JOC*Article*

Synthesis and Conformational Analysis of 1-[2,4-Dideoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine

Veerle Vanheusden,† Roger Busson,‡ Piet Herdewijn,‡ and Serge Van Calenbergh*,†

Laboratory for Medicinal Chemistry (FFW), Ghent University, Harelbekestraat 72, 9000 Gent, Belgium, and Laboratory for Medicinal Chemistry, Rega Institute, Catholic University of Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

serge.vancalenbergh@ugent.be

Received February 9, 2004

Previously different types of nucleosides with a six-membered carbohydrate moiety have been evaluated for their potential antiviral and antibiotic properties and as building blocks in nucleic acid synthesis. However, a pyranose nucleoside with a 1,4-substitution pattern like 1-[2,4-dideoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine (**4**) has not been studied yet. Modeling suggested that this nucleoside would show the $^4C_1$ conformation in contrast to anhydrohexitol nucleosides (**1**) whose most stable conformation is $^1C_4$. The key to the synthesis of **4** involves the stereoselective introduction of the hydroxymethyl group onto the C-4 carbon of the pyranose sugar. Attempts to achieve this via hydroboration/oxidation of a C-4′-exocyclic vinylic intermediate selectively yielded the undesired α-directed hydroxymethyl group. Therefore, we envisaged another approach in which the C-4 substituent was introduced upon treatment of 2,3-*O*-isopropylidene-1-*O*-methyl-4-*O*-phenoxythiocarbonyl-α-L-lyxopyranose with *β*-tributylstannyl styrene. This allowed stereoselective *β*-directed introduction of a 2-phenylethenyl group at C-4, which was converted via oxidation/reduction (OsO_4, $NaIO_4$/$NaBH_4$) into the desired 4-hydroxymethyl group (**20**). The resulting 1-*O*-methyl-2,3,6-tri-*O*-acetyl-protected sugar was coupled with silylated thymine, using $SnCl_2$ as Lewis acid (**22**). After suitable protection, Barton deoxygenation of the 2′-hydroxyl function of the obtained ribo-nucleoside yielded the desired 2′-deoxynucleoside **4**, indeed showing the expected equatorial orientation of the thymine ring ($^4C_1$).

Introduction

Nucleosides with a six-membered carbohydrate moiety have been evaluated for their potential antiviral[1−4] and antibiotic[5] properties and as building blocks in nucleic acid synthesis.[6,7] Antiviral activity[1−3] has been found in the hexitol series (**1**) (Figure 1). These molecules are characterized by the presence of an axial base moiety in the most stable conformation.[1] When evaluated as ligand for HSV-1 TK, it was observed that the hexitol nucleoside cocrystallizes with the enzyme in a conformation with an equatorial base moiety (which is a high energy conformation).[3] This conformation, however, is the most stable one for the carbocyclic congener (**2**).[4] When incorporated in oligonucleotides, it is suggested that the carbocyclic nucleoside undergoes a chair flip and that it adopts the same conformation as found in HNA.[8] These observations clearly show the possibility of conformational adaptation of 1,4-substituted (when considering the

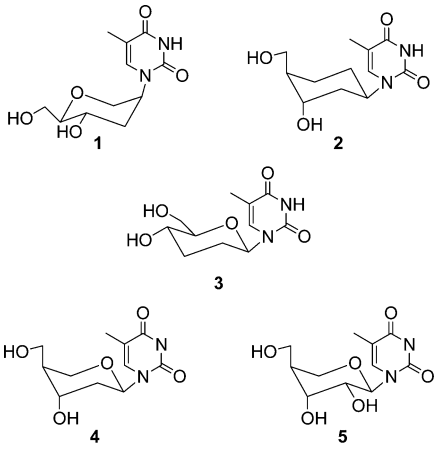


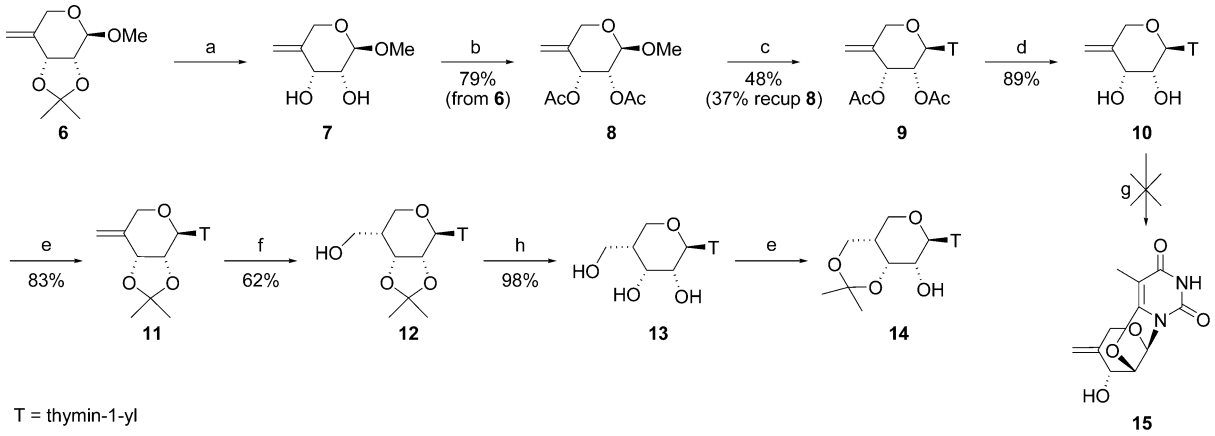
FIGURE 1. Structures of compounds **1**−**5**.

* To whom correspondence should be addressed. Tel: +32 (0)9 264 81 24. Fax: +32 (0)9 264 81 46.
† Ghent University.
‡ Catholic University of Leuven.

(1) Verheggen, I.; Van Aerschot, A.; Toppet, S.; Snoeck, R.; Janssen, G.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, *36*, 2033−2040.
(2) Verheggen, I.; Van Aerschot, A.; Van Meervelt, L.; Rozenski, J.; Wiebe, L.; Snoeck, R.; Andrei, G.; Balzarini, J.; Claes, P.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1995**, *38*, 826−835.
(3) Ostrowski, T.; Wroblowski, B.; Busson, R.; Rozenski, J.; De Clercq, E.; Bennet, M. S.; Champness, J. N.; Summers, W. C.; Sanderson, M. R.; Herdewijn, P. *J. Med. Chem.* **1998**, *41*, 4343−4353.
(4) Maurinsh, Y.; Schraml, J.; De Winter, H.; Blaton, N.; Peeters, O.; Lescrinier, E.; Rozenski, J.; Van Aerschot, A.; De Clercq, E.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1997**, *62*, 2861−2871.
(5) Haouz, A.; Vanheusden, V.; Munier-Lehmann, H.; Froeyen, M.; Herdewijn, P.; Van Calenbergh, S.; Delarue, M. *J. Biol. Chem.* **2003**, *278*, 4963−4971.
(6) Vastmans, K.; Pochet, S.; Peys, A.; Kerremans, L.; Van Aerschot, A.; Hendrix, C.; Marliere, P. Herdewijn P. *Biochemistry* **2000**, *39*, 12757−12765.
(7) Vastmans, K.; Froeyen, M.; Kerremans, L.; Pochet, S.; Herdewijn, P. *Nucleic Acids Res.* **2001**, *29*, 3154−3163.

10.1021/jo040130g CCC: $27.50
Published on Web 06/02/2004

SCHEME 1. Synthesis of 14[a]



[a] Reagents: (a) CF_3COOH, H_2O; (b) $(Ac)_2O$, pyridine; (c) 5-methyl-2,4-bis[(trimethylsilyl)oxy]pyrimidine, CH_3CN, $SnCl_2$; (d) NH_3, MeOH; (e) 2,2-dimethoxypropane, acetone, *p*-toluenesulfonic acid; (f) (i) 9-BBN-H, THF, (ii) H_2O_2, NaOH; (g) $(PhO)_2CO$, $NaHCO_3$, DMF; (h) HOAc, H_2O.

base moiety and the hydroxymethyl substituent) nucleosides dependent on their "biological" environment.

