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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 1-[2,4-DIDEOXY-4-C-HYDROXYMETHYL- α -L-LYXO-PYRANOSYL]THYMINE.

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Abstract

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. Modelling 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^{1,2,3,4} and antibiotic⁵ properties and as building blocks in nucleic acid synthesis.^{6,7}

Antiviral activity^{1,2,3} 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 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, due to 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

crystallised 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.

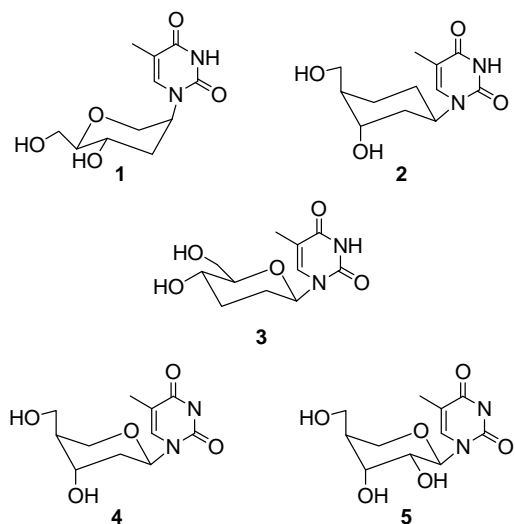


Figure 1: structures of compounds 1-5.

Results and Discussion

Chemistry

Two strategies towards 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 due to low yields and very difficult separation problems at different stages. In one of these attempts Doboszewski and Herdewijn¹² experienced that treatment 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 H₂O₂ yielded mainly the undesired 4- α -hydroxymethyl sugar, probably caused by sterical 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 ⁴C₁ conformation of the pyranose, which reduces the sterical hindrance caused by the isopropylidene protective group (Figure 2). We hoped this would influence the stereochemical outcome of this reaction towards the formation of the 4- β -hydroxymethyl compound (**5**).

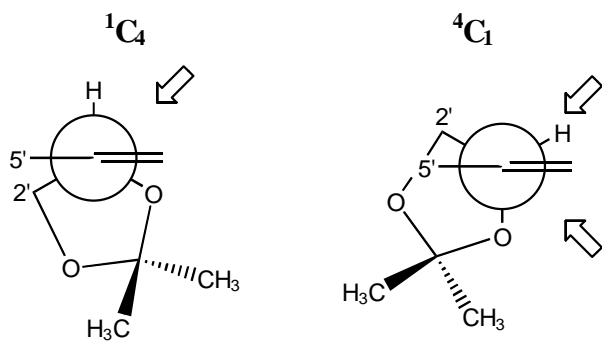
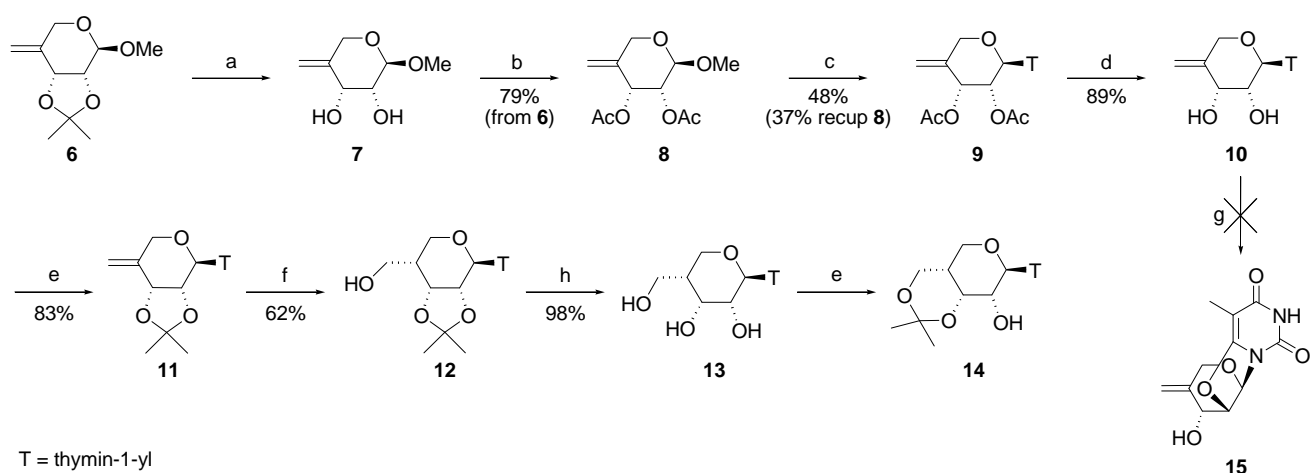


