer, M. *Tetrahedron Lett.* **1994**, *35*, 2683.
11. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
12. Drew, M. G. B.; Ennis, S. C.; Gridley, J. J.; Osborn, H. M. I.; Spackman, D. G. *Tetrahedron* **2001**, *57*, 7919.
13. Bhandari, P.; Crombie, L.; Harper, M. F.; Rossiter, J. T.; Sanders, M.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1685.
14. Use of *i*-Pr_2NEt instead of Et_3N in this reaction lowered the yield of **6** to 32%.
15. Harpp, D. N.; Aida, T.; DeCesare, J.; Tisnes, O.; Chan, T. H. *Synthesis* **1984**, 1037.
16. Of the two protons at the 5′-position, the one that appears at a lower field is designated as H-5′b, and the other as H-5′a, throughout the text and the Experimental section. The same applies to the two protons at the 2′-position.
17. The ^{13}C NMR spectrum of the 4′-chloro derivative (**14**) gave the C-4′ resonance at 114.15 ppm (in CD_2Cl_2), which is reasonable as compared with those of the 4′-benzenesulfonyl derivative (**8α**: 103.57 ppm in $CDCl_3$) and the 4′-methyl derivative (**16α**: 87.08 ppm in $CDCl_3$).
18. The ^{1}H and ^{13}C NMR data for the methyl phenyl sulfoxide obtained in these reactions are as follows: ^{1}H NMR ($CDCl_3$) δ 2.74 (3H, s), 7.49–7.68 (5H, m); ^{13}C NMR ($CDCl_3$) δ 43.95, 123.47, 129.34, 131.01, 145.69. These data are identical with those of commercially available sample (purchased from Aldrich). Reaction of benzenesulfonyl chlorides with trialkylaluminums has been reported to yield alkyl aryl sulfoxide: Jahnke, D.; Reinheckel, H. *Organomet. Chem. Syn.* **1970/1971**, 31.
19. Kubota, Y.; Kunikata, M.; Haraguchi, K.; Tanaka, H. *J. Org. Chem.* **2009**, *74*, 3402.
20. Partial 5′-*O*-desilylation of **18α** to yield **6** was the sole event observed.
21. Compound **6** and its β-D-*erythro*-isomer were separated by HPLC ($CHCl_3$/MeOH=100/2). Physical data for the β-D-*erythro*-isomer, 4′-benzenesulfenyl-3′-*O*-(*tert*-butyldimethyl silyl)thymidine, are as follows: UV (MeOH) λ_{max} 263 nm (ε 11,700), λ_{min} 236 nm (ε 3900); ^{1}H NMR ($CDCl_3$) δ 0.14 and 0.18 (6H, each as s), 0.96 (9H, s), 1.82 (3H, d, *J*=1.2 Hz), 2.34 (1H, ddd, *J*=4.1, 8.3 and 13.4 Hz), 2.69 (1H, ddd, *J*=8.0, 8.3 and 13.4 Hz), 2.85 (1H, dd, *J*=4.9 and 8.0 Hz), 3.68 (1H, d, *J*=4.9 and 12.4 Hz), 3.75 (1H, dd, *J*=8.0 and 12.4 Hz), 4.92 (1H, dd, *J*=8.0 and 8.3 Hz), 6.58 (1H, dd, *J*=4.1 and 8.3 Hz), 7.14 (1H, d, *J*=1.2 Hz), 7.33–7.59 (5H, m), 8.45 (1H, br); NOE experiment 5′-OH/H-6 (1.9%); ^{13}C NMR ($CDCl_3$) δ −5.03, −4.69, 12.45, 18.01, 25.62, 39.15, 63.14, 71.61, 83.59, 98.90, 111.43, 128.85, 128.89, 130.18, 136.38, 137.12, 149.73, 163.48; FABMS (*m*/*z*) 465 (M^++H). Anal. Calcd for $C_{22}H_{32}N_2O_5SSi$: C, 56.87; H, 6.94; N, 6.03. Found: C, 56.97; H, 7.07; N, 5.88.
22. The yield was calculated based on ^{1}H NMR measurement of a mixture of **22β**, **22α**, **20β**, and **21β** by integrating the respective H-6 resonance.
23. When **8β** was reacted with $Me_3SiC{\equiv}CAl(Et)Cl$, the reagent used in our previous study in Ref. 6, the α-L-nucleoside **22α** was formed as the sole product in 58% yield, presumably through chlorination at the 4′-position.
24. This reagent was prepared by reacting $AlCl_3$ with a THF solution of PhMgBr as described in the Experimental section.
25. No reaction took place by reacting **8β** with Et_2AlCN in toluene at rt for 16 h.
26. Based on ^{1}H NMR analysis of this mixture, it was confirmed that, in addition to **8β** and the 4′-cyano-β-D-isomer, there were formed **23** and the 4′-cyano-α-L-isomer. At this stage, a small portion of the 4′-cyano-α-L-isomer, 1-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-4-cyano-2-deoxy-α-L-*threo*-pentofuranosyl]thymine, was isolated by HPLC (hexane/EtOAc=2/1). Physical data for this compound are as follows: IR (neat) 2254 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ 0.13, 0.149, 0.153 and 0.16 (12H, each as s), 0.92 and 0.93 (18H, each as s), 1.98 (3H, *J*=1.2 Hz), 2.37 (1H, ddd, *J*=3.4, 9.0 and 13.4 Hz), 2.48 (1H, dd, *J*=5.6 and 13.4 Hz), 3.84 (1H, d, *J*=10.0 Hz), 3.95 (1H, d, *J*=10.0 Hz), 4.70 (1H, d, *J*=3.4 Hz), 6.51 (1H, dd, *J*=5.6 and 9.0 Hz), 7.36 (1H, d, *J*=1.2 Hz), 8.33 (1H, br); NOE experiment H-1′/H-5′b (0.3%); ^{13}C NMR ($CDCl_3$) δ −5.45, −5.33, −5.15, −4.84, 12.75, 17.97, 18.34, 25.57, 25.82, 40.44, 61.85, 75.39, 84.86, 86.58, 112.34, 119.51, 134.58, 150.04, 163.08; FABMS (*m*/*z*) 496 (M^++H). FAB-high resolution MS (*m*/*z*) calcd for $C_{23}H_{42}N_3O_5Si_2$: 496.2663, found: 496.2675 (M^++H).