β-Pyranose nucleosides (**3**) have a base moiety in the 1′-position and an hydroxymethyl group in the 5′-position.[9] Both substituents are equatorially oriented. This conformation is very stable, no chair flip has been observed, and oligonucleotides built up out of the pyranose nucleosides show only a very small helical twist.[10] No biological activity has been determined for this type of natural-like nucleosides. A pyranose nucleoside with a 1,4-substitution pattern (**4**) has not been studied yet because of its difficult synthetic availability. Sugar-base condensation reaction of its appropriate 2′-deoxy sugar precursor is expected to give rise to the thermodynamically most stable α-nucleoside.[11] Therefore the synthetic scheme should involve the introduction of the base moiety using anchimeric assistance of a 2′-acetoxy group in order to be able to isolate the *β*-nucleoside. Pyranose nucleoside **4** is a structural analogue of an anhydrohexitol nucleoside (**1**) as crystallized with the active site of HSV-1 TK and an analogue of a carbocyclic nucleoside (**2**) in its most stable conformation, which motivates the synthesis and biological evaluation of this new type of six-membered nucleoside analogue.

Results and Discussion

Chemistry. Two strategies toward the synthesis of **5**, the ribo-precursor of the target nucleoside, were already attempted.[12] Both reaction schemes are not useful for the synthesis of significant amounts of the target molecule because of low yields and very difficult separation problems at different stages. In one of these attempts Doboszewski and Herdewijn[12] experienced that treatment

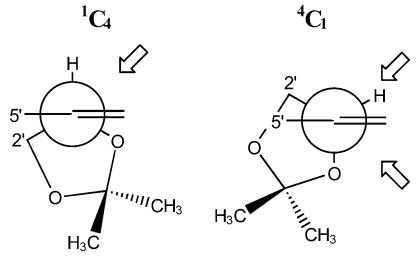


FIGURE 2. Image of the steric hindrance caused by the 2′,3′-*O*-isopropylidene in the $^1C_4$ and $^4C_1$ conformation.

of 4-deoxy-2,3-*O*-isopropylidene-1-*O*-methyl-4-*C*-methylene-*β*-D-*erythro*-pentopyranose (**6**) with borane in THF, followed by oxidation with H_2O_2, yielded mainly the undesired 4-α-hydroxymethyl sugar, probably caused by steric hindrance of the 2,3-*O*-isopropylidene protective group during borane addition.

In other studies, we observed that preferential attack of borane on an exo double bond is not always predictable and may be governed by complexation of the reagent and steric effects.[13] By carrying out the hydroboration/oxidation of the 4-methylene function after sugar-base coupling, we postulated that the presence of the thymine moiety would favor a $^4C_1$ conformation of the pyranose, which reduces the steric hindrance caused by the isopropylidene protective group (Figure 2). We hoped this would influence the stereochemical outcome of this reaction toward the formation of the 4-*β*-hydroxymethyl compound (**5**).

Synthesis was started from 4-deoxy-2,3-*O*-isopropylidene-1-*O*-methyl-4-*C*-methylene-*β*-D-*erythro*-pentopyranose (**6**), obtained in four steps from L-lyxose (Scheme 1).[12]

Because acid-catalyzed exchange of the 1-*O*-methyl group of **6** with an 1-*O*-acetyl group is known to cause partial ring opening,[12] it was decided to maintain the methyl protective group at the 1-*O*-position. The 2,3-*O*-isopropylidene protective group of **6** was selectively removed upon short treatment with CF_3COOH,[12] and the 2- and 3-hydroxyl groups were reprotected by acetylation.

(8) Maurinsh, Y.; Rosemeyer, H.; Esnouf, R.; Medvedovici, A.; Wang, J.; Ceulemans, G.; Lescrinier, E.; Hendrix, C.; Busson, R.; Sandra, P.; Seela, F.; Van Aerschot, A.; Herdewijn, P. *Chem. Eur. J.* **1999**, *5*, 2139−2150.

(9) Yamazaki, T.; Matsuda, K.; Sugiyama, H.; Seto, S.; Yamaoka, N. *J. Chem. Soc., Perkin Trans. 1* **1977**, *14*, 1654−1659.

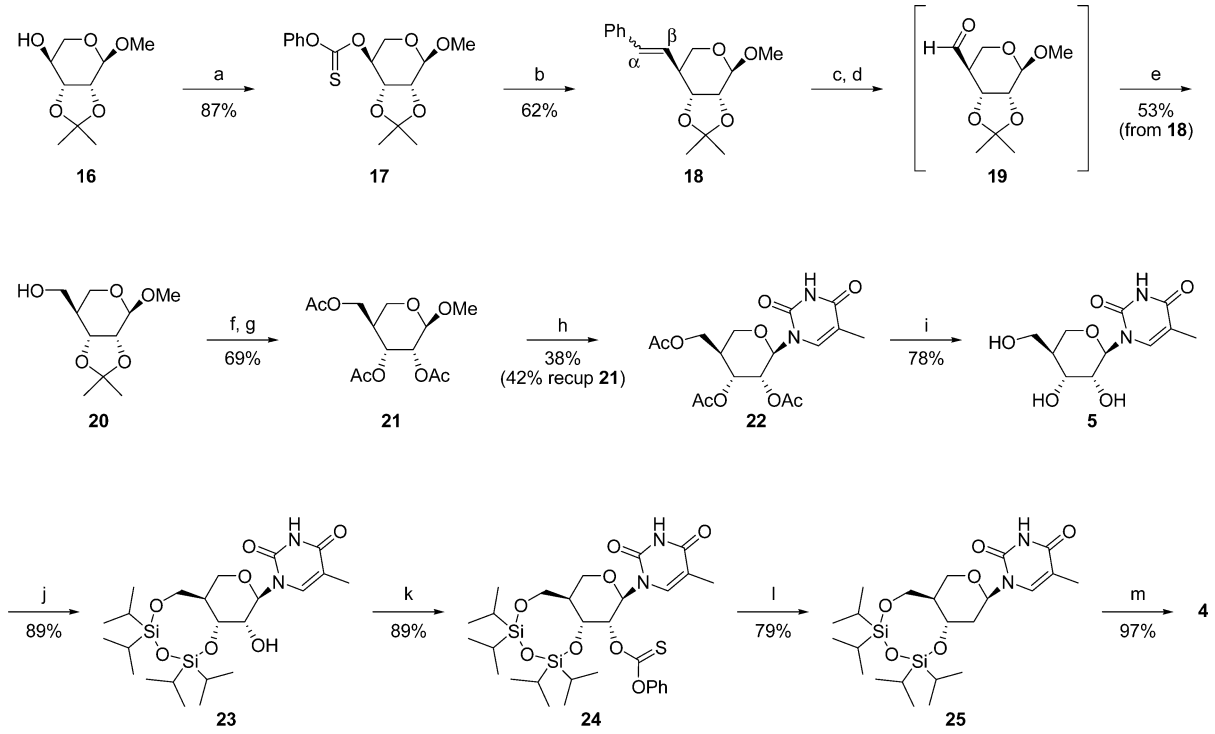
(10) Lescrinier, E.; Froeyen, M.; Herdewijn, P. *Nucleic Acids Res.* **2004**, *32*, 863−864.

(11) Augustyns, K.; Rozenski, J.; Van Aerschot, A.; Busson, R.; Claes, P.; Herdewijn, P. *Tetrahedron* **1994**, *50*, 1189−1198.

