Stereoselective Synthesis of 2′-Deoxy-β-D-*threo*-pentofuranosyl Nucleosides by the NBS-Promoted Coupling Reaction of Thioglycosides with Silylated Heterocyclic Bases

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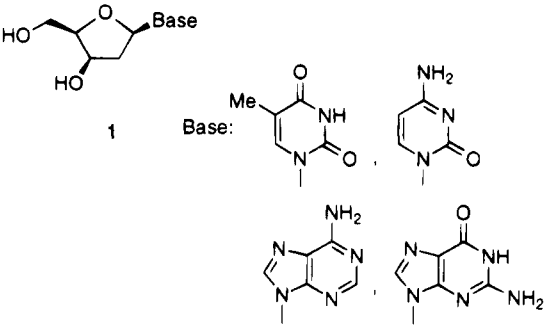
The NBS-promoted coupling reaction of phenyl 3,5-*O*-isopropylidene-2-deoxy-1-thio-α-D-*threo*-pentofuranoside (**5e**) with silylated pyrimidine bases was found to proceed in a highly stereoselective manner (α:β = 1:24–0:1) to afford 2′-deoxy-β-D-*threo*-pentofuranosyl pyrimidine nucleosides in satisfactory yields. The highly stereoselective outcome is thought to result from an *in situ* anomerization-type mechanism, in which intimate ionic intermediates would be in equilibrium and anomerize to the sterically preferable α form. A subsequent S_N2 type attack to the intermediate will lead to the β-nucleosides. By using this method, the synthesis of L-nucleosides, 1-(2-deoxy-β-L-*threo*-pentofuranosyl)thymine and cytosine derivatives, was also demonstrated by starting from the L-enantiomer of the thioglycoside. On the other hand, the reaction with purine bases was accompanied by the production of undesirable N-7 regioisomers besides the desired N-9 products. The product distribution of the regioisomers was, however, proved to change with reaction time. For instance, a long reaction period allowed the thermodynamically stable N-9 isomers to be exclusively produced with moderate selectivity (α:β = 1:2–1:4.8). The isolated yields of the 9-β isomers after purification were acceptable for practical use.

Introduction

In recent years, there has been considerable interest in sugar-modified nucleosides as potent antiviral and antitumor agents,[1] and a number of studies have reported the synthesis of these nucleoside derivatives.[2,3] 2′-Deoxy-β-D-*threo*-pentofuranosyl nucleosides **1** have been shown to be one of the useful intermediates for synthesizing such sugar-modified nucleosides,[4] including 3′-azido-3′-deoxythymidine (AZT) and 3′-deoxy-3′-fluorothymidine (FLT), well-known antiviral agents against human immunodeficiency virus (HIV).



Compounds **1** are usually derived from the corresponding β-D-ribofuranosyl or 2′-deoxy-β-D-ribofuranosyl nucleosides by the modification of the sugar moiety.[4e,f,5] They can also be prepared by the direct coupling of sugar residues with heterocyclic bases. The latter approach, however, may result in the formation of both α- and β-anomers because of the absence of a participating group at the C-2 position in sugars. Therefore, alternative strategies for the stereoselective construction of **1** have appeared. These include the coupling of the 2-*O*-acylated xylofuranose derivative followed by deoxygenation of the 2′-hydroxyl group[6] or the route starting from a glycal derivative via 2′-(phenylseleno)-2′-deoxy nucleosides.[7]

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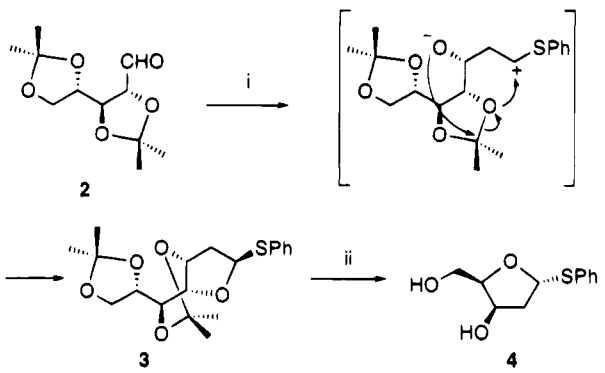
Scheme 1[a]



[a] Reagents and conditions: (i) CH_2=CHSPh, BF_3·OEt_2, −78 °C, 1 h, (ii) 10% CF_3COOH/EtOH−H_2O, rt, 4 h; $NaIO_4$, 0 °C, 0.5 h; $NaBH_4$, 0 °C, 1 h (one-pot).

Although these methods exhibit good stereoselectivity in each coupling step, additional steps for removal of the 2′-substituents are required. In this paper, we report the straightforward stereoselective route to **1** by the direct coupling of 2-deoxy-D-*threo*-pentofuranose derivatives with heterocyclic bases.

Results and Discussion

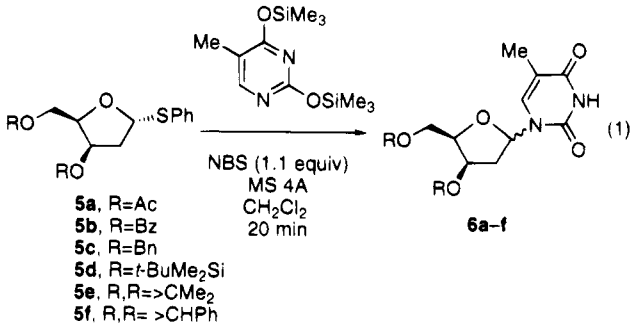
Recently, we have found that phenyl 2-deoxy-1-thio-D-*threo*-pentofuranoside (**4**) is easily prepared from phenyl vinyl sulfide and 2,3;4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose (**2**) in four steps via a novel BF_3·OEt_2-promoted cyclization reaction of an α-sulfonium ion intermediate[8] (Scheme 1). In general, thioglycosides have been shown to be efficient glycosyl donors for constructing *O*-glycosyl compounds due to the stability of the *S*-glycosyl bond under a variety of protection and deprotection conditions as well as functioning as powerful glycosylating agents by activation with an appropriate thiophilic reagent. Therefore, numerous methods have been developed for their activation.[9] *N*-Bromosuccinimide (NBS), introduced by Hanessian[10] and used extensively by Nicolaou,[11] is an effective promoter, which can activate thioglycosides under almost neutral conditions. In the preceding studies,[12] we have disclosed that this NBS-promoted coupling procedure is also applicable to nucleoside construction. We, therefore, decided to adopt this strategy for constructing the nucleoside derivatives **1** starting with thioglycosides derived from **4**.

Synthesis of Pyrimidine Nucleosides. In a preliminary paper,[13] we reported the coupling of various protected phenyl 2-deoxy-1-thio-D-*threo*-pentofuranosides **5a−f** with silylated thymine activated by NBS. The protective groups used in the sugar component were interestingly found to affect the anomeric ratio of the products. The results are summarized in Table 1. Although the reactions of acylated thioglycosides, **5a** and **5b**, resulted in poor selectivity, the use of the protective group containing an ethereal linkage (e.g., benzyl ether, silyl ether, and cyclic ketal or acetal) led to an increase in the ratio of the β-anomers. In particular, the 3,5-*O*-isopropylidene derivative **5e** proved most effective in obtaining the β-nucleoside. The β configuration was confirmed by comparison of the spectral data with those of an authentic sample, prepared by transformation of thymidine into 1-(2-deoxy-β-D-*threo*-pentofuranosyl)-thymine according to the literature,[5b] followed by isopropylidenation.

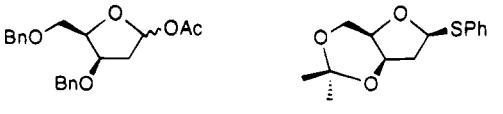
Table 1. Synthesis of 1-(2-Deoxy-D-*threo*-pentofuranosyl)thymine Derivatives

run	glycosyl donor	product	yield (%)	α:β[a]
1	**5a**	**6a**	93	1:1.5
2	**5b**	**6b**	86	1:2
3	**5c**	**6c**	92	1:4
4	**5d**	**6d**	92	1:5
5	**5e**	**6e**	85	1:50
6	**5f**	**6f**	88	1:12
7[b]	**5c**	**6c**	86	1:1.2
8[c]	**7**	**6c**	87	1:1

[a] The anomeric ratios were determined by 400 MHz ^{1}H NMR integration of the anomeric protons or the H-6 on the pyrimidine ring. [b] Combination of NIS (1.1 equiv) and TMSOTf (1.1 equiv) was used as a promoter. [c] The reaction was carried out using TMSOTf (1.1 equiv) as a promoter for 1 h.