Figure 2: Image of the sterical hindrance caused by the 2',3'-*O*-isopropylidene in the 1C_4 and 4C_1 conformation.

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

Scheme 1.^a Synthesis of 14



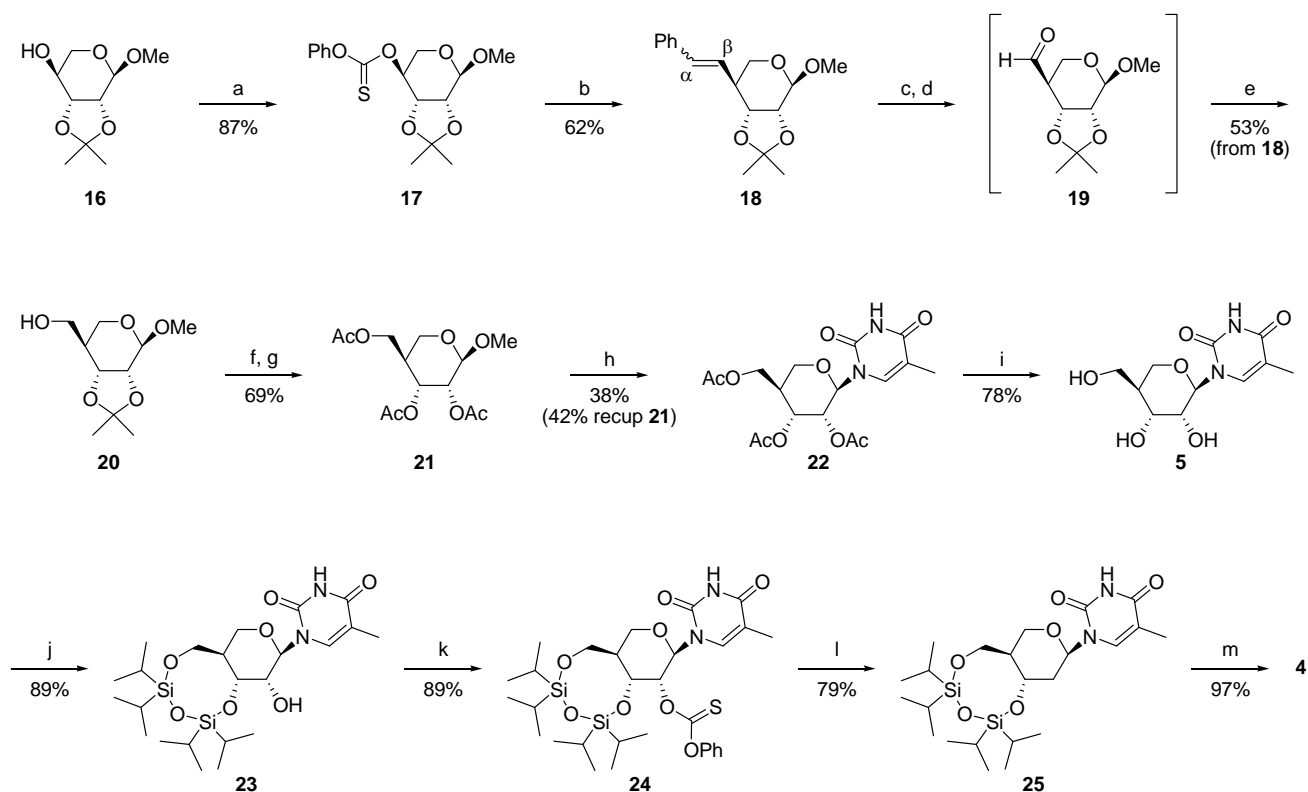
^aReagents: (a) CF_3COOH , H_2O ; (b) $(\text{Ac})_2\text{O}$, pyridine; (c) 5-methyl-2,4-bis[(trimethylsilyl)oxy]pyrimidine, CH_3CN , SnCl_2 ; (d) NH_3 , MeOH ; (e) 2,2-dimethoxypropane, acetone, *p*-toluenesulphonic acid; (f) (i) 9-BBN-H, THF, (ii) H_2O_2 , NaOH ; (g) $(\text{PhO})_2\text{CO}$, NaHCO_3 , DMF; (h) HOAc , H_2O .