(12) Doboszewski, B.; Herdewijn, P. A. M. *Nucleosides Nucleotides* **1996**, *15*, 1495−1518.

(13) Wang, J.; Busson, R.; Blaton, N.; Rozenski, J.; Herdewijn, P. *J. Org. Chem.* **1998**, *63*, 3051−3058.

SCHEME 2. Synthesis of 4[a]



[a] Reagents: (a) PhOC(S)Cl, DMAP, CH_3CN; (b) β-tributylstannyl styrene, AIBN, benzene; (c) NMMO, OsO_4, dioxane; (d) $NaIO_4$, H_2O; (e) $NaBH_4$, EtOH, H_2O; (f) CF_3COOH, H_2O; (g) $(Ac)_2O$, pyridine; (h) 5-methyl-2,4-bis[(trimethylsilyl)oxy]pyrimidine, CH_3CN, $SnCl_2$; (i) NH_3, MeOH; (j) $(iPr_2SiCl)_2O$, DMF; (k) PhOC(S)Cl, DMAP, CH_3CN; (l) Bu_3SnH, AIBN, toluene; (m) Bu_4NF, THF.

Coupling of the resulting sugar **8** with silylated thymine in the presence of trimethylsilyl triflate or $SnCl_4$ as catalysts proceeded slowly and yielded an uncharacterized side product with a similar polarity as **9**, rendering purification of the desired nucleoside difficult. This problem could be overcome by performing the coupling reaction under reflux conditions in CH_3CN using $SnCl_2$ as a Lewis acid, which selectively yielded the desired 1-β-nucleoside in 48% yield.[14] The remaining starting material **8** could be recuperated (37%). To avoid possible side reactions during hydroboration,[15] the 2′- and 3′-hydroxyl groups were deprotected and reprotected with an isopropylidene protective group to yield **11**. Reaction of **11** with 9-BBN-H exclusively yielded **12**, the undesired epimer. The selectivity of the formation of **12** was most unexpected. Analysis of its ^1H NMR spectrum reveals an axial-axial coupling between H-1′ and H-2′ and another one between H-4′ and H-5′. The former is indicative for an equatorial orientation of the thymine ring, while the latter and the narrow H-3′ signal (half bandwidth of 7.8 Hz) suggest a $^4C_1$ chair conformation with an α-directed 4′-hydroxymethyl. This assumption was supported by a NOEDIF experiment showing a weak increase (0.53%) of the H-2′ signal upon irradiation of the H-4′ signal. After deprotection of **12** with acetic acid (to give **13**), the α-orientation of the 4′-CH_2OH was confirmed via protection of the 6′- and 3′-hydroxyls with an isopropylidene protective group (**14**), which would be formed less likely for **5**. Apparently, steric hindrance of the 2′,3′-*O*-isopropylidene and the formation of the thermodynamically most stable product (both the 4′-hydroxymethyl and the base are oriented equatorially)[11] govern the stereochemical outcome of the hydroboration. Attempts to increase the steric hindrance at the β-side of the sugar ring, through the formation of a 2,2′-anhydronucleoside (**15**) failed. Upon treatment of **10** with diphenyl carbonate and $NaHCO_3$, elimination of the base occurred, yielding an uncharacterized highly volatile sugar analogue.

Because synthesis of **4** from **10** failed, it was decided to exploit the steric space at the β-side of the sugar ring through radical-mediated introduction of a carbon group (Scheme 2).

Thus 2,3-*O*-isopropylidene-1-*O*-methyl-4-*O*-phenoxythiocarbonyl-α-L-lyxopyranose (**17**), obtained through reaction of **16** with phenyl chlorothionocarbonate,[16] was reacted with β-tributylstannylstyrene.[17] This led to stereoselective introduction of a 2-phenylethenyl group at the β-side of the sugar ring (**18**) as indicated by its $^1C_4$ conformation and the positive NOEDIF effect between H-3′ and H-β of the styrene moiety (3.9% enhancement).[18] Via oxidative cleavage of the double bond and in situ reduction (OsO_4, $NaIO_4/NaBH_4$), the phenylethenyl group of **18** was converted into a 4-hydroxymethyl group in a 53% overall yield (**20**).[18] A similar reaction sequence as described for the synthesis of **10** was employed for the conversion of **20** to ribo-analogue **5**. The yield of the sugar-base condensation reaction was only 38%. The presence of the acetoxymethyl moiety in the 4′-position

(14) Martin, P. *Helv. Chim. Acta* **1996**, *79*, 1930−1938.
(15) Koga, M.; Schneller, S. W. *J. Org. Chem.* **1993**, *58*, 6471−6473.
(16) Lin, T. S.; Zhu, J.-L.; Dutschman, G. E.; Cheng, Y.-C.; Prusoff, W. H. *J. Med. Chem.* **1993**, *36*, 353−362.
(17) Saihi, M. L.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1977**, 1251−1255.
(18) An, H. Y.; Wang, T. M.; Maier, M. A.; Manoharan, M.; Ross, B. S.; Cook, P. D. *J. Org. Chem.* **2001**, *66*, 2789−2801.

TABLE 1. ^{1}H NMR Chemical Shifts (δ) and Coupling Constants (J) in Sugar Parts of 4, 5, 13, 23, and 25[a]

		13		5		23		25		4	
proton	coupling	δ	J	δ	J	δ	J	δ	J	δ	J
1′		5.60		5.59		5.36		5.93		5.82	
	1′−2′A		9.6		9.6		2.7		4.8		11.4
	1′−2′B								0		0
2′A		3.63		3.66		4.49		2.18		1.51	
	2′A−2′B								14.7		11.4
	2′A−3′		3.6		*b*		2.7		10.4		*b*
	2′A−2′OH		*b*		*b*		5.1				
2′B								2.54		1.96	
	2′B−3′								3.3		<1
3′		3.95		3.97		3.99		4.26		4.02	
	3′−4′		*b*		*b*		10.2		10.4		*b*
	3′−3′OH		*b*		*b*						2.7
4′		1.91		1.77		2.22		1.79		1.51	
	4′−5′A		11.7		0		11.4		11.7		0
	4′−5′B		4.8		2.4		5.7		4.8		2.1
	4′−6′A		*b*		*b*		0		0		7.2
	4′−6′B		6.3		*b*		2.1		2.7		8.4
5′A		3.52		3.66		3.75		3.72		3.77	
	5′A−5′B		11.7		11.7		11.4		11.7		11.4
5′B		3.68		3.83		3.87		3.86		3.92	
6′A		under H_2O		3.50		3.55		3.57		3.50	
	6′A−6′B		10.8		11.7		11.1		11.7		10.1
	6′A−6′OH		*b*		*b*						5.1
6′B		3.41		3.59		3.92		4.14		3.60	
	6′B−6′OH		*b*		*b*						5.1

[a] Chemical shifts indicated in the first column are δ values relative to the residual solvent peak in DMSO-d_6 (2.48 ppm) in the case of **4**, **5**, **13,** and **23** and in $CDCl_3$ (7.26 ppm) in the case of **25**. Coupling constants between the protons indicated in the second column are values in Hz. Protons are labeled by the number of the carbon atom to which they are bonded; if two protons are bonded to the same carbon atom, the one resonating at a higher field is denoted by A and the other by B. [b] Not determined.