On the other hand, either the use of *N*-iodosuccinimide (NIS)-TMSOTf[14] as a promoter instead of NBS in the reaction of **5e** or the reaction using 1-acetoxy-2-deoxy-D-*threo*-pentofuranose (**7**) as a glycosyl donor in the presence of TMSOTf[15] resulted in a significant loss of the stereoselectivity. These findings suggest that the combination of thioglycoside as a substrate and NBS as a promoter is indispensable for the stereoselective formation of the β-nucleosides.



7 β-**5e**

The effect of solvent on the anomeric ratio was examined in the reaction of **5e**. The results are summarized in Table 2. A polar solvent such as acetonitrile decreased the stereoselectivity, whereas the use of less polar solvents such as benzene and carbon tetrachloride led to a high level of selectivity similar to dichloromethane. The

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(9) For reviews: (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235. (b) Fügedi, P.; Garegg, P. J.; Lönn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97−108. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.
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(13) Sugimura, H.; Sujino, K.; Osumi, K. *Tetrahedron Lett.* **1992**, *33*, 2515−2516.
(14) The combination of NIS and TMSOTf is a modification of the method developed by Fraser-Reid; see, Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313−4316.
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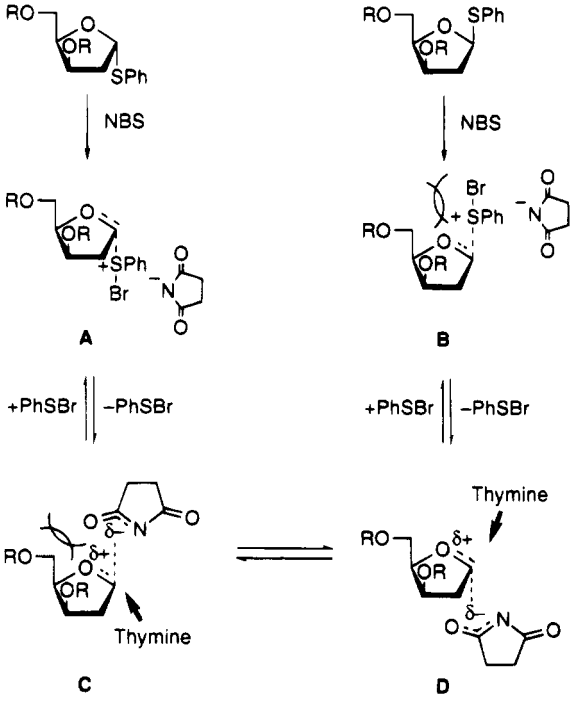
Table 2. Solvent Effect in the Reaction of 5e with Silylated Thymine

run	solvent	yield (%)	α:β[a]
1	benzene	81	1:47
2	CCl_4	81	1:22
3	CH_3CN	81	1:8
4	Et_2O	42	1:17

[a] The anomeric ratios were determined by 400 MHz ^{1}H NMR integration of the C-3′ proton.

Scheme 2



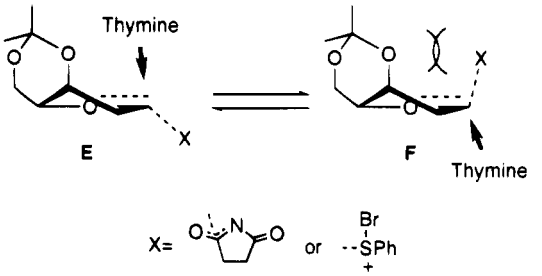
reaction in ether was sluggish and the yield was less satisfactory than the others.

It is noteworthy that β-thioglycoside, β-**5e**, similarly gave only the β form of **6e** in the same yield. This reveals that the stereochemical outcome at C-1 in the coupling products is independent of the anomeric configuration of the starting thioglycoside. Hence, the reaction is thought to proceed through an *in situ* anomerization-type pathway.[16]

The exact reason for the stereoselective formation of the β-nucleosides remains unclear. However, on the basis of these observations, it is speculated that counter anion species of the oxonium intermediates may play an important role in the appearance of the selectivity. For the reactions in the presence of TMSOTf, the counter ion is anticipated to be triflate ion. In contrast, for the reaction intermediate activated by NBS, the counterpart will be succinimide ion. More basic succinimide ion may interact with the oxonium ion more tightly than triflate ion. Consequently, the succinimide ion would be located on the sterically favored α face and the thymine derivative would be introduced exclusively to the β face (**D** in Scheme 2).

An alternative mechanism based on anomerization of bromosulfonium intermediates seems more likely. As depicted in Scheme 2, if rapid equilibrium exists between the α- and β-bromosulfonium intermediates, **A** and **B**, the β-intermediate will anomerize via the oxonium intermediates, **C** and **D**, to the sterically preferred α form, which reacts with the thymine derivative via an S_N2 type mechanism to give the β-nucleosides. The mechanism by way of the sulfonium intermediates has been originally proposed by van Boom et al. for the stereoselective *O*-glycosylation with a 1-thio-L-fucopyranoside derivative promoted by iodonium dicollidine perchlorate (IDCP).[17] They actually observed the anomerization of the thioglycoside to the favored configuration in the presence of a catalytic amount of IDCP. This seems to strongly support their proposal. However, a similar attempt to anomerize a thioglycoside by using a catalytic amount of NBS was unsuccessful.

Scheme 3



High selectivity observed during the reaction of the ketal (or acetal)-protection thioglycoside is probably attributed to the fixed conformation. Conformational analysis of compounds **5e** and **6e** by the ^{1}H NMR coupling constants at C-1 suggests that an N-type conformation (C3′-endo) would be preferred for both **5e** and **6e** over the S-type form (C2′-endo).[18,20,21] Assuming that this rigid conformation is applicable to the reaction intermediates, an α-intermediate **E** would be highly preferable to the β-one **F** because of steric repulsion as shown in Scheme 3.

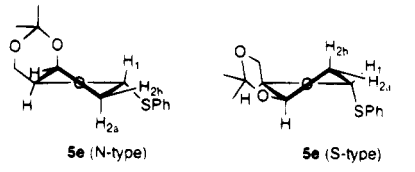
In contrast, the conformation of the intermediates bearing the other protective groups seems to be more flexible. In such a case, other conformers escaping from the steric repulsion as illustrated in **F** may be possible for the β-intermediates and, therefore, the α-anomer content would increase.

The observation of lowering selectivity during the reaction using acetonitrile as a solvent (Table 2, run 3) seems substantiate the intimate ion pair mechanisms

(16) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.

(17) Smid, P.; de Ruiter, G. A.; van der Marel, G. A.; Rombouts, F. M.; van Boom, J. H. *J. Carbohydr. Chem.* **1991**, *10*, 833–849.

(18) The N- and S-type conformations for **5e** are illustrated below. The observed coupling constants at C-1 in **5e** were $J_{1,2a}$ = 7.3 Hz and $J_{1,2b}$ = 6.8 Hz. Since the torsion angles H(1)–C(1)–C(2)–H(2a) and H(1)–C(1)–C(2)–H(2b) in **5e** can be estimated to be 153° and 24°, respectively, from the Karplus equation,[19] the N-type conformation will be appropriate to **5e**.

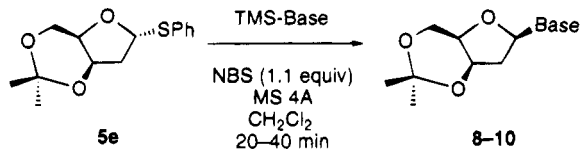


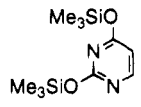
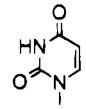
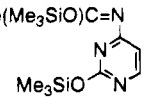
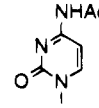
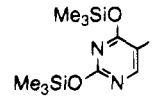
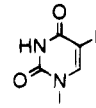
(19) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870–2871.

(20) It has been recently reported that 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine, which corresponds to **6e** without the protective group, revealed 84% of N-type conformation in DMSO solution: see, Rosemeyer, H.; Seela, F. *Helv. Chim. Acta* **1991**, *74*, 748–760.

(21) Conformation of nucleoside analogs bearing the cis-fused 3,9-dioxabicyclo[4.3.0]nonane system as the sugar part has been studied in detail. The structure of the sugar moiety, which is closely related to **6e**, was shown to have a rigid conformation which was locked in either the N or S form. The coupling constants of **6e** agreed well with those of the analogs assigned as the N-type conformation: see, Xi, Z.; Agback, P.; Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1991**, *47*, 9675–9690.

Table 3. Synthesis of Pyrimidine Nucleosides



Run	TMS-Base	Product	Base	Yield (%)	α:β[a]
1		8		76[b]	0:1[c]
2		9		96	1:24
3		10		62	0:1[c]

[a] The anomeric ratios were determined by 400 MHz ^{1}H NMR. [b] N-3 regioisomer was also produced in 6% yield. [c] The α-anomer could not be detected by ^{1}H NMR.