Because acid catalysed exchange of the 1-*O*-methylgroup of **6** with an 1-*O*-acetylgroup 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. Coupling of the resulting sugar **8** with silylated thymine in the presence of trimethylsilyl triflate

or SnCl₄ 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 CH₃CN using SnCl₂ 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 band width of 7.8 Hz), suggest a ⁴C₁ 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'-CH₂OH 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, sterical 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 sterical hindrance at the β-side of the sugar ring, through the formation of a 2,2'-anhydronucleoside (**15**) failed. Upon treatment of **10** with diphenylcarbonate and NaHCO₃, elimination of the base occurred, yielding an uncharacterised 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).

Scheme 2.^a Synthesis of **4**



^aReagents: (a) PhOC(S)Cl, DMAP, CH₃CN; (b) β -tributylstannyl styrene, AIBN, benzene; (c) NMMO, OsO₄, dioxane; (d) NaIO₄, H₂O; (e) NaBH₄, EtOH, H₂O; (f) CF₃COOH, H₂O; (g) (Ac)₂O, pyridine; (h) 5-methyl-2,4-bis[(trimethylsilyl)oxy]pyrimidine, CH₃CN, SnCl₂; (i) NH₃, MeOH; (j) (*i*Pr₂SiCl)₂O, DMF; (k) PhOC(S)Cl, DMAP, CH₃CN; (l) Bu₃SnH, AIBN, toluene; (m) Bu₄NF, THF.

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 $^1\text{C}_4$ 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 , $\text{NaIO}_4/\text{NaBH}_4$), 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 (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 neighbouring group effect of the 2'-acetoxymethyl group 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 as 1,1,3,3-tetraisopropylidisiloxan-1,3-diyl (TIPDS). At room temperature this reaction was unsuccessful due to the axial position of the 4'-hydroxymethyl- and 3'-hydroxyl functions. Heating to 30°C allowed conformational change of the sugar moiety in order to adopt the $^1\text{C}_4$ 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 $^4\text{C}_1$ 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 ^1H -NMR results for **4**, **5**, **13**, **23** and **25** are summarized in Table 1. Due to occasional overlapping of ^1H -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.

Table 1. ^1H NMR Chemical shifts (δ) and Coupling Constants (J) in sugar parts of **4**, **5**, **13**, **23** and **25**.

proton	coupling	13		5		23		25		4	
		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 ₂ O		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-d₆ (2.48 ppm) in the case of **4**, **5**, **13** and **23** and in CDCl₃ (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.

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°, 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 and thus lead to the chair

conformation as shown in Figure 3. Herein the 4'-hydroxymethyl is necessarily directed equatorially.

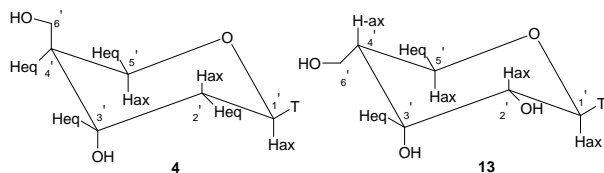


Figure 3. Structure of 4 and 13.

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 band width ($\nu/2$) 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.

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).