(instead of the 5′-position in natural sugars) has an important effect on the reaction. The 4′-acetoxymethyl group would favor α-attack of the base moiety,[11] while the neighboring group effect of the 2′-acetoxygroup would favor β-attack of the thymine base.[11] To allow selective deoxygenation of the 2′-hydroxyl of **5**, we envisaged a simultaneous protection of the 3′- and 6′-hydroxyl groups with a 1,1,3,3-tetraisopropyldisiloxan-1,3-diyl (TIPDS) group. At room temperature this reaction was unsuccessful as a result of the axial position of the 4′-hydroxylmethyl and 3′-hydroxyl functions. Heating to 30 °C allowed conformational change of the sugar moiety in order to adopt the $^1C_4$ conformation, positioning both groups equatorially and resulting in a successful protection.[19] Esterification of the 2′-hydroxyl as a phenyl thionocarbonate ester, followed by Barton deoxygenation and removal of the TIPDS group with TBAF, yielded the desired six-membered ring nucleoside **4**. Upon removal of the TIPDS protective group, the chair conformation of the sugar ring was restored to the $^4C_1$ conformation ($J_{1',2'}$ = 11.4 Hz), indicating that the thymine ring of **4** indeed adopts an equatorial orientation.

Conformational Analysis. The conformations of nucleosides **4**, **5**, **13**, **23**, and **25** were studied by NMR spectroscopy. The data are given for each compound in the Experimental Section. A standard numbering system is used for carbon atoms as exemplified for **4** in Figure 3. All ^{13}C resonances were consistently assigned by gHMQC experiments. The ^{1}H NMR results for **4**, **5**, **13**, **23**, and **25** are summarized in Table 1. Because of occasional overlapping of ^{1}H NMR spectra, full spectral analysis was difficult in the case of **5** and **13**. Coupling constants in the pentopyranosyl parts of **4** and **5** are essentially the same; hence the conformational analysis for compound **4** applies to compound **5** as well. This is also the case for the **23**−**25** couple.

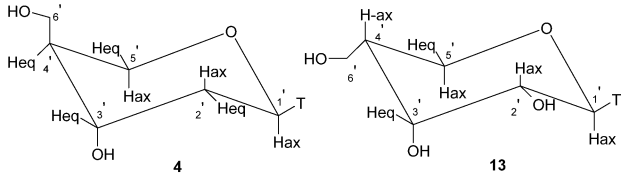
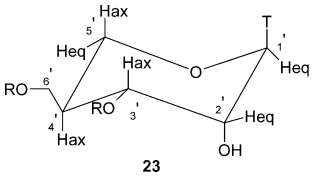


FIGURE 3. Structure of **4** and **13**.

According to the Karplus equation, the coupling between H-1′ and H-2′ ($J_{1',2'}$ = 9.6 Hz) in compound **13** indicates that the dihedral angle between these protons is close to 180 °C, consistent with an axial-axial arrangement of these bonds in a chair conformation. This points to an equatorially oriented base. The $J_{4',5'A}$ (11.7 Hz) and the small coupling for H-3′ indicate that H-4′ and H-5′A are in axial and H-3′ in an equatorial arrangement, thus leading to the chair conformation as shown in Figure 3. Herein the 4′-hydroxymethyl is necessarily directed equatorially.

In **4**, proton H-1′ shows also a large coupling (11.4 Hz) with H-2′A, indicating an axial position of both protons. The 3′ proton is in an equatorial conformation because its half bandwidth ($\nu_{1/2}$) is about 7.2 Hz for three couplings. This cannot contain an axial-axial coupling. Also the absence of a large coupling between H-4′−H-5′A or H-4′−H-5′B points to an equatorial H-4′ proton and further proves that **4** is in a chair conformation with the base in an equatorial position and the 4′-hydroxymethyl axially oriented as depicted in Figure 3.

(19) Moyroud, E.; Biala, E.; Strazewski, P. *Tetrahedron* **2000**, *56*, 1475−1484.



23

FIGURE 4. Structure of **23**.

In **23**, a $J_{1',2'}$ value of 2.7 Hz indicates an equatorial orientation of both protons and thus an axially directed thymine ring. From $J_{3',4'}$ (10.2 Hz) and $J_{4',5'A}$ (11.4 Hz) it can be concluded that H3′, H4′, and H5′A are all three in an axial orientation, hereby confirming the flipping of the chair conformation from $^4C_1$ to $^1C_4$ upon introduction of a TIPDS protective group on **5** (Figure 4).

Summarizing, the values of the vicinal H,H-coupling constants lead to the conclusion that **13**, **4**, and **5** are in chair conformations with the base in an equatorial position, contrary to **23** and **25** where the base is in an axial orientation.

The data for **4** and **5** indicate that the conformational preference of 4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl nucleosides is opposite to that of the anhydrohexitol nucleosides (Figure 1).[1] When **4** is considered, an axially oriented heterocycle would lead to an unfavorable 1,3-diaxial interaction between the nucleoside base and the 3′- and 5′-postions. With an equatorially oriented heterocycle, this unfavorable interaction is present between the 4′-hydroxymethyl function and the hydrogen atom in the 2′-positon and also between the 3′-OH and the H-5′ and H-1′. These latter interactions may be less unfavorable than the ones with the thymine ring. Considering the anhydro-hexitol nucleosides, on the contrary, only one sterically unfavorable 1,3-diaxial interaction is present when the nucleoside base is oriented axially. Apart from this, a hydrogen bond between the 6′-CH_2-OH and the ring oxygen may also stabilize the $^4C_1$ conformation in **4** and **5**.

Conclusions

We have successfully developed a stereoselective approach for the synthesis of 1-[2,4-dideoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine (**4**) from 2,3-*O*-isopropylidene-1-*O*-methyl-α-L-lyxopyranose (**16**) in 13 steps. The key steps of this synthetic route involve the stereoselective introduction of the 6′-carbon on the β-side of the sugar ring, via radical-mediated substitution of the 4′-hydroxyl group by a phenylethenyl group (**17** → **18**) followed by the introduction of the base via a $SnCl_2$-mediated coupling. Conformational analysis proves that **4** shows the expected $^4C_1$ conformation with an equatorially oriented thymine ring. Biological evaluation of this nucleoside will be published elsewhere.

Experimental Section

See Supporting Information for general synthetic methods and materials.

2,3-Di-*O*-acetyl-4-deoxy-1-*O*-methyl-4-methylene-β-D-*erythro*-pentopyranose (8). Compound **6**[12] (1.02 g, 5.08 mmol) was treated with 90% trifluoroacetic acid (9 mL) during 5 min. After evaporation, water was added, followed by Dowex 1×2 (OH^- form) to neutralize residual acid. The resin was removed by filtration and washed with water. The combined water filtrates were evaporated, and the residue was thoroughly dried under high vacuum. The resulting 4-deoxy-1-*O*-methyl-4-methylene-β-D-*erythro*-pentopyranose (**7**) was dissolved in pyridine. Ac_2O was added, and the mixture was stirred at room temperature for 2 h. Evaporation and coevaporation with toluene yielded crude **8** (980 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (6H, s, $OCOCH_3$), 3.43 (3H, s, OCH_3), 4.09 (1H, d, J = 12.3 Hz, H-5A), 4.34 (1H, ddd, J = 12.3, 1.5 and 0.6 Hz, H-5B), 4.72 (1H, d, J = 2.4 Hz, H-1), 5.02 and 5.10 (2H, 2m, methylene), 5.14 (1H, m, H-2), 5.78 (1H, m, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 ($OCOCH_3$), 21.0 ($OCOCH_3$), 55.6 (OCH_3), 64.2 (C-5), 68.8 (C-3), 70.7 (C-2), 100.0 (C-1), 110.6 (C-6), 138.2 (C-4), 169.8 (CO), 170.4 (CO). HRMS (ESI-MS) for $C_{11}H_{16}O_6$ $[M + Na]^+$: found, 267.0849; calcd, 267.0844.