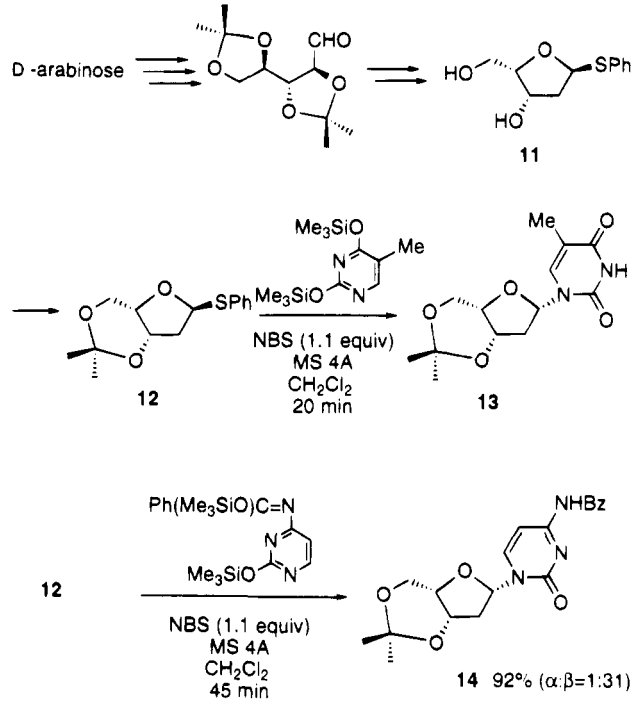
previously described. The polar solvent may affect these ionic intermediates and dissociate the ion pairs, and as a consequence, the ratio of the β-anomer will be reduced.

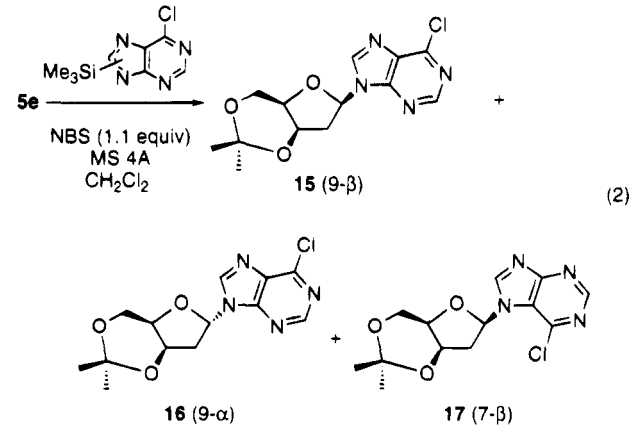
The NBS-promoted reaction of **5e** was successfully applied to other silylated pyrimidine bases derived from uracil, cytosine, and 5-fluorouracil as shown in Table 3. A high level of stereoselectivity was observed again in each case, though the yields of **8** and **10** were somewhat lower due to the formation of the N-3 regioisomer (run 1) or several unidentified products (run 3).

The synthesis of nucleosides containing L-sugars (L-nucleosides) has been of current interest due to their potent antiviral activity[22-25] or as building blocks of oligodeoxynucleotides.[26-28] We next demonstrated the synthesis of 1-(2-deoxy-β-L-*threo*-pentofuranosyl)thymine and cytosine derivatives, **13** and **14**, starting from D-arabinose by the identical sequence already described. Compounds **13** and **14** obtained here are useful intermediates for the synthesis of various pyrimidine 2′-deoxy- and 3′-substituted 2′,3′-dideoxy-L-nucleosides.

Synthesis of Purine Nucleosides. In general, the synthesis of purine nucleosides by the coupling reaction is somewhat complicated because of, in addition to the formation of α- and β-anomers, production of regioisomers; besides the desired N-9 isomers, N-7 and in some cases N-3 isomers may be produced.[15,29] It has been well documented that kinetically favored N-7 isomers will convert to thermodynamically stable N-9 isomers under the Lewis acid's conditions.[29a,d] To clarify the relationship between the reaction period and the distribution of the regioisomers in the NBS-promoted reaction, we explored the product distributions by ^{1}H NMR analysis of the crude reaction mixtures at appropriate intervals during the reaction of thioglycoside **5e** with silylated 6-chloropurine (eq 2). Figure 1 depicts the results. The thioglycoside was completely consumed within 15 min to afford the coupling products. During the early stage of the reaction, three isomers were formed as major com-

Scheme 4. Synthesis of 2-Deoxy-β-L-*threo*-pentofuranosyl Nucleosides





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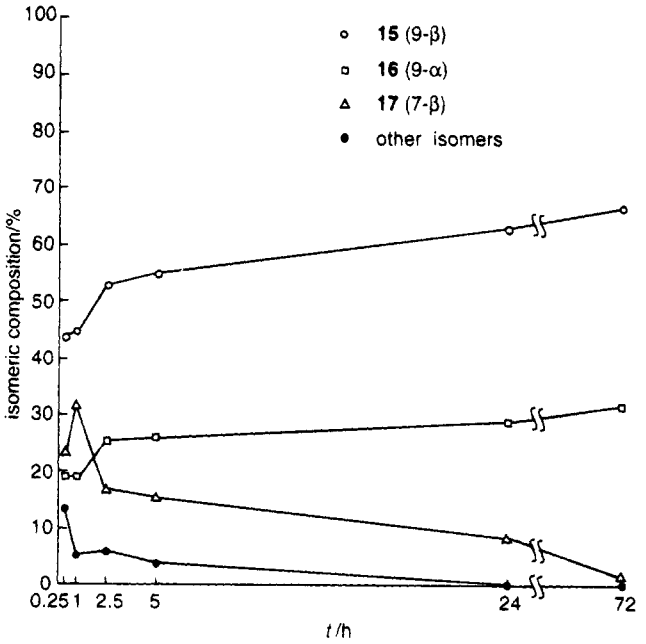
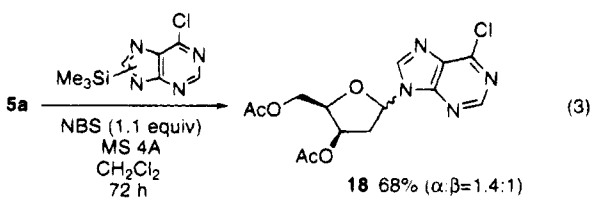


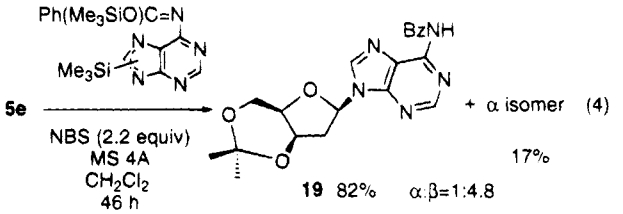
Figure 1. Time course of the reaction of **5e** with silylated 6-chloropurine in the presence of NBS.

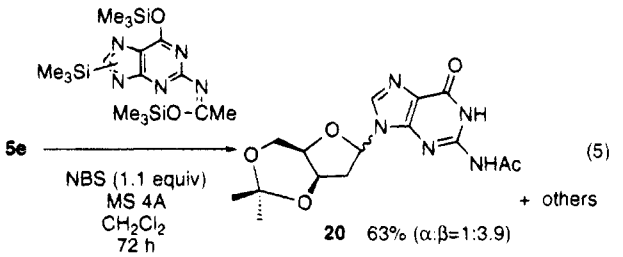
ponents with small amounts of several unidentified isomers. The major isomers were identified by ^{1}H NMR analysis. Their C-1′ protons appeared as two doublets at δ 6.55 and 6.76 with J = 7.3 Hz and a pseudotriplet at δ 6.52 with J = 7.1 Hz. Generally, N-7 isomers can be characterized by downfield shifts of the C-1′ proton signals relative to the resonance of the N-9 isomers.[29c,g,30] Furthermore, the anomeric configuration can be established based on the splitting pattern at C-1′ by reference to those obtained from the pyrimidine derivatives. Consequently, the signal at δ 6.76 could be assigned to the 7-β isomer and the signals at δ 6.52 and 6.55 could be assigned to the 9-α and 9-β isomers, respectively.

As shown in Figure 1, with the lapse of time, the proportion of the 7-β and other minor isomers gradually decreased and, eventually, the 9-β and 9-α isomers accounted for 99% of the coupling products in a ratio of ca. 2:1. Indeed, when the reaction period in eq 2 was 72 h, **15** and **16** were isolated in 65 and 33% yields, respectively. We also concluded that these observations will result from the interconversion of 7-β and other minor isomers to thermodynamically stable 9-α and 9-β under the reaction conditions. Under the same conditions, the diacetate derivative **5a** yielded the corresponding N-9 products **18** (68%) in an α: β ratio of 1.4:1 (eq 3). Hence, the protection using an isopropylidene group seems again to contribute to the stereochemical outcome in favor of the β-anomer.