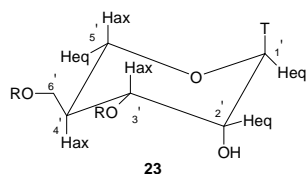


Figure 4. Structure of 23.

Summarising, 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*-*lyxo*-pyranosyl nucleosides is opposite to that of the anhydro-hexitol 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'-positions. With an equatorially oriented heterocycle, this unfavorable interaction is present between the 4'-hydroxymethyl function and the hydrogen atom in the 2'-position 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'-CH₂OH and the ring oxygen may also stabilise the ⁴C₁ 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 synthesis 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** \rightarrow **18**) followed by the introduction of the base via a SnCl₂-mediated coupling. Conformational analysis proves that **4** shows the expected ⁴C₁ conformation with an equatorially oriented thymine ring. Biological evaluation of this nucleoside will be published elsewhere.

Experimental Section

See the 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 1x2 (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. Ac₂O was added and the mixture was stirred at room temperature for 2h. Evaporation and coevaporation with toluene yielded crude **8** (980 mg, 79 %). ¹H-NMR (300 MHz, CDCl₃): δ 2.10 (6H, s, OCOCH₃), 3.43 (3H, s, OCH₃), 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); ¹³C NMR (75 MHz, CDCl₃): δ 20.1 (OCOCH₃), 21.0 (OCOCH₃), 55.6 (OCH₃), 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 C₁₁H₁₆O₆ [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 trimethylsilylchloride (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 co-evaporated with toluene. The resulting residue and **8** (980 mg, 4.01 mmol) were dissolved in CH₃CN (27 mL), SnCl₂ (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 % Na₂CO₃ and extracted with

CH₂Cl₂. After drying and evaporation of the organic layer, the obtained residue was purified by column chromatography (CH₂Cl₂–MeOH, 100:0 → 98:2) yielding **9** (640 mg, 48%) as a white foam and recuperated starting material **8** (355 mg, 37 %). ¹H-NMR (300 MHz, DMSO-d₆): δ 1.73 (3 H, s, 5-CH₃), 1.90 (3H, s, OCOCH₃), 2.11 (3H, s, OCOCH₃), 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 C₁₅H₁₈N₂O₇ [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 methanolic ammonia solution 7 N (5 mL) was stirred 2h at room temperature and was evaporated under reduced pressure. The resulting residue was purified by column chromatography (CH₂Cl₂–MeOH, 90:10) yielding **10** (20 mg, 89%) as a white foam. ¹H-NMR (300 MHz, DMSO-d₆): δ 1.75 (3 H, d, *J* = 1.2 Hz, 5-CH₃), 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); ¹³C NMR (75 MHz, DMSO-d₆): δ 12.5 (5-CH₃), 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 C₁₁H₁₄N₂O₅Na [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*-toluenesulphonic acid monohydrate (97 mg, 0.51 mmol). After 4 h the resulting solution was poured slowly into stirred aqueous 0.5 M NaHCO₃ (2 mL). The solution was concentrated *in vacuo* to ca 1.5 mL, diluted with water and extracted with CH₂Cl₂. The combined organic layers were dried, evaporated under reduced

pressure and quickly sent over a silica gel column (CH₂Cl₂–MeOH, 97:3) yielding **11** (124 mg, 83%) as a white foam. HRMS (ESI-MS) for C₁₄H₁₈ N₂O₅Na [M + Na]⁺: found, 317.1109; calcd, 317.1113.

1-[4-Deoxy-4-(hydroxymethyl)-2,3-O-isopropylidene-β-D-ribofuranosyl]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 24h. The reaction mixture was cooled to 0°C, treated sequentially with EtOH (1.6 mL), a 2 N solution of NaOH (0.78 mL, 1.56 mmol) and 30% aqueous H₂O₂ solution (0.78 mL, 6.8 mmol). The resulting mixture was stirred 24 h and then poured into a mixture of EtOAc (10mL) and water (10mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over MgSO₄ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (CH₂Cl₂–MeOH, 95:5→98:2) yielding pure **12** (77 mg, 62%) as a white foam. ¹H-NMR (300 MHz, DMSO-d₆): δ 1.09 (3 H, s, C(CH₃)₂), 1.26 (3H, s, C(CH₃)₂), 1.76 (3H, s, 5-CH₃), 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); ¹³C NMR (75 MHz, DMSO-d₆): δ 12.5 (5-CH₃), 28.4 and 27.0 (C(CH₃)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(CH₃)₂, 137.3 (C-6), 151.4 (C-2), 164.2 (C-4); HRMS (ESI-MS) for C₁₄H₂₀N₂O₆Na [M+H]⁺: found, 335.1232; calcd, 335.1219; UV 265 (10640).

