The UGent Institutional Repository is the electronic archiving and dissemination platform for all UGent research publications. Ghent University has implemented a mandate stipulating that all academic publications of UGent researchers should be deposited and archived in this repository. Except for items where current copyright restrictions apply, these papers are available in Open Access.

This item is the archived peer-reviewed author-version of:

**Title:** Synthesis and conformational analysis of 1-[2,4-dideoxy-4-C-hydroxymethyl-alpha-L-lyxopyranosyl]thymine

**Author(s):** V Vanheusden, R Busson, P Herdewijn and Serge Van Calenbergh

**Source:** JOURNAL OF ORGANIC CHEMISTRY (2004), 69(13), 4446-4453, DOI: 10.1021/jo040130g
REVISED

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

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

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

*Address communication to:
Dr. S. Van Calenbergh
Laboratorium voor Medicinale Chemie (FFW)
Harelbekestraat 72
B-9000 Gent, Belgium
Tel.: +32 (0)9 264 81 24; Fax +32 (0)9 264 81 46;
e-mail: serge.vancalenbergh@Ugent.be
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 β-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 (OsO₄, NaIO₄/ NaBH₄) 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 SnCl₂ 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\textsuperscript{1,2,3,4} and antibiotic\textsuperscript{5} properties and as building blocks in nucleic acid synthesis.\textsuperscript{6,7}

Antiviral activity\textsuperscript{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.\textsuperscript{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).\textsuperscript{3} This conformation, however, is the most stable one for the carbocyclic congener (2).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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 Herdewijn 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 H$_2$O$_2$ 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. 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 $^4$C$_1$ 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 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 1C₄ and 4C₁ 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 1.⁹ Synthesis of 14**

![Scheme 1](image)

T = thymin-1-yl

⁹Reagents: (a) CF₃COOH, H₂O; (b) (Ac)₂O, pyridine; (c) 5-methyl-2,4-bis[(trimethylsilyl)oxy]pyrimidine, CH₃CN, SnCl₂; (d) NH₃, MeOH; (e) 2,2-dimethoxypropane, acetone, p-toluenesulphonic acid; (f) (i) 9-BBN-H, THF, (ii) H₂O₂, NaOH; (g) (PhO)₂CO, NaHCO₃, DMF; (h) HOAc, H₂O.

Because acid catalysed 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 CF₃COOH¹² and the 2- and 3-hydroxy 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. The remaining starting material 8, could be recuperated (37 %). To avoid possible side reactions during hydroboration, 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) 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.** Synthesis of 4

**Reagents:** (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) (iPr₂SiCl)₂O, DMF; (k) PhOC(S)Cl, DMAP, CH₃CN; (l) Bu₃SnH, AIBN, toluene; (m) Bu₄NF, THF.

Thus 2,3-0-isopropylidene-1-0-methyl-4-O-phenoxythiocarbonyl-α-L-lyxopyranose (17), obtained through reaction of 16 with phenyl chlorothionocarbonate, was reacted with β-tributylstannylstyrene. This led to stereoselective introduction of a 2-phenylethenyl group at the
β-side of the sugar ring (18) as indicated by its \(^1\)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\(_4\), 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 acetoxyethyl moiety in the 4’-position (instead of the 5’-position in natural sugars) has an important effect on the reaction. The 4’-acetoxyethyl group would favor α-attack of the base moiety,\(^{11}\) while the neighbouring group effect of the 2’-acetoxy 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-tetraisopropyldisiloxan-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 \(^1\)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 \(^4\)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 gHMOC experiments. The $^1$H-NMR results for 4, 5, 13, 23 and 25 are summarized in Table 1. Due to 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.