In consideration of these results, the synthesis of adenosine and guanosine derivatives was attempted. The 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine derivative **19** was obtained in 82% yield using 2.2 equiv of NBS, accompanied by a 17% yield of the 9-α isomer which could be easily separated by chromatography on silica gel (eq 4). The regio- and stereochemistry of the products was again confirmed by the ^{1}H NMR signals at C-1′. The reaction of **5e** with a silylated guanine derivative also proceeded with moderate stereoselectivity to give a chromatographically inseparable anomeric mixture of the N-9 product **20** in 63% yield (α: β = 1:3.9 by ^{1}H NMR) (eq 5). The pure β-anomer could be obtained by recrystallization from ethanol.





The lower selectivity observed with purine bases can be explained as the steric hindrance of the bulky purine molecule, which would be difficult to approach the β face of the intermediate **E** (see Scheme 3).

Conclusion

A stereoselective route to 2′-deoxy-β-D-*threo*-pentofuranosyl nucleosides was established by the NBS-promoted direct coupling of phenyl 3,5-*O*-isopropylidene-2-deoxy-1-thio-D-*threo*-pentofuranoside. The reaction with pyrimidine bases proceeded uniformly with high stereoselectivity to afford the corresponding β-nucleosides in satisfactory yields. In contrast, the reaction with purine bases is somewhat limited in utility because a long reaction time is required in order to suppress the production of the N-7 isomer and the anomeric selectivity is moderate. However, the isolated yields of each 9-β isomer may be acceptable for practical use. Since the L-form of the starting thioglycoside is also obtainable according to the identical procedures from D-arabinose, the synthesis of L-nucleoside derivatives was also demonstrated.

Experimental Section

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively, with Me_4Si as an internal reference and $CDCl_3$ as the solvent unless otherwise stated. J Values are given in hertz. All solvents were distilled from an appropriate drying agent and stored over molecular sieves. All reagents were distilled or recrystallized prior to use.

Preparation of Phenyl 2-Deoxy-1-thio-α-D-*threo*-pentofuranoside (4). To a solution of freshly distilled 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose[31] (23.37 g, 0.101 mol)

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and phenyl vinyl sulfide (16.58 g, 0.122 mol) in 500 mL of dry CH_2Cl_2 was added a solution of BF_3·OEt_2 (15.77 g, 0.111 mol) in 50 mL of CH_2Cl_2 dropwise over 40 min at −78 °C under Ar. After the mixture was stirred at the same temperature for 1 h, 15 mL of Et_3N was slowly added, and then the reaction mixture was allowed to warm to room temperature. After 100 mL of saturated aqueous $NaHCO_3$ was added, the aqueous layer was separated and washed twice with 100 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (9:1)) to give 28.16 g (76%) of phenyl 3,5;6,7-di-*O*-isopropylidene-2-deoxy-1-thio-L-*gluco*-heptofuranoside (**3**) as a white solid. An analytical sample was obtained by recrystallization from hexane: mp 68−69 °C; $[\alpha]^{28}_D$ +228.6° (*c*, 0.84, $CHCl_3$); ^1H NMR δ 1.36 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 2.07 (ddd, 1H, *J* = 4.9, 7.3, 14.2), 2.47 (dd, 1H, *J* = 7.1, 14.2), 3.92−3.97 (m, 2H), 3.99 (t, 1H, *J* = 2.2), 4.06 (dd, 1H, *J* = 6.4, 8.5), 4.33 (q, 1H, *J* = 6.4), 4.41 (dd, 1H, *J* = 2.2, 4.6), 5.70 (t, 1H, *J* = 7.1), 7.24−7.30 (m, 3H), 7.56−7.58 (m, 2H); ^{13}C NMR δ 19.4, 25.4, 26.8, 29.3, 40.7, 66.8, 69.7, 70.4, 71.8, 74.8, 85.9, 98.0, 108.9, 127.3, 128.6, 132.4, 134.8; IR (KBr) 1380, 1220, 1155, 1080, 1040 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.28; H, 7.15; S, 8.73. Found: C, 62.51; H, 7.18; S, 9.05.

3 (5.16 g, 14.5 mmol) was dissolved in 50 mL of EtOH, and 50 mL of 20% aqueous CF_3COOH was added to the solution. After stirring at room temperature for 4 h, the reaction mixture was neutralized with solid $NaHCO_3$ and then cooled using an ice−water bath. An aqueous solution of $NaIO_4$ (7.75 g, 36 mmol) was added to the mixture and the stirring continued at 0 °C for 30 min. $NaBH_4$ (2.70 g, 72 mmol) was then added portionwise to the solution, and the reaction mixture was allowed to warm to room temperature. After 1 h, EtOH was removed by evaporation under reduced pressure and the residue was extracted five times with 100 mL of AcOEt. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (1:1)) to give 2.30 g of **4** (70%) as a white solid: mp 72.5−73.0 °C (hexane−AcOEt); $[\alpha]^{28}_D$ +265° (*c*, 0.96, $CHCl_3$); ^1H NMR δ 2,23 (dd, 1H, *J* = 6.3, 14.2), 2.2−2.3 (br (overlapped), 1H), 2.47 (ddd, 1H, *J* = 2, 6.8, 14.2), 3.21−3.27 (m, 1H), 3.99−4.11 (m, 2H), 4.12−4.17 (m, 1H), 4.54−4.60 (m, 1H), 5.84 (t-like, 1H, *J* = 6.4, 6.8), 7.23−7.36 (m, 3H), 7.50−7.55 (m, 2H); ^{13}C NMR δ 43.2, 61.5, 73.3, 79.6, 85.9, 127.3, 128.9, 131.4, 134.9; IR (KBr) 3340, 1440, 1090, 1070, 1060, 1030 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.39; H, 6.24; S, 14.17. Found: C, 58.44; H, 6.28, S, 14.15.

Phenyl 3,5-Di-*O*-acetyl-2-deoxy-1-thio-α-D-*threo*-pentofuranoside (5a). A mixture of **4** (317 mg, 1.40 mmol) and Ac_2O (0.6 mL) in 1 mL of pyridine was stirred for 4 h. The mixture was poured into ice−water and then extracted three times with $CHCl_3$. The organic layer was washed successively with dilute HCl, water, and aqueous $NaHCO_3$ and then dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (4:1)) to give **5a** (391 mg, 90%) as a colorless syrup: ^1H NMR δ 2.07 (s, 3H), 2.08 (s, 3H), 2.34 (dt, 1H, *J* = 6.1, 14.7), 2.50 (ddd, 1H, *J* = 2.0, 7.3, 14.9), 4.25 (dd, 1H, *J* = 6.8, 11.7), 4.31(dd, 1H, *J* = 4.9, 11.7), 4.44 (ddd, 1H, *J* = 3.7, 5.1, 6.8), 5.41 (ddd, 1H, *J* = 2.0, 3.9, 5.9), 5.75 (t, 1H, *J* = 6.8), 7.26−7.34 (m, 3H), 7.51−7.53 (m, 2H); ^{13}C NMR δ 20.8, 20.9, 40.2, 61.6, 73.2, 85.8, 127.4, 128.9, 131.6, 134.5, 170.2, 170.6; IR (neat) 1740, 1370, 1230, 1060 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_5S$: C, 58.05; H, 5.84: S, 10.33. Found: C, 58.14; H, 5.90; S, 10.35.

Phenyl 3,5-Di-*O*-benzoyl-2-deoxy-1-thio-α-D-*threo*-pentofuranoside (5b). A mixture of **4** (159 mg, 0.70 mmol) and BzCl (0.2 mL) in 2 mL of pyridine was stirred at room temperature for 1 h. The mixture was poured into ice-water and then extracted three times with ether. The combined extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (9:1)) to give **5b** (291 mg, 95%) as a colorless gum: ^1H NMR δ 5.06 (dt, 1H, *J* = 6.1, 15.1), 2.68 (dd, 1H, *J* = 7.3, 15.1), 4.65−4.75 (m, 3H), 5.75 (s, 1H), 5.86 (t, 1H, *J* = 6.6), 7.26−7.30 (m, 3H), 7.43 (t, 3H, *J* = 7.8), 7.55−7.57 (m, 5H), 8.02 (d, 4H, *J* = 7.3); ^{13}C NMR δ 40.5, 62.2, 74.0, 77.5, 86.0, 127.6, 128.4, 128.5, 128.9, 129.4, 129.7, 132.2, 133.1, 133.5, 134.3, 165.7, 166.2; IR (neat) 1730, 1715, 1600, 1585, 1450, 1440, 1275, 1175, 1110, 1030 cm^{-1}. Anal. Calcd for $C_{25}H_{22}O_5S$: C, 69.11; H, 5.10: S, 7.38. Found: C, 68.74; H, 5.08; S, 7.32.