1-[4-Deoxy-4-(hydroxymethyl)-β-D-ribofuranosyl]thymine (13)

Compound **12** (70 mg, 0.21 mmol) was refluxed for 3 hours in a 1:1 mixture of HOAc–H₂O (5 mL). The mixture was evaporated under reduced pressure, co-evaporated with EtOH and the resulting residue was purified by column chromatography (CH₂Cl₂–MeOH, 95:5), yielding **13** (51 mg, 98%) as a white foam. ¹H-NMR (300 MHz, DMSO-d₆): δ 1.76 (1H, d, *J* = 0.9 Hz, 5-CH₃), 1.91 (1H, m, H-4'), under H₂O-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); ¹³C NMR (75 MHz, DMSO-d₆): δ 12.7 (5-CH₃), 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 C₁₁H₁₆N₂O₆Na [M + Na]⁺: found, 295.9010; calcd, 295.0906; UV 265 (10320).

1-[4-Deoxy-4-(hydroxymethyl)-3,6-O-isopropylidene-β-D-ribofuranosyl]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*-toluenesulphonic acid monohydrate (0.15 mg, 0.8 μmol). After 1 h the resulting solution was poured slowly into stirred aqueous 0.5 M NaHCO₃ (2 mL). The solution was concentrated *in vacuo*, diluted with water and extracted with CH₂Cl₂. The combined organic layers were dried, evaporated under reduced pressure and purified by column chromatography (CH₂Cl₂–MeOH, 98:2 → 97:3) yielding pure **14**. ¹H-NMR (300 MHz, DMSO-d₆): δ 1.33 (3 H, s, C(CH₃)₂), 1.41 (3H, s, C(CH₃)₂), 1.76 (4H, m, 5-CH₃ and H-4'), 3.45-4.05 (5H, m, H-5', H-6' and H-2'), 4.38 (1H, m, *v*1/2 = 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); ¹³C NMR (75 MHz, DMSO-d₆): δ 12.6 (5-CH₃), 19.3 and 30.3 (C(CH₃)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(CH₃)₂), 110.1 (C-5), 137.4 (C-6), 151.7 (C-2), 164.4 (C-4); HRMS (ESI-MS) for C₁₄H₂₀N₂O₆ [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 CH₃CN (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 CH₂Cl₂. The solution was washed with water, dried over anhydrous MgSO₄, filtered, and evaporated *in vacuo*. The obtained residue was purified by column chromatography (CH₂Cl₂–MeOH, 95:5) to give **17** (3.6 g, 87 %) as a syrup. ¹H NMR (300 MHz, CDCl₃): δ 1.39 (3H, s, C(CH₃)₂), 1.58 (3H, s, C(CH₃)₂), 3.46 (3H, s, OCH₃), 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); ¹³C NMR (75 MHz, CDCl₃): δ 26.5 and 28.1 (C(CH₃)₂), 56.1 (OCH₃), 58.7 (C-5), 74.5 (C-3), 75.4 (C-2), 78.9 (C-4), 100.3 (C-1), 110.2 (C(CH₃)₂), 122.1 (arom C^o), 126.9 (arom C^p), 129.8 (arom C^m), 153.6 (arom Cⁱ), 194.7 (O(CS)O); HRMS (ESI-MS) for C₁₆H₂₀O₆S₁Na [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 2h. 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 2h. This procedure was repeated until the starting material disappeared (6 times). The solvent was