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

<table>
<thead>
<tr>
<th></th>
<th>13</th>
<th>5</th>
<th>23</th>
<th>25</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>proton coupling</td>
<td>$\delta$</td>
<td>$J$</td>
<td>$\delta$</td>
<td>$J$</td>
<td>$\delta$</td>
</tr>
<tr>
<td>1'</td>
<td>–</td>
<td>5.60</td>
<td>5.59</td>
<td>5.36</td>
<td>5.93</td>
</tr>
<tr>
<td>1'–2'A</td>
<td>9.6</td>
<td>9.6</td>
<td>2.7</td>
<td>4.8</td>
<td>11.4</td>
</tr>
<tr>
<td>1'–2'B</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2'A</td>
<td>–</td>
<td>3.63</td>
<td>3.66</td>
<td>4.49</td>
<td>2.18</td>
</tr>
<tr>
<td>2'A–2'B</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>14.7</td>
<td>11.4</td>
</tr>
<tr>
<td>2'A–3'</td>
<td>3.6</td>
<td>b</td>
<td>2.7</td>
<td>10.4</td>
<td>b</td>
</tr>
<tr>
<td>2'A–2'OH</td>
<td>b</td>
<td>b</td>
<td>5.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2'B</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.54</td>
<td>1.96</td>
</tr>
<tr>
<td>2'B–3'</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3'</td>
<td>–</td>
<td>3.95</td>
<td>3.97</td>
<td>3.99</td>
<td>4.26</td>
</tr>
<tr>
<td>3'–4'</td>
<td>b</td>
<td>b</td>
<td>10.2</td>
<td>10.4</td>
<td>b</td>
</tr>
<tr>
<td>3'–3'OH</td>
<td>b</td>
<td>b</td>
<td>–</td>
<td>–</td>
<td>2.7</td>
</tr>
<tr>
<td>4'</td>
<td>–</td>
<td>1.91</td>
<td>1.77</td>
<td>2.22</td>
<td>1.79</td>
</tr>
<tr>
<td>4'–5'A</td>
<td>11.7</td>
<td>0</td>
<td>11.4</td>
<td>11.7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4'–5'B</td>
<td>4'–6'A</td>
<td>4'–6'B</td>
<td>5'A</td>
<td>5'A–5'B</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>4'–5'B</td>
<td>4.8</td>
<td>2.4</td>
<td>5.7</td>
<td>4.8</td>
<td>2.1</td>
</tr>
<tr>
<td>4'–6'A</td>
<td>b</td>
<td>b</td>
<td>0</td>
<td>0</td>
<td>7.2</td>
</tr>
<tr>
<td>4'–6'B</td>
<td>6.3</td>
<td>b</td>
<td>2.1</td>
<td>2.7</td>
<td>8.4</td>
</tr>
<tr>
<td>5'A</td>
<td>–</td>
<td>3.52</td>
<td>3.66</td>
<td>3.75</td>
<td>3.72</td>
</tr>
<tr>
<td>5'A–5'B</td>
<td>11.7</td>
<td>11.7</td>
<td>11.4</td>
<td>11.7</td>
<td>11.4</td>
</tr>
<tr>
<td>5'B</td>
<td>–</td>
<td>3.68</td>
<td>3.83</td>
<td>3.87</td>
<td>3.86</td>
</tr>
<tr>
<td>6'A</td>
<td>–</td>
<td>under H₂O</td>
<td>3.50</td>
<td>3.55</td>
<td>3.57</td>
</tr>
<tr>
<td>6'A–6'B</td>
<td>10.8</td>
<td>11.7</td>
<td>11.1</td>
<td>11.7</td>
<td>10.1</td>
</tr>
<tr>
<td>6'A–6'OH</td>
<td>b</td>
<td>b</td>
<td>–</td>
<td>–</td>
<td>5.1</td>
</tr>
<tr>
<td>6'B</td>
<td>–</td>
<td>3.41</td>
<td>3.59</td>
<td>3.92</td>
<td>4.14</td>
</tr>
<tr>
<td>6'B–6'OH</td>
<td>b</td>
<td>b</td>
<td>–</td>
<td>–</td>
<td>5.1</td>
</tr>
</tbody>
</table>

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' (∆₃,2' = 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 ∆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 ($v_2/2$) 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 4C1 to 1C4 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-\(\alpha\)-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 \(4C_1\) conformation in 4 and 5.