Phenyl 3,5-Di-*O*-benzyl-2-deoxy-1-thio-α-D-*threo*-pentofuranoside (5c). To a solution of **4** (170 mg, 0.75 mmol) in 7.5 mL of DMF was added NaH (50%, 115 mg, 2.4 mmol). After 30 min, BnBr (0.27 mL, 2.3 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. After MeOH was added, DMF was removed under reduced pressure. The residue was added to aqueous NH_4Cl and extracted three time with ether. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (9:1)) to give **5c** (74 mg, 24%) and monobenzylated product (152 mg, 64%), which was again benzylated in a similar manner. Total yield of **5c** was 284 mg (93%) as a colorless syrup: ^1H NMR δ 2.08 (ddd, *J* = 5.4, 6.4, 14.7), 2.59 (ddd, 1H, *J* = 1.7, 7.1, 14.7), 3.77 (dd, 1H, *J* = 5.9, 9.8), 3.88 (dd, 1H, *J* = 6.1, 10.3), 4.17 (ddd, 1H, *J* = 1.5, 3.9, 5.4), 4.36 (dt, 1H, *J* = 6.1., 3.9), 4.45 (d, 1H, *J* = 12.2), 4.54 (d, 1H, *J* = 11.7), 4.58 (d, 1H, *J* = 12.2), 5.61 (d, 1H, *J* = 12.2), 5.77 (t, 1H, *J* = 6.8), 7.20−7.33 (m, 13H), 7.50−7.53 (m, 2H); ^{13}C NMR δ 39.1, 67.9, 71.4, 73.4, 78.0, 80.2, 85.7, 126.9, 127.5, 127.6, 127.7, 128.3, 128.4, 128.8, 131.2, 135.2, 138.0, 138.2; IR (neat) 1455, 1095, 1060 cm^{-1}. Anal. Calcd for $C_{25}H_{26}O_3S$: C, 73.86; H, 6.45: S, 7.89. Found: C, 73.83; H, 6.53; S, 7.87.

Phenyl 3,5-Di-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-1-thio-α-D-*threo*-pentofuranoside (5d). A mixture of **4** (180 mg, 0.8 mmol), *t*-$BuMe_2SiCl$ (307 mg, 2.0 mmol), and imidazole (278 mg, 4.1 mmol) in 8 mL of DMF was stirred at room temperature for 16 h. After water was added, the mixture was extracted three times with ether. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (100:1)) to give **5d** (305 mg, 84%) as a colorless oil: ^1H NMR δ 0.06 (s, 3H), 0.07 (s × 3, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 2.10 (ddd, 1H, *J* = 4.9, 7.3, 13.7), 2.35 (ddd, 1H, *J* = 1.5, 6.8, 13.7), 3.77 (dd, 1H, *J* = 5.9, 10.3), 3.84 (dd, 1H, *J* = 6.7, 10.5), 4.05 (dt, 1H, *J* = 5.9, 3.2), 4.37 (ddd, 1H, *J* = 1.6, 3.1, 4.7), 5.72 (t, 1H, *J* = 7.1), 7.20−7.34 (m, 3H), 7.48−7.58 (m, 2H); ^{13}C NMR δ −5.3, −5.1, −4.7, 18.1, 18.3, 25.7, 25.9, 42.9, 61.0, 71.4, 83.0, 85.6, 126.9, 128.7, 131.2, 135.4; IR (neat) 1470, 1255, 1095, 1055 cm^{-1}. Anal. Calcd for $C_{23}H_{42}O_3SSi_2$: C, 60.74; H, 9.31; S, 7.05. Found: C, 60.68; H, 9.19; S, 6.96.

Phenyl 3,5-*O*-Isopropylidene-2-deoxy-1-thio-α-D-*threo*-pentofuranoside (5e). To a solution of **4** (4.44 g, 19.6 mmol) in 150 mL of acetone and 5.3 mL of 2,2-dimethoxypropane was added *p*-TsOH·H_2O (152 mg), and then the mixture was stirred at room temperature for 1.5 h. After the reaction mixture was neutralized by the addition of solid $NaHCO_3$, the acetone was removed under reduced pressure. The residue was then poured into water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (9:1)) to give **5e** (4.72 g, 90%) as a colorless oil: bp 160−170 °C/1 mmHg (bath temp., Kugelrohr distillation); ^1H NMR δ 1.39 (s, 3H), 1.45 (s, 3H), 2.13 (ddd, 1H, *J* = 2, 7.3, 14.2), 2.53 (dd, 1H, *J* = 6.8, 14.2), 3.97 (dd, 1H, *J* = 2.9, 4.9), 4.04 (dd, 1H, *J* = 2.0, 13.2), 4.12 (dd, 1H, *J* = 2.9, 13.2), 4.43 (dd, 1H, *J* = 2.4, 4.9), 5.86 (t, 1H, *J* = 7.3), 7.20−7.37 (m, 3H), 7.51−7.56 (m, 2H); ^{13}C NMR δ 19.2, 28.7, 41.0, 60.3, 69.8, 73.0, 86.0, 97.7, 126.9, 128.8, 130.8, 135.3; IR (neat) 1382, 1375, 1195, 1154, 1106, 1070 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81; S, 12.04. Found: C, 63.11; H, 7.12; S, 12.04.

Preparation of β-Anomer of 5e. To a solution of **5a** (570 mg, 1.84 mmol) and MeOH (0.37 mL, 9.2 mmol) in 18 mL of CH_2Cl_2 was added NBS (360 mg, 2.02 mmol). This reaction mixture was stirred at room temperature for 15 min. After aqueous $Na_2S_2O_3$ was added, the aqueous layer was separated and washed with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt (4:1)) to give methyl 3,5-*O*-diacetyl-2-deoxy-D-*threo*-pentofuranoside (408 mg, 1.76 mmol, 96%), which was subsequently dissolved with $PhSSiMe_3$ (0.67 mL, 3.51 mmol) in 18 mL of CH_2Cl_2 under Ar. TMSOTf (0.37 mL, 1.93 mmol) was added to the solution and the mixture was stirred at room temperature for 30 min. The addition of

saturated aqueous $NaHCO_3$ was followed by extraction with CH_2Cl_2. A similar workup as described above gave **5a** (372 mg, 68%) as a mixture of α- and β-anomers (ca. 2:1), which could be roughly separated by chromatography. The β rich fractions were collected and used in a subsequent reaction. β-**5a** (α:β = ca.1:2) was dissolved in 0.5 M ethanolic KOH (5 mL) and stirred for 10 min. After the solution was neutralized by the addition of saturated aqueous NH_4Cl, EtOH was removed under reduced pressure. The residue was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in 5 mL of acetone, and then 0.5 mL of 2,2-dimethoxypropane and a trace of *p*-TsOH·H_2O were added. After 30 min, the reaction mixture was neutralized by the addition of solid $NaHCO_3$ and the acetone was removed under reduced pressure. The residue was poured into water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was carefully separated by chromatography on silica gel (hexane–AcOEt (9:1)) to give **5e** (33 mg, 28%) and β-**5e** (60 mg, 52%, as a white solid): ^1H NMR δ 1.38 (s, 3H), 1.46 (s, 3H), 2.28 (dd, J = 3, 14.2, 1H), 2.26 (ddd, J = 5.2, 8, 14.2, 1H), 3.87–4.18 (m, 3H), 4.32–5.51 (m, 1H), 5.57 (dd, J = 3, 8, 1H), 7.05–7.66 (m, 5H).

Phenyl 3,5-*O*-Benzylidene-2-deoxy-1-thio-α-D-*threo*-pentofuranoside (5f). To a solution of **4** (225 mg, 0.99 mmol) and benzaldehyde dimethyl acetal (228 mg, 1.5 mmol) in 10 mL of CH_2Cl_2 was added *p*-TsOH·H_2O (10 mg). The mixture was stirred at room temperature for 1 h. After saturated aqueous $NaHCO_3$ was added, the aqueous layer was separated and washed with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt (9:1)) to give **5f** (289 mg, 93%) as a white solid: mp 56–57 °C; ^1H NMR δ 2.18 (ddd, 1H, J = 4.9, 7.8, 14.2), 2.70 (dd, J = 6.8, 14.7), 4.03 (s, 1H), 4.18 (dd, 1H, J = 2.4, 13.2), 4.48 (d, 1H, J = 13.2), 4.54 (dd, 1H, J = 2.0, 4.4), 5.48 (s, 1H), 5.96 (t, 1H, J = 7.3), 7.24–7.39 (m, 6H), 7.44–7.76 (m, 4H); ^{13}C NMR δ 40.8, 66.9, 73.3, 76.2, 86.4, 99.5, 126.1, 126.9, 128.3, 128.9, 129.0, 130.7, 135.2, 137.8; IR (KBr) 1390, 1120, 1070, 1020 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_3S$: C, 68.76; H, 5.77; S, 10.20. Found: C, 68.54; H, 5.75; S, 10.12.