evaporated, and the residue was purified by column chromatography (CH₂Cl₂–MeOH, 98:2) to give **18** (773 mg, 62 %) as an oil. ¹H NMR (300 MHz, CDCl₃): δ 1.26 (3H, s, CCH₃), 1.44 (3H, s, CCH₃), 2.55 (1H, m, H-4), 3.46 (3H, s, OCH₃), 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); ¹³C NMR (75 MHz, CDCl₃): δ 26.6 (CCH₃), 28.5 (CCH₃), 42.8 (C-4), 55.7 (OCH₃), 61.3 (C-5), 73.9 (C-3), 76.1 (C-2), 99.9 (C-1), 109.3 (CCH₃), 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 Cⁱ); HRMS (ESI-MS) for C₁₇H₂₂O₄Na [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 osmium tetroxide 4% in H₂O (0.3 mL, 0.04 mmol). The flask was covered by aluminium foil, and the reaction mixture was stirred at room temperature overnight. A solution of NaIO₄ (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 2h 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 Na₂S₂O₃ solution until the color of the aqueous phase disappeared. The organic phase was further washed with water, dried (MgSO₄) and concentrated. The obtained aldehyde was dissolved in EtOH–H₂O (4:1 v/v, 16 mL). NaBH₄ (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 (MgSO₄) and concentrated. The obtained residue was purified by column chromatography

(CH₂Cl₂–MeOH, 9:1) to give **20** (127 mg, 53 % over three steps) as an oil. ¹H NMR (300 MHz, DMSO-d₆): δ 1.24 (3H, s, CCH₃), 1.38 (3H, s, CCH₃), 1.78 (1H, m, H-4), 3.28 (3H, s, OCH₃), 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); ¹³C NMR (75 MHz, DMSO-d₆): δ 26.9 (CCH₃), 22.8 (CCH₃), under DMSO signal (C-4), 55.5 (OCH₃), 59.9 and 60.1 (C-5 and C-6), 72.5 (C-3), 73.8 (C-2), 100.5 (C-1), 108.6 (CCH₃); HRMS (ESI-MS) for C₁₀H₁₈O₅Na [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–H₂O (9:1 v/v, 1 mL) was stirred for 5 minutes. The solution was neutralized with Dowex 1x2 (OH⁻). The resin was removed by filtration and washed with MeOH–H₂O (3:1). The filtrate was evaporated under diminished pressure and purified by column chromatography (CH₂Cl₂–MeOH, 90:10), yielding 4-deoxy-4-*C*-hydroxymethyl-1-*O*-methyl- α -L-lyxopyranose¹² (45 mg, 77 %) as a glassy solid. ¹H NMR (300 MHz, DMSO-d₆): δ 1.91 (1H, m, H-4), 3.20 (3H, s, OCH₃), 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); ¹³C NMR (75 MHz, DMSO-d₆): δ under DMSO signal (C-4), 54.9 (OCH₃), 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 C₇H₁₄O₅Na [M + Na]⁺: found, 201.0750; calcd, 201.0739. The above mentioned 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 (CH₂Cl₂–MeOH, 99:1) to yield **21** (60 mg, 89 %) as a foam. ¹H NMR (300 MHz, CD₃OD): δ 1.97, 2.02 and 2.10 (OCOCH₃), 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 $\text{C}_{13}\text{H}_{20}\text{O}_8\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 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 trimethylsilylchloride (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 co-evaporated 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 \rightarrow 97:3) yielding pure **22** (367 mg, 38%) as a white foam and residual starting product **21** (315 mg, 42 %). ^1H 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 H-6'B), 5.30 (1H, dd, $J = 2.7$ Hz 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 $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_9\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 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 7N methanolic ammonia solution (30 mL) at room temperature for 7 h. Evaporation yielded a residue which was purified by column chromatography (CH₂Cl₂–MeOH, 90:10) to afford **5** (218 mg, 78%) as a white foam. ¹H NMR (300 MHz, DMSO-d₆): δ 1.77 (4H, br s, 5-CH₃ 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); ¹³C NMR (75 MHz, DMSO-d₆): δ 12.6 (5-CH₃), 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 C₁₁H₁₆N₂O₆Na [M + Na]⁺: found, 295.0902; calcd, 295.0906; Anal. (C₁₁H₁₆N₂O₆) C, H, N; UV 265 (10120).