**Conclusions**

We have successfully developed a stereoselective approach for the synthesis of 1-[2,4-dideoxy-4-C-hydroxymethyl-\(\alpha\)-L-lyxopyranosyl]thymine (4) from 2,3-O-isopropylidene-1-O-methyl-\(\alpha\)-L-lyxopyranose (16) in 13 steps. The key steps of this synthesis route involve the stereoselective introduction of the 6'-carbon on the \(\beta\)-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 \(\text{SnCl}_2\)-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 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.

Ac\(_2\)O was added and the mixture was stirred at room temperature for 2h. Evaporation and coevaporation with toluene yielded crude 8 (980 mg, 79 %). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.10 (6H, s, OC\(\text{OCH}_3\)), 3.43 (3H, s, O\(\text{CH}_3\)), 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\(_3\)): \(\delta\) 20.1 (OC\(\text{OCH}_3\)), 21.0 (OC\(\text{OCH}_3\)), 55.6 (O\(\text{CH}_3\)), 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 trimethylsilylchloride (0.71 mL, 5.6 mmol) and pyridine (7 mL). The mixture was heated to 125\(^\circ\) 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 CH\(_3\)CN (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\(_2\)CO\(_3\) 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...
pressure and quickly sent over a silica gel column (CH$_2$Cl$_2$–MeOH, 97:3) yielding 11 (124 mg, 83%) as a white foam. HRMS (ESI-MS) for C$_{14}$H$_{18}$N$_2$O$_5$Na [M + Na$^+$]: found, 317.1109; calcd, 317.1113.

1-[4-Deoxy-4-(hydroxymethyl)-2,3-O-isopropylidene-$\beta$-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, treated sequentially with EtOH (1.6 mL), a 2 N solution of NaOH (0.78 mL, 1.56 mmol) and 30% aqueous H$_2$O$_2$ solution (0.78 mL, 6.8 mmol). The resulting mixture was stirred 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 (3 times). The combined organic layers were dried over MgSO$_4$ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (CH$_2$Cl$_2$–MeOH, 95:5→98:2) yielding pure 12 (77 mg, 62%) as a white foam. 1H-NMR (300 MHz, DMSO-d$_6$): $\delta$ 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$_6$): $\delta$ 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$_2$O$_6$Na [M+H$^+$]: found, 335.1232; calcd, 335.1219; UV 265 (10640).

1-[4-Deoxy-4-(hydroxymethyl)-$\beta$-D-ribopyranosyl]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 C11H16N2 O6Na [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-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, v1/2 = 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(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$_2$O$_6$ [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$_3$CN (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$_2$Cl$_2$. 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$_2$Cl$_2$–MeOH, 95:5) to give 17 (3.6 g, 87 %) as a syrup. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 26.5 and 28.1 (C(CH$_3$)$_2$), 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$^\text{m}$), 126.9 (arom C$^\text{o}$), 129.8 (arom C$^\text{i}$), 153.6 (arom C$^\text{i}$), 194.7 (O(CS)O); HRMS (ESI-MS) for C$_{16}$H$_{20}$O$_6$SNa [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 (CH$_2$Cl$_2$–MeOH, 98:2) to give 18 (773 mg, 62 %) as an oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 26.6 (C C$_3$H$_3$), 28.5 (CCH$_3$), 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 (CCH$_3$), 126.5 (arom C$^\beta$), 127.2 and 127.7 (arom C$^\alpha$ styryl), 128.7 (arom C$^\alpha$), 132.8 (C$^{\beta}$ styryl), 137.1 (arom C$^\beta$); HRMS (ESI-MS) for C$_{17}$H$_{22}$O$_4$Na $[M + Na]^+$: 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 tetraoxide 4% in H$_2$O (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 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$_2$S$_2$O$_3$ 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$_2$O (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$_2$Cl$_2$–MeOH, 9:1) to give 20 (127 mg, 53 % over three steps) as an oil. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.24 (3H, s, CCH$_3$), 1.38 (3H, s, CCH$_3$), 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$_6$): $\delta$ 26.9 (CCH$_3$), 22.8 (CCH$_3$), 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 (CCH$_3$); HRMS (ESI-MS) for C$_{10}$H$_{18}$O$_5$Na $[M + Na]^+$: found, 241.1050; calcd, 241.1052.