1-*O*-Acetyl-3,5-di-*O*-benzyl-2-deoxy-D-*threo*-pentofuranose (7). The procedure of van Boom[32] was applied to transform **5c** into **7**: To a solution of **5c** (116 mg, 0.29 mmol) in 1.5 mL of ether and 1.5 mL of 1,2-dichloroethane were added 16 μL of CH_3CO_2H and NIS (64 mg) at 0 °C and then the mixture was stirred at 0 °C for 1 h. After aqueous $Na_2S_2O_3$ was added, aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt (4:1)) to give **7** (69 mg, 68%, 1.6:1 mixture of anomers) as a colorless syrup: ^1H NMR δ 2.02 (s, 3H), 2.03 (s, 3H), 2.14–2.20 (m), 2.32 (d, J = 14.7), 2.43 (ddd, J = 2.9, 5.9, 14.7), 3.71–3.90 (m), 4.18–4.63 (m), 6.28 (d, J = 5.4), 6.42 (dd, J = 2.4, 5.9), 7.25–7.33 (m, 10H); IR (neat) 1720, 1455, 1275, 1070 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.80; H, 6.95.

General Procedure for the Coupling Reaction. Silylated heterocyclic bases were prepared according to a method reported in the literature[33] and used *in situ* without any purification. A suspension of heterocyclic base (e.g., thymine, uracil, 5-fluorouracil, 6-chloropurine, and N^6-benzoyladenine) (2 mmol) in hexamethyldisilazane (1.2 mL) and DMF (0.1 mL) was heated at reflux for 16 h under Ar. (In the case of cytosine and guanine derivatives, silylation was performed by using an excess of hexamethyldisilazane and a catalytic amount of $(NH_4)_2SO_4$.) The resulting clear solution was allowed to cool to room temperature. Excess hexamethyldisilazane and DMF were removed under reduced pressure. The residue and thioglycoside (1 mmol) were dissolved in 10 mL of dry CH_2Cl_2 under Ar, and then 500 mg of powdered molecular sieves 4A was added. After 20 min, NBS (1.1 mmol) was added to the solution, and the progress of the reaction was followed by TLC. After completion of the reaction, the addition of aqueous $Na_2S_2O_3$ was followed by filtration and then extraction with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (hexane–AcOEt or $CHCl_3$–MeOH). The following nucleosides were prepared according to this procedure.

1-(3,5-Di-*O*-acetyl-2-deoxy-D-*threo*-pentofuranosyl)-thymine (6a). A colorless gum (mixture of α- and β-anomers): ^1H NMR δ 1.95 (d, J = 1.0 (α)), 1.97 (d, J = 1.0 (β)), 2.08 (s (β)), 2.10 (s (α)), 2.11 (s (β)), 2.12 (s (α)), 2.12–2.15 (m (β)), 2.45 (ddd, J = 5.9, 7.3, 14.6 (α)), 2.57 (ddd, J = 2.0, 6.3, 14.6 (α)), 2.80 (ddd, J = 5.9, 7.8, 15.6 (β)), 4.19–4.30 (m), 4.38 (s (β)), 4.39 (s (β)), 4.65 (dt, J = 4.3, 7.1 (α)), 5.44–5.47 (m (β)), 5.56–5.59 (m (α)), 6.17 (t, J = 6.8 (α)), 6.25 (dd, J = 2.9, 7.8 (β)), 7.08 (d, J = 1.5 (α)), 7.45 (d, J = 0.98 (β)), 8.5 (br); ^{13}C NMR δ 12,9 (α), 13.0 (β), 21.1, 39.1 (α), 39.8 (β), 61.8 (β), 63.6 (α), 72.2 (β), 73.5 (α), 80.3, 84.5 (β), 87.3 (α), 111.1 (β), 111.7 (α), 135.5 (β), 135.8 (α), 150.3 (α), 150.4 (β), 163.6 (β), 163.7 (α), 169.6, 170.2, 170.8; IR (KBr) 3200, 3050, 1750, 1700, 1230, 1050 cm^{-1}.

1-(3,5-Di-*O*-benzoyl-2-deoxy-D-*threo*-pentofuranosyl)-thymine (6b). A colorless gum, partially crystallized on standing (mixture of α- and β-anomers): ^1H NMR δ 1.83 (s (β)), 1.96 (s (α)), 2.34 (dd, J = 2.5, 15.6 (β)), 2.62 (dt, J = 5.9, 14.7 (α)), 2.77 (ddd, J = 2.0, 6.4, 14.7 (α)), 2.95 (ddd, J = 5.9, 7.8, 15.6 (β)), 4.52–4.94 (m, 3H), 5.78–5.82 (m (β)), 5.88–5.97 (m (α)), 6.29 (t, J = 6.8 (α)), 6.33 (dd, J = 2.9, 7.8 (β)), 7.14 (s (α)), 7.38–7.65 (m), 7.94–8.06 (m, 4H), 8.1 (br); ^{13}C NMR δ 12.5 (β), 12.6(α), 39.6 (α), 39.7 (β), 62.0 (β), 62.8 (α), 72.7 (β), 74.0 (α), 80.3 (α), 80.6 (β), 84.4 (β), 87.3 (α), 111.0 (β), 111.4 (α), 128.5, 128.6, 128.9, 129.0, 129.3, 129.5, 129.5, 129.7, 129.8, 133.3, 133.4, 133.7, 134.0, 135.2, 135.8, 150.4, 150.5, 163.9, 164.0, 165.2, 165.5, 166.2; IR (neat) 3400, 3200, 3070, 1720, 1690, 1270, 1095 cm^{-1}. Anal. Calcd for $C_{24}H_{22}O_7N_2$: C, 63.99; H, 4.92; N, 6.22. Found: C, 63.78; H, 4.83; N, 6.22.

1-(3,5-Di-*O*-benzyl-2-deoxy-D-*threo*-pentofuranosyl)-thymine (6c). A colorless syrup, crystallized on standing (mixture of α- and β-anomers): ^1H NMR δ 1.68 (s (β)), 1.93 (s (α)), 2.06 (ddd, J = 4.9, 7.3, 14.2 (α)), 2.21 (dd, J = 2.0, 14.7 (β)), 2.51 (ddd, J = 4.9, 7.8, 14.7 (β)), 2.71 (dd, J = 6.4, 14.2 (α)), 3.76–3.49 (m), 4.14–4.29 (m), 4.41–4.68 (m, 4H), 6.21 (t, J = 6.4 (α)), 6.29 (dd, J = 2.0, 7.8 (β)), 7.14 (s (α)), 7.20–7.38 (m, 10H), 7.57 (s (β)), 8.1 (br); ^{13}C NMR δ 12.28 (β), 12.5 (α), 37.9 (β), 38.1 (α), 67.7 (β), 68.7 (α), 71.4, 73.5, 82.7, 84.1, 110.3 (β), 110.9 (α), 127.5, 127.7, 128.0, 128.4, 128.5, 136.6, 137.1, 137.7, 150.6, 163.9; IR (neat) 3030, 2925, 1690, 1275, 1070 cm^{-1}. Anal. Calcd for $C_{24}H_{26}O_5N_2$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.17; H, 6.35; H, 6.53.

1-(3,5-Di-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*threo*-pentofuranosyl)thymine (6d). A colorless oil, crystallized on standing (mixture of α- and β-anomers): ^1H NMR δ 0.06 (s, 12H), 0.83 (s, 9H), 0.87 (s, 9H), 1.87 (s (β)), 1.90 (s (α)), 1.96 (d, J = 14.7 (β)), 2.07 (ddd, J = 4.9, 7.3, 14.2 (α)), 2.44 (dd, J = 6.3, 14.2 (α)), 2.54 (ddd, J = 4.9, 7.8, 14.6 (β)), 3.75–3.96 (m), 4.13–4.19 (m), 4.26–4.35 (m), 4.43–4.47 (m), 6.15 (d, J = 7.8 (β)), 7.15 (s (α)), 7.54 (s (β)), 9.77 (br); ^{13}C NMR δ −4.9, −4.7, −4.5, 12.9, 18.2, 18.6, 25.8, 25.9, 26.2, 42.5, 61.2 (β), 61.9 (α), 70.8 (β), 72.0 (α), 85.1 (β), 85.5 (α), 85.8 (β), 86.9 (α), 110.0 (β), 110.9 (α), 135.7 (α), 136.9 (β), 150.6 (α), 151.0 (β), 164.6; IR (neat) 2955, 2860, 1695, 1680, 1470, 1270, 1260, 1095, 1075 cm^{-1}. Anal. Calcd for $C_{22}H_{42}O_5N_2Si_2$: C, 56.13; H, 8.99; N, 5.95. Found: C, 56.22; H, 9.05; N, 5.95.