1-[4-Deoxy-4-C-hydroxymethyl-3,6-O-(1,1,3,3-tetraisopropylidisiloxan-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-tetraisopropylidisiloxane (58 μL, 0.19 mmol) was added dropwise. The mixture was stirred 3h at room temperature and overnight at 30°C. Water was added and the mixture was extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (CH₂Cl₂–MeOH, 99:1) to afford **23** (78 mg, 89%) as a white foam. ¹H NMR (300 MHz, DMSO-d₆): δ 0.95 (28H, m, CH(CH₃)₂), 1.75 (3H, s, 5-CH₃), 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); ¹³C NMR (75 MHz, DMSO-d₆): δ 12.6, 12.7, 12.8, 13.4, 13.5 (CH(CH₃)₂) and

5-CH₃), 17.1, 17.8, 17.8, 17.9, 17.9 (CH(CH₃)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 C₂₃H₄₃N₂O₇Si₂ [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 CH₃CN (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 μ L, 0.33 mmol) was added dropwise and the resulting solution was stirred overnight at room temperature. After adding 7% NaHCO₃ solution (7mL), the mixture was evaporated to dryness, the obtained residue was dissolved in EtOAc, washed with water, dried over MgSO₄, evaporated under reduced pressure and purified by column chromatography (CH₂Cl₂–MeOH, 99.5:0.5) to afford **24** (140 mg, 89%) as a white foam. ¹H NMR (300 MHz, CDCl₃): δ 1.03 (28H, m, CH(CH₃)₂), 1.94 (3H, s, 5-CH₃), 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); ¹³C NMR (75 MHz, CDCl₃): δ 12.6 (5-CH₃), 12.8, 13.0, 13.5, 13.7 (CH(CH₃)₂), 17.4, 17.5, 17.6, 17.7, 17.7 (CH(CH₃)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 Cⁱ), 153.6 (C-2), 163.4 (C-4), 194.8 (OC(S)O); HRMS (ESI-MS) for C₃₀H₄₆N₂O₈SSi₂Na [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 co-evaporated three times with anhydrous toluene, dissolved in toluene (32 mL) and degassed with nitrogen for 30 minutes. In a second flask, AIBN (17 mg, 0.10 mmol) and Bu₃SnH (166 μL, 0.62 mmol) in toluene (2 mL) were degassed with nitrogen for 30 minutes. The first flask was heated to 80°C, the second solution was added dropwise via a syringe. The mixture was heated to 90°C for 2h. After cooling to room temperature, the mixture was evaporated, and the residue was purified by column chromatography (CH₂Cl₂–MeOH, 99.5:0.5) to afford **25** (81 mg, 79%) as a white foam. ¹H NMR (300 MHz, CDCl₃): δ 1.05 (28H, m, CH(CH₃)₂), 1.79 (1H, m, H-4'), 1.90 (3H, s, 5-CH₃), 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); ¹³C NMR (75 MHz, CDCl₃): δ 12.7 (5-CH₃), 12.8, 13.5, 13.8 (CH(CH₃)₂), 17.4, 17.4, 17.5, 17.5, 17.6, 17.6 (CH(CH₃)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 C₂₃H₄₃N₂O₆Si₂ [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 Bu₄NF (1M in THF, 0.76 mL, 0.76 mmol) was added. The mixture was stirred for 1h at room temperature, evaporated to dryness and purified by column chromatography (CH₂Cl₂–MeOH, 93:7) to afford **4** (38 mg, 97%) as a white foam. ¹H NMR (300 MHz, DMSO-d₆): δ 1.51 (2H, m, H-2'A and H-4'), 1.76 (3H, s, 5-CH₃), 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 $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$: found, 279.0952; calcd, 279.0957; Anal. ($\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_5$) C, H, N; UV 265 (10590).

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

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