1-[2,3-Di-*O*-acetyl-4-deoxy-4-methylene-β-D-*erythro*-pentopyranosyl]thymine (9). Thymine (991 mg, 7.86 mmol) was suspended in hexamethyldisilazane (87.8 mL, 416 mmol), containing trimethylsilyl chloride (0.71 mL, 5.6 mmol) and pyridine (7 mL). The mixture was heated to 125 °C and stirred overnight. The reaction mixture was evaporated and coevaporated with toluene. The resulting residue and **8** (980 mg, 4.01 mmol) were dissolved in CH_3CN (27 mL), $SnCl_2$ (anhydrous, 1.98 g, 10.5 mmol) was added, and the mixture was refluxed under nitrogen during 39 h. After cooling, the mixture was poured in 10% Na_2CO_3 and extracted with CH_2Cl_2. After drying and evaporation of the organic layer, the obtained residue was purified by column chromatography (CH_2Cl_2−MeOH, 100:0 → 98:2) yielding **9** (640 mg, 48%) as a white foam and recuperated starting material **8** (355 mg, 37%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.73 (3 H, s, 5-CH_3), 1.90 (3H, s, $OCOCH_3$), 2.11 (3H, s, $OCOCH_3$), 4.28 (1H, d, J = 12.6 Hz, H-5′A), 4.35 (1H, d, J = 12.1 Hz, H-5′B), 5.16 (1H, dd, J = 3.3 and 9.9 Hz, H-2′), 5.34 and 5.36 (2H, 2s, methylene), 5.78 (1H, d, J = 3.0 Hz, H-3′), 5.93 (1H, d, J = 9.9 Hz, H-1′), 7.67 (1H, s, H-6). HRMS (ESI-MS) for $C_{15}H_{18}N_2O_7$ $[M + Na]^+$: found, 361.1011; calcd, 361.1011. UV 265 (9839).

1-[4-Deoxy-4-methylene-β-D-*erythro*-pentopyranosyl]-thymine (10). A solution of **9** (30 mg, 0.089 mmol) in 7 N methanolic ammonia solution (5 mL) was stirred for 2 h at room temperature and was evaporated under reduced pressure. The resulting residue was purified by column chromatography (CH_2Cl_2−MeOH, 90:10) yielding **10** (20 mg, 89%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.75 (3 H, d, J = 1.2 Hz, 5-CH_3), 3.68 (1H, m, H-2′), 4.02 and 4.28 (3H, d and m, H-3′ and H-5′), 5.00 (1H, br s, methylene), 5.07 (1H, d, J = 1.8 Hz, methylene), 5.74 (1H, d, J = 9.3 Hz, H-1′), 7.52 (1H, q, H-6). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.5 (5-CH_3), 67.4, 69.9 and 73.0 (C-2′, C-3′ and C-5′), 80.3 (C-1′), 110.3 (C-5), 114.5 (C-6′), 137.5 (C-6), 144.0 (C-4′), 151.7 (C-2), 164.6 (C-4). HRMS (ESI-MS) for $C_{11}H_{14}N_2O_5Na$ $[M + Na]^+$: found, 277.0812; calcd, 277.0800. UV 265 (10830).

1-[4-Deoxy-2,3-*O*-isopropylidene-4-methylene-β-D-*erythro*-pentopyranosyl]thymine (11). To a stirred suspension of **10** (129 mg, 0.51 mmol) in anhydrous acetone (3 mL) and 2,2-dimethoxypropane (0.31 mL, 2.52 mmol) was added *p*-toluenesulfonic acid monohydrate (97 mg, 0.51 mmol). After 4 h the resulting solution was poured slowly into stirred aqueous 0.5 M $NaHCO_3$ (2 mL). The solution was concentrated in vacuo to ca. 1.5 mL, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were dried, evaporated under reduced pressure, and quickly sent over a silica gel column (CH_2Cl_2−MeOH, 97:3) yielding **11** (124 mg, 83%) as a white foam. HRMS (ESI-MS) for $C_{14}H_{18}N_2O_5Na$ $[M + Na]^+$: found, 317.1109; calcd, 317.1113.

1-[4-Deoxy-4-(hydroxymethyl)-2,3-*O*-isopropylidene-β-D-ribopyranosyl]thymine (12). To an ice-cooled solution of **11** (102 mg, 0.40 mmol) in anhydrous THF (1 mL), under nitrogen, was added dropwise 9-BBN-H (2.0 mL of a 0.5 M solution in THF, 1.0 mmol). The mixture was slowly warmed to room temperature and stirred for 24 h. The reaction mixture was cooled to 0 °C and treated sequentially with EtOH (1.6

mL), a 2 N solution of NaOH (0.78 mL, 1.56 mmol), and 30% aqueous H_2O_2 solution (0.78 mL, 6.8 mmol). The resulting mixture was stirred for 24 h and then poured into a mixture of EtOAc (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (three times). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (CH_2Cl_2−MeOH, 95:5 → 98:2) yielding pure **12** (77 mg, 62%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.09 (3 H, s, C(CH_3)$_2$), 1.26 (3H, s, C(CH_3)$_2$), 1.76 (3H, s, 5-CH_3), 2.23 (1H, m, H-4′), 3.20 (1H, dd, J = 11.2 and 5.4 Hz, H-6′A), 3.37 (1H, dd, J = 8.31 and 10.8 Hz, H-5′A), 3.43 (1H, t, J = 11.72, H-6′B), 3.53 (1H, dd, J = 10.8 and 6.35 Hz, H-5′B), 4.33 (1H, m, H-2′), 4.42 (1H, m, H-3′), 4.71 (1H, t, 6′-OH), 5.41 (1H, d, J = 9.0 Hz, H-1′), 7.63 (1H, q, J = 0.9 Hz, 6-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.5 (5-CH_3), 28.4 and 27.0 (C(CH_3)$_2$), under DMSO signal (C-4′), 59.5 (C-6′), 66.6 (C-5′), 72.7 and 74.1 (C-2′ and C-3′), 82.0 (C-1′), 110.1 (C-5), 110.8 *C*(CH_3)$_2$), 137.3 (C-6), 151.4 (C-2), 164.2 (C-4). HRMS (ESI-MS) for $C_{14}H_{20}N_2O_6Na$ [M + H]$^+$: found, 335.1232; calcd, 335.1219. UV 265 (10640).

1-[4-Deoxy-4-(hydroxymethyl)-β-D-ribopyranosyl]thymine (13). Compound**12** (70 mg, 0.21 mmol) was refluxed for 3 h in a 1:1 mixture of HOAc−H_2O (5 mL). The mixture was evaporated under reduced pressure and coevaporated with EtOH, and the resulting residue was purified by column chromatography (CH_2Cl_2−MeOH, 95:5), yielding **13** (51 mg, 98%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.76 (1H, d, J = 0.9 Hz, 5-CH_3), 1.91 (1H, m, H-4′), under H_2O signal (1H, H-6′A), 3.41 (1H, dd, J = 6.3 and 10.8 Hz, H-6′B), 3.52 (1H, t, J = 11.7 Hz, H-5′A), 3.63 (1H, dd, J = 3.6 and 9.3 Hz, H-2′), 3.68 (1H, dd, J = 4.8 and 10.8 Hz, H-5′B), 3.95 (1H, br s, H-3′), 4.49 (1H, br s, 6′-OH), 4.92 (1H, br s, 3′-OH, 5.11 (1H, br s, 2′-OH), 5.60 (1H, d, J = 9.6 Hz, H-1′), 7.57 (1H, q, J = 1.2 Hz, 6-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.7 (5-CH_3), 43.9 (C-4′), 59.8 (C-6′), 64.9 (C-5′), 68.8 and 69.4 (C-2′ and C-3′), 80.7 (C-1′), 109.9 (C-5), 137.7 (C-6), 151.8 (C-2), 164.5 (C-4). HRMS (ESI-MS) for $C_{11}H_{16}N_2O_6Na$ [M + Na]$^+$: found, 295.9010; calcd, 295.0906. UV 265 (10320).