1-(3,5-*O*-Isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6e). A white solid: mp 169–170 °C (ether); ^1H NMR δ 1.39 (s, 3H), 1.49 (s, 3H), 1.96 (s, 3H), 2.18 (d, 1H, J = 15.1), 2.58 (ddd, 1H, J = 4.9, 7.8, 15.1), 3.82 (s-like, 1H), 4.19 (s-like, 2H), 4.43–4.49 (m, 1H, J = 2.4, 4.4), 6.16 (d, 1H, J = 7.8), 8.01 (s, 1H), 8.4 (br, 1H); ^{13}C NMR δ 12.6, 18.6, 29.0, 40.8, 60.5, 68.5, 75.3, 84.9, 98.0, 109.4, 137.3, 150.4, 163.9; IR (KBr) 3170, 2995, 1690, 1475, 1280, 1080 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_5N_2$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.11; H, 6.49; N, 9.91.

The distinguishable ^1H NMR signals of the α-anomer appeared at δ 1.40 (s, 3H, Me), 1.46 (s, 3H), 1.93 (s, 3H), 2.30–2.37 (m, 1H), 2.51–2.55 (m, 1H), 4.57 (m, 1H), 7.11 (s, 1H), 8.6 (br, 1H).

1-(3,5-*O*-Benzylidene-2-deoxy-β-D-*threo*-pentofuranosyl)-

(32) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334.
(33) Wittenburg, E. *Chem. Ber.* **1966**, *99*, 2380.

thymine (6f). A white solid: mp 199–200 °C (hexane–AcOEt); ^{1}H NMR δ 1.62 (s, 3H), 2.31 (d-like, 1H, J = 15.6), 2.68 (ddd, 1H, J = 4.9, 8.3, 15.1), 3.95 (s-like, 1H), 4.26 (dd, 1H, J = 1.5, 13.2), 4.53–4.63 (m, 2H), 5.57 (s, 1H), 6.28 (dd, 1H, J = 1.5, 8.3), 7.32–7.49 (m, 5H), 7.98 (s, 1H), 8.2 (br, 1H); ^{13}C NMR δ 12.1, 40.4, 67.0, 74.6, 75.8, 85.0, 99.4, 109.7, 125.8, 128.3, 129.1, 137.2, 150.7, 164.2; IR (KBr) 3180, 3050, 1720, 1695, 1480, 1280, 1200, 1115, 1080, 1045 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_5N_2$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.81; H, 5.55; N, 8.48.

1-(3,5-*O*-Isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)uracil (8). A white solid: mp 178–180 °C ($CHCl_3$); ^{1}H NMR δ 1.36 (s, 3H), 1.47 (s, 3H), 2.24 (d, 1H, J = 14.7), 2.58 (ddd, 1H, J = 4.5, 7.7, 14.9), 3.86 (d, 1H, J = 1.5), 4.20 (s, 2H), 4.46 (dd, 1H, J = 2.4, 4.4), 5.73 (d, 1H, J = 8.3), 6.11 (d, 1H, J = 7.3), 8.16 (d, 1H, J = 8.3), 9.5 (br, 1H); ^{13}C NMR δ 18.5, 29.0, 41.0, 60.5, 68.4, 75.7, 85.6, 98.0, 100.8, 141.5, 141.5, 150.6, 163.9; IR (KBr) 3390, 2970, 1710, 1690, 1640, 1450, 1370, 1260, 1100, 1060 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_5N_2$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.64; H, 6.10; N, 10.31.

***N*^{4}-Acetyl-1-(3,5-*O*-isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)cytosine (9).** A pale yellow solid: mp 210 °C dec (EtOH); ^{1}H NMR δ 1.31 (s, 3H, Me), 1.44 (s, 3H), 2.29 (s, 3H), 2.32 (d, 1H, J = 15.6), 2.61 (ddd, 1H, J = 4.3, 7.4, 15.0), 3.95 (s, 1H), 4.20 (dd, 1H, J = 2.2, 13.9), 4.26 (d, 1H, J = 13.7), 4.44 (dd, 1H, J = 2.4, 3.9), 6.10 (d, 1H, J = 7.3), 7.46 (d, 1H, J = 7.8), 8.56 (d, 1H, J = 7.3), 10.08 (br, 1H); ^{13}C NMR δ 18.4, 24.9, 29.1, 40.9, 60.6, 68.5, 76.2, 87.2, 95.4, 97.9, 146.3, 155.3, 162.9, 171.0; IR (KBr) 3400, 2970, 1710, 1640, 1555, 1480, 1380, 1300, 1230, 1110, 1070 cm^{-1}. Anal. Calcd for $C_{14}H_{19}O_5N_3$: C, 54.36; H, 6.19; N, 13.59. Found: C, 54.13; H, 6.21; N, 13.34.

The ^{1}H NMR signal for H-1′ of the α-anomer appeared at δ 6.19 (t, J = 6.6).

5-Fluoro-1-(3,5-*O*-isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)uracil (10). A white solid: mp 188–190 °C ($CHCl_3$); ^{1}H NMR δ 1.32 (s, 3H), 1.41 (s, 3H), 2.16 (d, 1H, J = 15.1), 2.52 (ddd, 1H, J = 4.6, 7.6, 15.1), 3.79 (t, 1H, J = 1.8), 4.13 (d, 1H, J = 2.4), 4.14 (s, 1H), 4.40 (dd, 1H, J = 2.4, 4.4), 6.05 (d, 1H, J = 7.8), 8.28 (d, 1H, J = 6.8), 9.41 (br, 1H); ^{13}C NMR δ 18.5, 28.8, 40.9, 60.4, 68.3, 75.8, 85.6, 98.2, 126.1 (J_{CCF} = 34.9), 139.8 (J_{CF} = 235.0), 148.8, 157.0 (J_{CF} = 26.1); IR (KBr) 3380, 3060, 1710, 1690, 1640, 1260, 1190, 1060 cm^{-1}. Anal. Calcd for $C_{12}H_{15}FN_2O_5$: C, 50.35; H, 5.28; N, 9.79. Found: C, 50.42; H, 5.14; N, 9.45.

Synthesis of L-Nucleosides. 1-(3,5-*O*-Isopropylidene-2-deoxy-β-L-*threo*-pentofuranosyl)thymine (**13**) was synthesized by entirely the same sequence described for the synthesis of **6e**. The spectral data of the products in each step were identical to those of the D-series. The selected physical data are given as follows: enantiomer of **3**: mp 69–70 °C; $[\alpha]^{27}_D$ −227° (c, 1.00, $CHCl_3$). **11**: mp 72–72.5 °C; $[\alpha]^{28}_D$ −261° (c, 1.04, $CHCl_3$). **12**: $[\alpha]^{28}_D$ −227° (c, 0.95, $CHCl_3$). **13**: mp 166–167 °C.[34]

N^4-Benzoyl-1-(3,5-*O*-isopropylidene-2-deoxy-β-L-*threo*-pentofuranosyl)cytosine (**14**) was synthesized from **12** and *N*^{4}-benzoylcytosine according to the general procedure. A white solid: mp 180–181 °C (benzene); ^{1}H NMR δ 1.34 (s, 3H), 1.46 (s, 3H), 2.40 (d, 1H, J = 15.2), 2.63 (ddd, 1H, J = 4.2, 7.6, 14.7), 3.96 (d, 1H, J = 0.97), 4.22 (dd, 1H, J = 2.2, 13.9), 4.29 (d, 1H, J = 14.2), 4.47 (dd, 1H, J = 2.7, 4.2), 6.14 (d, 1H, J = 6.8), 7.49–7.63 (m, 4H), 7.88–7.89 (m, 2H), 8.59 (br, 1H), 9.63 (d, 1H, J = 7.3); ^{13}C NMR δ 18.4, 29.2, 40.9, 60.6, 68.6, 76.2, 87.3, 95.3, 97.9, 127.6, 129.0, 133.1, 146.5, 155.2, 162.2, 166.5; IR (KBr) 3400, 3065, 2985, 1695, 1655, 1635, 1560, 1485, 1395, 1280, 1260, 1200, 1120, 1085 cm^{-1}. Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70. Found: C, 61.52; H, 6.09.