2,3,6-Tri-O-acetyl-4-deoxy-4-C-hydroxymethyl-1-O-methyl-$\alpha$-L-lyxopyranose (21)$^{12}$

A solution of 20 (72 mg, 0.3 mmol) in trifluoroacetic acid–H$_2$O (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–H$_2$O (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-$\alpha$-L-lyxopyranose $^{12}$ (45 mg, 77 %) as a glassy solid. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 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$_6$): $\delta$ 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$_7$H$_{14}$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$_2$Cl$_2$–MeOH, 99:1) to yield 21 (60 mg, 89 %) as a foam. $^1$H NMR (300 MHz, CD$_3$OD): $\delta$ 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$_3$OD): $\delta$ 19.3, 19.4 and 19.5 (OCO$_2$C$_3$H$_3$), 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$_8$Na $[\text{M} + \text{Na}]^+$: found, 327.1058; calcd, 327.1056.

1-[2,3,6-O-Tri-acetyl-4-deoxy-4-C-hydroxymethyl-\(\alpha\)-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$_3$CN (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$_2$CO$_3$ and extracted with CH$_2$Cl$_2$. After drying and evaporation of the organic layer, the obtained residue was purified by column chromatography (CH$_2$Cl$_2$–MeOH 99:1 $\rightarrow$ 97:3) yielding pure 22 (367 mg, 38%) as a white foam and residual starting product 21 (315 mg, 42 %). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 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 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$_6$): $\delta$ 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$_2$O$_9$Na $[\text{M} + \text{Na}]^+$: found, 421.1253; calcd, 421.1223; UV 265 (8800).

1-[4-Deoxy-4-C-hydroxymethyl-\(\alpha\)-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 (CH$_2$Cl$_2$–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$_2$O$_6$Na $[M + Na]^+$: found, 295.0902; calcd, 295.0906; Anal. (C$_{11}$H$_{16}$N$_2$O$_6$Na) C, H, N; 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 3 h at room temperature and overnight at 30°C. Water was added and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (CH$_2$Cl$_2$–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 (CH(CH$_3$)$_2$ and
Compound 23 (126 mg, 0.24 mmol) was dissolved in anhydrous CH$_3$CN (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 (7mL), the mixture was evaporated to dryness, the obtained residue was dissolved in EtOAc, washed with water, dried over MgSO$_4$, evaporated under reduced pressure and purified by column chromatography (CH$_2$Cl$_2$–MeOH, 99.5:0.5) to afford 24 (140 mg, 89%) as a white foam. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 12.6 (5-CH$_3$), 12.8, 13.0, 13.5, 13.7 (CH(CH$_3$)$_2$), 17.4, 17.5, 17.6, 17.7, 17.7 (CH(CH$_3$)$_2$), 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$^c$), 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$_2$O$_8$SSi$_2$Na [M + Na]$^+$: found, 673.2409; calcd, 673.2411; UV 265 (10000).
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, m, 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-$d_6$): $\delta$ 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$_2$O$_5$Na [M + Na]$^+$: found, 279.0952; caled, 279.0957; Anal. (C$_{11}$H$_{16}$N$_2$O$_5$) C, H, N; UV 265 (10590).

Acknowledgements. V. Vanheusden is indebted to the "Fonds voor Wetenschappelijk Onderzoek - Vlaanderen" for a position as Aspirant. The FWO, EEC (BIO98 CT-0354).

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.

References


Table of Content graphic

(i) β-tributylstannyl-styrene, AIBN
(ii) OsO₄, NaIO₄
(iii) NaBH₄