1-[4-Deoxy-4-(hydroxymethyl)-3,6-*O*-isopropylidene-β-D-ribopyranosyl]thymine (14). To a stirred suspension of **13** (13 mg, 0.048 mmol) in anhydrous acetone (0.1 mL) and 2,2-dimethoxypropane (0.03 mL, 0.24 mmol) was added *p*-toluenesulfonic acid monohydrate (0.15 mg, 0.8 μmol). After 1 h the resulting solution was poured slowly into stirred aqueous 0.5 M $NaHCO_3$ (2 mL). The solution was concentrated in vacuo, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were dried, evaporated under reduced pressure, and purified by column chromatography (CH_2Cl_2−MeOH, 98:2 → 97:3) yielding pure **14**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.33 (3 H, s, C(CH_3)$_2$), 1.41 (3H, s, C(CH_3)$_2$), 1.76 (4H, m, 5-CH_3 and H-4′), 3.45−4.05 (5H, m, H-5′, H-6′ and H-2′), 4.38 (1H, m, ν1/2 = 6.6 Hz, H-3′), 5.09 (1H, br s, 2-OH), 5.59 (1H, d, J = 9.9 Hz, H-1′), 7.58 (1H, s, 6-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.6 (5-CH_3), 19.3 and 30.3 (C(*C*H_3)$_2$), 34.0 (C-4′), 60.1 (C-6′), 64.8, 67.4 and 69.3 (C-2′, C-3′ and C-5′), 80.2 (C-1′), 99.2 (*C*(CH_3)$_2$), 110.1 (C-5), 137.4 (C-6), 151.7 (C-2), 164.4 (C-4). HRMS (ESI-MS) for $C_{14}H_{20}N_2O_6$ [M + Na]$^+$: found, 335.1207; calcd, 335.1219. UV 265 (10625).

2,3-*O*-Isopropylidene-1-*O*-methyl-4-*O*-phenoxythiocarbonyl-α-L-lyxopyranose (17). To an ice-cold solution of **16** (2.50 g, 12.2 mmol) and DMAP (3.00 g, 24.5 mmol) in CH_3CN (100 mL) was gradually added phenyl chlorothionocarbonate (2.3 mL, 16.4 mmol). The mixture was stirred at 0 °C for 5 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2. The solution was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The obtained residue was purified by column chromatography (CH_2Cl_2−MeOH, 95:5) to give **17** (3.6 g, 87%) as a syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, s, C(CH_3)$_2$), 1.58 (3H, s, C(CH_3)$_2$), 3.46 (3H, s, OCH_3), 3.83 (1H, dd, J = 7.5 and 12.0 Hz, H-5A), 3.92 (1H, dd, J = 4.2 and 12.1 Hz, H-5B), 4.16 (1H, dd, J = 5.4 and 3.2 Hz, H-2), 4.45 (1H, m, H-3), 4.71 (1H, d, J = 3.0 Hz, H-1), 5.49 (1H, m, H-4), 7.10−7.44 (5H, m, arom H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5 and 28.1 (C(*C*H_3)$_2$), 56.1 (OCH_3), 58.7 (C-5), 74.5 (C-3), 75.4 (C-2), 78.9 (C-4), 100.3 (C-1), 110.2 (*C*(CH_3)$_2$), 122.1 (arom C^o), 126.9 (arom C^p), 129.8 (arom C^m), 153.6 (arom C^i), 194.7 (O(CS)O). HRMS (ESI-MS) for $C_{16}H_{20}O_6S_1Na$ [M + Na]$^+$: found, 363.0865; calcd, 363.0878.

2,3-*O*-Isopropylidene-1-*O*-methyl-4-*C*-(2-phenylethenyl)-α-L-lyxopyranose (18). To a solution of **17** (1.47 g, 4.3 mmol) in benzene (34 mL) was added β-tributylstannylstyrene (4.02 g, 10.22 mmol). The resulted solution was degassed three times with nitrogen at room temperature and 45 °C. After 2,2′-azobisisobutyronitrile (AIBN) (230 mg, 1.4 mmol) was added, the solution was refluxed for 2 h. Another part of AIBN (230 mg, 1.4 mmol) was added after cooling the reaction mixture to 40 °C. The reaction mixture was then refluxed for 2 h. This procedure was repeated until the starting material disappeared (six times). The solvent was evaporated, and the residue was purified by column chromatography (CH_2Cl_2−MeOH, 98:2) to give **18** (773 mg, 62%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, s, CCH_3), 1.44 (3H, s, CCH_3), 2.55 (1H, m, H-4), 3.46 (3H, s, OCH_3), 3.50 (2H, app d, H-5), 3.92 (1H, dd, J = 2.1 and 5.1 Hz, H-2), 4.11 (1H, dd, J = 5.1 and 7.2 Hz, H-3), 4.78 (1H, d, J = 2.1 Hz, H-1), 6.15 (1H, dd, J = 16.2 and 7.8 Hz, H-β styrene), 6.52 (1H, d, J = 16 Hz, H-α styrene), 7.11−7.40 (5H, m, arom H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6 (C*C*H_3), 28.5 (C*C*H_3), 42.8 (C-4), 55.7 (OCH_3), 61.3 (C-5), 73.9 (C-3), 76.1 (C-2), 99.9 (C-1), 109.3 (*C*CH_3), 126.5 (arom C^o), 127.2 and 127.7 (arom C^p and Cα styryl), 128.7 (arom C^m), 132.8 (Cβ styryl), 137.1 (arom C^i). HRMS (ESI-MS) for $C_{17}H_{22}O_4Na$ [M + Na]$^+$: found, 313.1412; calcd, 313.1415.

4-Deoxy-4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-1-*O*-methyl-α-L-lyxopyranose (20). To a solution of styrene **18** (330 mg, 1.1 mmol) and *N*-methylmorpholine-*N*-oxide (NMMO) (200 mg, 1.7 mmol) in dioxane (20 mL), was added a catalytic amount of 4% osmium tetraoxide in H_2O (0.3 mL, 0.04 mmol). The flask was covered by aluminum foil, and the reaction mixture was stirred at room temperature overnight. A solution of $NaIO_4$ (731 mg, 3.4 mmol) in water (1 mL) was added to the stirred reaction mixture. It was stirred for 1 h at 0 °C and 2 h at room temperature, followed by addition of EtOAc (20 mL). The mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was washed three times with 10% aqueous $Na_2S_2O_3$ solution until the color of the aqueous phase disappeared. The organic phase was further washed with water, dried ($MgSO_4$), and concentrated. The obtained aldehyde was dissolved in EtOH−H_2O (4:1 v/v, 16 mL). $NaBH_4$ (190 mg, 5.0 mmol) was added in portions at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h and then treated with ice water. The mixture was extracted with EtOAc. The organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated. The obtained residue was purified by column chromatography (CH_2Cl_2−MeOH, 9:1) to give **20** (127 mg, 53% over three steps) as an oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (3H, s, C*CH*$_3$), 1.38 (3H, s, C*CH*$_3$), 1.78 (1H, m, H-4), 3.28 (3H, s, OCH_3), 3.30−3.55 (4H, m, H-5 and H-6), 3.79 (1H, dd, J = 3.0 and 5.4 Hz, H-2), 4.03 (1H, dd, J = 5.1 and 6.6 Hz, H-3), 4.60 (1H, d, J = 3.0 Hz, H-1), 4.66 (1H, t, J = 5.7 Hz, 6-OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.9 (C*C*H_3), 22.8 (C*C*H_3), under DMSO signal (C-4), 55.5 (OCH_3), 59.9 and 60.1 (C-5 and C-6), 72.5 (C-3), 73.8 (C-2), 100.5 (C-1), 108.6 (*C*CH_3). HRMS (ESI-MS) for $C_{10}H_{18}O_5Na$ [M + Na]$^+$: found, 241.1050; calcd, 241.1052.