6-Chloro-9-(3,5-*O*-isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)purine (15) and Its α-Anomer (16). 15: a white solid; mp 113–114 °C ($CHCl_3$); R_f = 0.22 (hexane–AcOEt (1:1)); ^{1}H NMR δ 1.40 (s, 3H), 1.49(s, 3H), 2.54 (d, 1H, J = 15.1), 2.77 (ddd, 1H, J = 4.4, 7.8, 14.7), 4.01 (dd, 1H, J = 2.4, 4.4), 4.21 (d, 2H, J = 2.4), 4.60 (dd, 1H, J = 2.9, 4.4), 6.55 (d, 1H, J = 7.3), 8.73 (s, 1H), 8.91 (s, 1H); ^{13}C NMR δ 18.8, 28.7, 40.7, 60.5, 68.8, 76.0, 84.3, 98.1, 132.0, 145.0, 150.6, 151.1, 151.7; IR (KBr) 3125, 2995, 2885, 1595, 1565, 1400, 1195, 1075 cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_4O_3Cl$: C, 50.25; H, 4.87; N, 18.03; Cl, 11.41. Found: C, 50.03; H, 4.90; N, 18.03; Cl, 11.36.

16: a colorless gum; R_f = 0.29 (hexane–AcOEt (1:1)); ^{1}H NMR δ 1.46 (s, 3H), 1.52 (s, 3H), 2.66 (dd, 1H, J = 6.8, 13.7), 3.14 (ddd, 1H, J = 4.4, 7.8, 13.7), 4.05 (d, 1H, J = 13.7), 4.16 (dd, 1H, J = 2.7, 13.7), 4.50 (dd, 1H, J = 2.0, 4.4), 4.76 (dd, 1H, J = 2.4, 3.9), 6.52 (t, 1H, J = 7.1), 8.22 (s, 1H), 8.73 (s, 1H); ^{13}C NMR δ 19.1, 28.8, 39.3, 60.3, 70.6, 75.7, 86.6, 97.8, 132.8, 144.7, 151.2, 151.4, 151.8.

6-Chloro-7-(3,5-*O*-isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)purine (17). A colorless gum: R_f = 0.16 (hexane–AcOEt (1:1)); ^{1}H NMR δ 1.34 (s, 3H), 1.47 (s, 3H), 2.54 (d, 1H, J = 14.6), 2.77 (ddd, 1H, J = 4.4, 7.3, 14.7), 4.07 (dd, 1H, J = 2.4, 3.4), 4.25 (dd, 1H, J = 2.2, 13.9), 4.31 (d, 1H, J = 13.7), 4.59 (dd, 1H, J = 2.9, 4.4), 6.76 (d, 1H, J = 7.3), 8.89 (s, 1H), 9.17 (s, 1H); ^{13}C NMR δ 18.5, 28.9, 42.5, 60.6, 68.7, 76.6, 87.2, 98.2, 121.5, 142.2, 148.4, 152.2, 162.8.

6-Chloro-9-(3,5-di-*O*-acetyl-2-deoxy-D-*threo*-pentofuranosyl)purine (18). A colorless gum (mixture of α- and β-anomers): ^{1}H NMR δ 2.02 (s (β)), 2.07 (s (α)), 2.11 (s (β)), 2.15 (s (α)), 2.65 (dt, J = 1.7, 15.1 (β)), 2.71 (ddd, J = 2.0, 7.3, 14.9 (α)), 2.96 (ddd, J = 5.5, 7.7, 15.1 (β)), 3.33 (dt, J = 5.9, 14.9 (α)), 4.26 (dd, J = 7.3, 11.7 (α)), 4.36 (dd, J = 4.1, 12.0 (α)), 4.39–4.50 (m (β)), 4.89 (dt, J = 4.2, 7.3 (α)), 5.60–5.61 (m (β)), 5.79–5.82 (m (α)), 6.44 (t, J = 6.6 (α)), 6.56 (dd, J = 2.0, 7.3 (β)), 8.20 (s (α)), 8.50 (s (β)), 8.75 (s (β)), 8.76 (s (α)); ^{13}C NMR δ 20.8, 20.9, 38.6 (α), 39.7 (β), 61.6 (β), 62.1 (α), 71.9 (β), 73.7 (α), 80.5 (α), 81.1 (β), 84.2 (β), 85.5 (α), 132.0 (β), 132.8 (α), 143.2 (β), 144.2 (α), 151.1, 151.2, 141.6, 152.1, 169.5, 170.0, 170.4, 170.6; IR (neat) 3585, 3470, 2955, 1745, 1590, 1560, 1240, 1130, 1035 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_4O_5Cl$: C, 47.40; H, 4.26. Found: C, 47.15; H, 4.37.

***N*^{6}-Benzoyl-9-(3,5-*O*-isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (19).** A white solid: R_f = 0.6 (5% MeOH in $CHCl_3$); mp 175–177 °C (AcOEt); ^{1}H NMR δ 1.40 (s, 3H), 1.50 (s, 3H), 2.53 (d, 1H, J = 14.7), 2.78 (ddd, 1H, J = 4.6, 7.8, 14.9), 3.99 (t, 1H, J = 2.7), 4.20 (d, 2H, J = 2.0), 4.59 (dd, 1H, J = 2.4, 4.4), 6.57 (d, 1H, J = 7.8), 7.52 (t, 2H, J = 7.3), 7.61 (t, 1H, J = 7.3), 8.03 (d, 2H, J = 7.3), 8.77 (s, 1H), 8.81 (s, 1H), 9.05 (s, 1H); ^{13}C NMR δ 18.8, 28.8, 40.7, 60.6, 68.9, 75.9, 83.8, 98.1, 123.1, 127.8, 128.9, 132.7, 133.8, 142.7, 149.2, 151.4, 152.5, 164.6; IR(KBr) 2990, 1695, 1600, 1575, 1510, 1445, 1250, 1190, 1070 cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_5O_4$: C, 60.75; H, 5.35; N, 17.71. Found: C, 60.60; H, 5.08; N, 17.78.

The α-anomer of **19**: A white solid; R_f = 0.7 (5% MeOH in $CHCl_3$); ^{1}H NMR δ 1,46 (s, 3H), 1.53 (s, 3H), 2.64 (dd, 1H, J = 6.6, 13.9), 3.22 (ddd, 1H, J = 4.5, 7.6, 12.9), 4.05 (d, 1H, J = 12.2), 4.16 (dd, 1H, J = 2.7, 13.4), 4.53 (d, 1H, J = 2.0), 4.77 (s, 1H), 6.51 (t, 1H, J = 6.8), 7.53 (t, 2H, J = 7.3), 7.60 (t, 1H, J = 7.3), 8.03 (d, 2H, J = 7.3), 8.09 (s, 1H), 8.78 (s, 1H), 9.08 (s, 1H); ^{13}C NMR δ 19.1, 28.9, 39.2, 60.4, 70.7, 75.5, 86.4, 97.7, 124.1, 127.9, 128.9, 132.8, 133.6, 142.5, 149.7, 151.4, 152.5, 164.6.

***N*^{2}-Acetyl-9-(3,5-*O*-isopropylidene-2-deoxy-β-D-*threo*-pentofuranosyl)guanine (20).** A white solid: mp 206 °C dec (EtOH); ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 3H), 1.43 (s, 3H), 2.16 (s, 3H), 2.28 (d, 1H, J = 14.7), 2.75 (ddd, 1H, J = 4.6, 8.1, 14.7), 3.92 (s, 1H), 3.94 (d, 1H, J = 13.7), 4.14 (d, 1H, J = 11.2), 4.54 (s, 1H), 6.15 (d, 1H, J = 7.8), 8.20 (s, 1H), 11.71 (br, 1H), 11.98 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 18.9, 23.8, 28.7, 38.9, 60.0, 68.5, 75.2, 83.1, 97.2, 120.0, 137.9, 147.9, 148.0, 154.9, 173.6; IR (KBr) 3400, 3200, 3160, 3080, 1675, 1615, 1560, 1480, 1265, 1225 cm^{-1}. Anal. Calcd for $C_{15}H_{19}N_5O_5$: C, 51.57; H, 5.48; N, 20.05. Found: C, 51.55; H, 5.41; N, 20.16.

The distinguishable ^{1}H NMR signals of the α-anomer appeared at δ 1.28 (s, 3H), 1.43 (s, 3H), 2.17 (s, 3H), 6.30 (t, 1H, J = 7.3), 8.23 (s, 1H), 11.40–11.80 (br, 2H).

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(34) The optical rotation of **13** was too small ($[\alpha]_D$ < −2°) to obtain an accurate value. Therefore, **13** was converted to 1-(2-deoxy-β-L-*threo*-pentofuranosyl)thymine by deprotection (*p*-TsOH·H_2O/MeOH) and its optical rotation was measured: $[\alpha]^{28}_D$ −15.0° (c, 1.01, H_2O); mp 167.5–168 °C (lit.[5b] D form; $[\alpha]^{23}_D$ +14° (c, 0.56, H_2O); mp 168–169 °C).