2,3,6-Tri-*O*-acetyl-4-deoxy-4-*C*-hydroxymethyl-1-*O*-methyl-α-L-lyxopyranose (21).[12] A solution of **20** (72 mg, 0.3 mmol) in trifluoroacetic acid−H_2O (9:1 v/v, 1 mL) was stirred for 5 min. The solution was neutralized with Dowex 1×2 (OH^-). The resin was removed by filtration and washed with MeOH−H_2O (3:1). The filtrate was evaporated under diminished pressure and purified by column chromatography (CH_2-

Cl_2−MeOH, 90:10), yielding 4-deoxy-4-*C*-hydroxymethyl-1-*O*-methyl-α-L-lyxopyranose[12] (45 mg, 77%) as a glassy solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.91 (1H, m, H-4), 3.20 (3H, s, OCH_3), 3.30−3.61 (6H, m, H-6, H-2, H-3 and H-5), 4.35 (2H, t, 6- and 3-OH), 4.45 (1H, d, J = 4.5 Hz, H-1), 4.47 (1H, app d, J = 2.1 Hz, 2-OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ under DMSO signal (C-4), 54.9 (OCH_3), 60.1, 61.8, 66.7 and 69.4 (C-6, C-2, C-3 and C-5), 102.5 (C-1). HRMS (ESI-MS) for $C_7H_{14}O_5$-Na $[M + Na]^+$: found, 201.0750; calcd, 201.0739. The above mentionned glassy solid (40 mg, 0.2 mmol) was dissolved in pyridine (2.5 mL) and acetic anhydride (2.5 mL) was added. The solution was stirred at room temperature for 3 h. The solvent was removed under vacuum, and the resulting residue was purified by column chromatography (CH_2Cl_2−MeOH, 99:1) to yield **21** (60 mg, 89%) as a foam. ^{1}H NMR (300 MHz, CD_3OD): δ 1.97, 2.02 and 2.10 (OCOCH_3), 2.47 (1H, m, H-4), 3.38 (3H, s, OMe), 3.70 (1H, t, J = 11.4 Hz, H-5A), 3.77 (1H, dd, J = 11.4 and 5.4 Hz, H-5B), 4.01 (1H, dd, J = 11.4 and 2.7 Hz, H-6A), 4.11 (1H, dd, J = 6.0 and 11.7 Hz, H-6B), 4.65 (1H, d, J = 5.1 Hz, H-1), 5.09 (1H, dd, J = 5.1 and 3.0 Hz, H-2), 5.13 (1H, dd, J = 3.0 and 11.0 Hz, H-3). ^{13}C NMR (75 MHz, CD_3OD): δ 19.3, 19.4 and 19.5 (OCOCH_3), 35.7 (C-4), 54.0 (OCH_3), 60.3 (C-5), 61.0 (C-6), 67.3 (C-3), 68.1 (C-2), 99.3 (C-1), 170.6, 170.9 and 170.2 (OCOCH$_3$). HRMS (ESI-MS) for $C_{13}H_{20}O_8Na$ $[M + Na]^+$: found, 327.1058; calcd, 327.1056.

1-[2,3,6-*O*-Tri-acetyl-4-deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine (22).[12] Thymine (615 mg, 4.9 mmol) was suspended in hexamethyldisilazane (55 mL, 260 mmol) containing trimethylsilyl chloride (0.48 mL, 3.8 mmol) and pyridine (4 mL). The mixture was heated to 125 °C and stirred overnight. The reaction mixture was evaporated and coevaporated with toluene. The resulting residue and **21** (744 mg, 2.44 mmol) were dissolved in CH_3CN (17 mL), $SnCl_2$ (anhydrous, 1.23 g, 6.5 mmol) was added, and the mixture was refluxed under nitrogen during 39 h. After cooling it was poured in 10% Na_2CO_3 and extracted with CH_2Cl_2. After drying and evaporation of the organic layer, the obtained residue was purified by column chromatography (CH_2Cl_2−MeOH 99:1 → 97:3) yielding pure **22** (367 mg, 38%) as a white foam and residual starting product **21** (315 mg, 42%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.75 (3H, s, 5-CH_3), 1.88, 2.04 and 2.11 ($OCOCH_3$), 2.18 (1H, m, H-4′), 3.86 (1H, d, J = 12.3 Hz, H-5′A), 3.97 (1H, d, J = 12.3 Hz, H-5′B), 4.36 (2H, m, H-6′A and H6′B), 5.30 (1H, dd, J = 2.7 and 9.9 Hz, H-2′), 5.45 (1H, br s, H-3′), 5.80 (1H, d, J = 9.9 Hz, H-1′), 7.82 (1H, s, 6-H), 11.40 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.5 (5-CH_3), 21.0, 21.3 and 21.5 ($OCOCH_3$), 55.6 (C-4′), 62.5 and 64.9 (C-5′ and C-6′), 66.2 and 68.4 (C-2′ and C-3′), 79.2 (C-1′), 110.7 (C-5), 137.1 (C-6), 151.4 (C-2), 164.2 (C-4), 169.8, 170.3 and 170.9 (OCOCH$_3$). HRMS (ESI-MS) for $C_{17}H_{22}N_2O_9Na$ $[M + Na]^+$: found, 421.1253; calcd, 421.1223. UV 265 (8800).

1-[4-Deoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]thymine (5).[12] Compound **22** (410 mg, 1.03 mmol) was treated with a 7 N methanolic ammonia solution (30 mL) at room temperature for 7 h. Evaporation yielded a residue that was purified by column chromatography (CH_2Cl_2−MeOH, 90:10) to afford **5** (218 mg, 78%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77 (4H, br s, 5-CH_3 and H-4′), 3.50 (1H, m, H-6′A), 3.59 (1H, m, H-6′B), 3.66 (2H, m, H-5′A and H-2′), 3.83 (1H, dd, J = 2.4 and 11.1 Hz, H-5′B), 3.97 (1H, br s, H-3′), 4.65 (1H, t, J = 5.1 Hz, 6′-OH), 4.97 (2H, br s, 2′-OH and 3′-OH), 5.59 (1H, d, J = 9.6 Hz, H-1′), 7.56 (1H, s, 6-H), 11.25 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.6 (5-CH_3), 46.0 (C-4′), 60.0 (C-6′), 63.9 (C-2′) and 66.2 (C-5′), 68.8 (C-3′), 81.2 (C-1′), 109.9 (C-5), 137.7 (C-6), 151.7 (C-2), 164.4 (C-4). HRMS (ESI-MS) for $C_{11}H_{16}N_2O_6Na$ $[M + Na]^+$: found, 295.0902; calcd, 295.0906. UV 265 (10120).

1-[4-Deoxy-4-*C*-hydroxymethyl-3,6-*O*-(1,1,3,3,-tetraisopropyldisiloxan-1,3-diyl)-α-L-lyxopyranosyl]thymine (23). Compound **5** (46 mg, 0.17 mmol) and imidazole (60 mg, 0.88 mmol) were dissolved in DMF (1 mL) at 0 °C. 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (58 μL, 0.19 mmol) was added dropwise. The mixture was stirred for 3 h at room temperature and overnight at 30 °C. Water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (CH_2Cl_2−MeOH, 99:1) to afford **23** (78 mg, 89%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.95 (28H, m, CH(CH_3)$_2$), 1.75 (3H, s, 5-CH_3), 2.22 (1H, m, H-4′), 3.55 (1H, d, J = 11.1 Hz, H-6′A), 3.75 (1H, t, J = 11.4 Hz, H-5′A), 3.87 (1H, dd, J = 5.7 and 11.4 Hz, H-5′B), 3.92 (1H, dd, J = 2.1 and 11.1 Hz, H-6′B), 3.99 (1H, dd, J = 2.7 and 10.2 Hz, H-3′), 4.49 (1H, br, H-2′), 5.30 (1H, d, J = 5.1 Hz, 2′-OH), 5.36 (1H, d, J = 2.7 Hz, H-1′), 7.41 (1H, s, 6-H), 11.31 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.6, 12.7, 12.8, 13.4, 13.5 (*C*H(CH$_3$)$_2$ and 5-CH$_3$), 17.1, 17.8, 17.8, 17.9, 17.9 (CH(*C*H$_3$)$_2$), 38.8 (C-4′), 59.4 (C-6′), 65.2 (C-5′), 66.5 (C-3′), 68.2 (C-2′), 88.5 (C-1′), 109.8 (C-5), 137.6 (C-6), 151.3 (C-2), 164.4 (C-4). HRMS (ESI-MS) for $C_{23}H_{43}N_2O_7$-Si_2 $[M + H]^+$: found, 515.2619; calcd, 515.2608. UV 265 (10090).

1-[4-Deoxy-4-*C*-hydroxymethyl-3,6-*O*-(1,1,3,3,-tetraisopropyldisiloxan-1,3-diyl)-2-*O*-phenoxythiocarbonyl-α-L-lyxopyranosyl]thymine (24). Compound **23** (126 mg, 0.24 mmol) was dissolved in anhydrous CH_3CN (4 mL). DMAP (58 mg, 0.48 mmol) was added at 0 °C. The mixture was stirred 15 min at 0°C, then phenylchlorothionocarbonate (46 μL, 0.33 mmol) was added dropwise, and the resulting solution was stirred overnight at room temperature. After adding 7% $NaHCO_3$ solution (7 mL), the mixture was evaporated to dryness, and the obtained residue was dissolved in EtOAc, washed with water, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (CH_2Cl_2−MeOH, 99.5:0.5) to afford **24** (140 mg, 89%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (28H, m, CH(CH_3)$_2$), 1.94 (3H, s, 5-CH_3), 2.25 (1H, m, H-4′), 3.60 (1H, d, J = 11.7 Hz, H-6′A), 3.82−3.99 (2H, m, H-5′A and H-5′B), 4.10 (1H, dd, J = 11.7 and 2.4 Hz, H-6′B), 4.52 (1H, dd, J = 2.8 and 11.1 Hz, H-3′), 5.61 (1H, d, J = 2.6 Hz, H-1′), 6.58 (1H, d, J = 2.7 Hz, H-2′), 7.09−7.44 (5H, m, arom H), 8.06 (1H, s, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6 (5-CH_3), 12.8, 13.0, 13.5, 13.7 (*C*H(CH$_3$)$_2$), 17.4, 17.5, 17.6, 17.7, 17.7 (CH-(*C*H$_3$)$_2$), 39.7 (C-4′), 58.7 (C-6′), 65.0 and 65.0 (C-3′ and C-5′), 80.8 (C-2′), 85.8 (C-1′), 112.0 (C-5), 122.0 (arom C^o), 126.9 (arom C^p), 129.8 (arom C^m), 136.7 (C-6), 150.0 (arom C^i), 153.6 (C-2), 163.4 (C-4), 194.8 (OC(S)O). HRMS (ESI-MS) for $C_{30}H_{46}N_2O_8$-SSi_2Na $[M + Na]^+$: found, 673.2409; calcd, 673.2411. UV 265 (10000).

1-[2,4-Dideoxy-4-*C*-hydroxymethyl-3,6-*O*-(1,1,3,3,-tetraisopropyldisiloxan-1,3-diyl)-α-L-lyxopyranosyl]thymine (25). Compound **24** (134 mg, 0.20 mmol) was coevaporated three times with anhydrous toluene, dissolved in toluene (32 mL), and degassed with nitrogen for 30 min. In a second flask, AIBN (17 mg, 0.10 mmol) and Bu_3SnH (166 μL, 0.62 mmol) in toluene (2 mL) were degassed with nitrogen for 30 min. The first flask was heated to 80 °C, and the second solution was added dropwise via a syringe. The mixture was heated to 90 °C for 2 h. After cooling to room temperature, the mixture was evaporated, and the residue was purified by column chromatography (CH_2Cl_2−MeOH, 99.5:0.5) to afford **25** (81 mg, 79%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (28H, m, CH(CH_3)$_2$), 1.79 (1H, m, H-4′), 1.90 (3H, s, 5-CH_3), 2.18 (1H, m, H-2′A), 2.54 (1H, dd, J = 3.3 and 14.1 Hz, H-2′B), 3.57 (1H, d, J = 11.7 Hz, H-6′A), 3.72 (1H, t, J = 11.7 Hz, H-5′A), 3.86 (1H, dd, J = 4.8 and 11.7 Hz, H-5′B), 4.14 (1H, dd, J = 2.7 and 12.0 Hz, H-6′B), 4.26 (1H, m, H-3′), 5.93 (1H, d, J = 4.8 Hz, H-1′), 8.04 (1H, s, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7 (5-CH_3), 12.8, 13.5, 13.8 (*C*H(CH$_3$)$_2$), 17.4, 17.4, 17.5, 17.5, 17.6, 17.6 (CH(*C*H$_3$)$_2$, 36.4 (C-2′), 45.7 (C-4′), 59.0 (C-6′), 64.8 and 63.3 (C-3′ and C-5′), 82.3 (C-1′), 110.5 (C-5), 136.6 (C-6), 150.5 (C-2), 163.5 (C-4). HRMS (ESI-MS) for $C_{23}H_{43}N_2O_6Si_2$ $[M + H]^+$: found, 499.2571; calcd, 499.2659. UV 265 (9900).

1-[2,4-Dideoxy-4-*C*-hydroxymethyl-α-L-lyxopyranosyl]-thymine (4). Compound **25** (76 mg, 0.15 mmol) was dissolved in THF (8 mL), and Bu_4NF (1 M in THF, 0.76 mL, 0.76 mmol) was added. The mixture was stirred for 1 h at room temperature, evaporated to dryness, and purified by column chromatography (CH_2Cl_2−MeOH, 93:7) to afford **4** (38 mg, 97%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.51 (2H, m, H-2′A and H-4′), 1.76 (3H, s, 5-CH_3), 1.96 (1H, app t, J = 11.4 Hz, H-2′B), 3.50 (1H, m, J = 8.4 and 10.2 Hz, H-6′A), 3.60 (1H, m, J = 7.2 and 10.2 Hz, H-6′B), 3.77 (1H, d, J = 11.4 Hz, H-5′A), 3.92 (1H, dd, J = 2.1 and 11.4 Hz, H-5′B), 4.02 (1H, m, H-3′), 4.58 (1H, t, J = 5.1 Hz, 6′-OH), 4.98 (1H, d, J = 2.7 Hz, 3′-OH), 5.82 (1H, d, J = 11.4 Hz, H-1′), 7.57 (1H, s, 6-H), 11.25 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.6 (5-CH_3), 33.8 (C-2′), 43.4 (C-4′), 60.5 (C-6′), 64.7 (C-5′), 64.8 (C-3′), 78.1 (C-1′), 110.1 (C-5), 137.3 (C-6), 150.9 (C-2), 164.4 (C-4). HRMS (ESI-MS) for $C_{11}H_{16}N_2O_5Na$ [M + Na]$^+$: found, 279.0952; calcd, 279.0957; UV 265 (10590).

Acknowledgment. V.V. is indebted to the "Fonds voor Wetenschappelijk Onderzoek-Vlaanderen" for a position as Aspirant.

Supporting Information Available: ^{13}C NMR spectra and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040130G