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Spiro-sulfamidate and sulfate nucleosides via 2′ and 3′-C-branched-chain sugars and nucleosides

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ABSTRACT

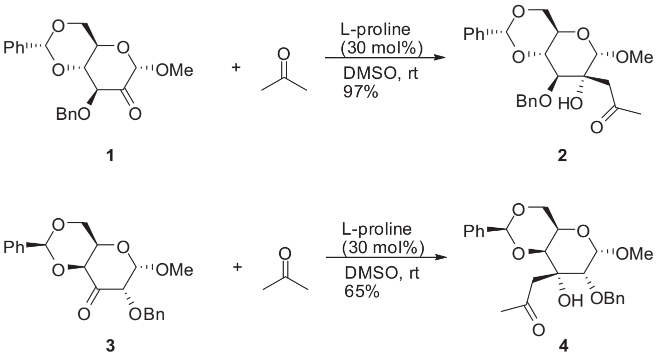
C-branched-chain sugars and nucleosides were obtained by organocatalysis from ulose derivatives. After a reduction step, the corresponding 1,3-diol was derivatized into 3′-spiro-sulfamidates and unexpected sulfates by treatment with a Burgess reagent. Deprotection of the Boc-derivatives was carried out while preserving the cyclic sulfate. An example of ring opening of the cyclic sulfate derivative with sodium azide leading to the corresponding 3′-*C*-azidoalkyl branched-chain nucleosides is given.

1. Introduction

Branched-chain sugars and particularly branched-chain nucleosides have received much attention as potential chemotherapeutic agent as well as in antisense oligonucleotide research. Some of these analogues have been shown to display a very interesting spectrum of antiviral and anticancer activities.[1] The key step in the total synthesis of these branched-chain sugar nucleosides is the stereocontrolled quaternization of 2′-*C* or 3′-*C* by the formation of a new C–C bond. One of the most used methods consists in adding the *C*-nucleophile to the corresponding ketonucleoside. However, ketonucleosides give generally moderate yields of the carbonyl addition product upon reaction with Grignard,[2] organolithium[2–4] and organoaluminium reagents.[5] The carbonyl addition reaction involving 2′-ketonucleosides with basic reagents is particularly problematic because β-elimination of the nucleobase readily occurs.[6,7] Organocatalysis is now widely used for stereocontrolled C–C bond formation, and its utility is well recognized in a plethora of organic reaction and synthesis of natural products. To the best of our knowledge, no direct metal-free aldol reaction involving nucleosides has been described, even if considerable attention has been devoted to the synthesis of *C*-3′-(2′)-branched-chain nucleosides.[6] Here, we introduce the synthesis of a new class of *C*-3′-(2′)-branched-chain nucleosides and investigate their use for the synthesis of spiro-sulfamidate derivatives.

2. Results and discussion

In continuation of our search for new spiro sugar-modified nucleosides of antiviral potential,[8] we first investigated the reactivity of the 4,6-*O*-benzylidene ketopyranose **1** (Scheme 1). Compound **1** was obtained after a Swern oxidation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside.[9] The crude 2-ulose **1** was submitted to acetone and L-proline (30 mol %) in DMSO and led exclusively to aldol **2** in 97% yield over two steps.



Scheme 1. Branched-chain sugars synthesis on pyranose ring.

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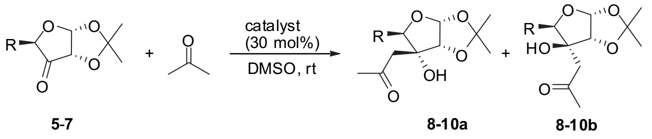
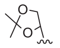
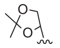
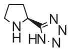
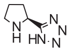
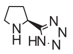
Similarly, starting from known ulose **3**,[10] the aldol **4** was obtained in 65% yield. In both cases, the attack took place from the β-face of the sugar moiety.

Next, we investigated the reactivity of the stereocontrolled proline-aldolisation in the 1,2-*O*-isopropylidene ketopentofuranoses series **5**–**7** with 5-*O*-trityl,[11] 5-*O*-*tert*-butyldimethylsilyl[12] and 5,6-*O*-isopropylidene[13] protecting groups (Table 1). Under similar conditions and using ulose **5**,**6** in acetone at room temperature, the desired aldol derivatives were obtained as mixture of isomers for **8a**/**8b** and **9a**/**9b** in 49% and 65%, respectively. In 1989, Camarasa[14] and co-workers have already described the stereoselective addition of acetone to various furanos-3-ulose using K_2CO_3. Despite a modest yield obtained for ulose **6** (58%), the authors only obtained the acetonyl derivative **8a** in 15% yield. This low yield was partially attributed to the acidity of the proton H-4 leading among others to a polycyclic derivative. In our conditions, such derivatives have not been detected. Finally, compounds **8a** and **9a** showed analytical and spectroscopic data in accordance to literature.[14] The reaction carried out from the trityl derivative **7** led to the only *C*-derivative **10a** in 86% yield. The proposed proline-aldol transition state clearly shows the preferential *Si*-facial attack for compound **7** (Fig. 1) oriented by the bulky 1,2-*O*-isopropylidene group. In contrast, transition state of ulose **5** does not show a preferential facial attack. Similar steric hindrance from both isopropylidene was observed and was confirmed by the isolated ratio of compounds **8a** (27%) and **8b** (22%).

Table 1
Effect of organocatalysts and protecting group in aldol reaction[a]



Entry	Substrate	Catalyst	Product (yield%)[b]
1	5 R = 	L-Proline	**8a** (27%)/**8b** (22%)
2	**6** R=CH_2OTBS	L-Proline	**9a** (60%)/**9b** (5%)
3	**7** R=CH_2OTrt	L-Proline	**10a** (86%)
4	5 R = 		**8a**+**8b** (45%)
5	**6** R=CH_2OTBS		**9a**+**9b** (68%)
6	**7** R=CH_2OTrt		**10a** (70%)

[a] Reaction conditions: ulose (1 equiv), catalyst (30 mol %) in DMSO at room temperature for 24 h.
[b] Isolated yield after column chromatography.

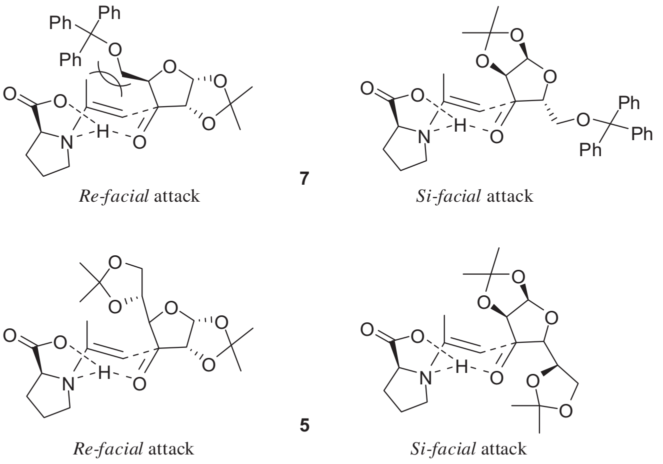
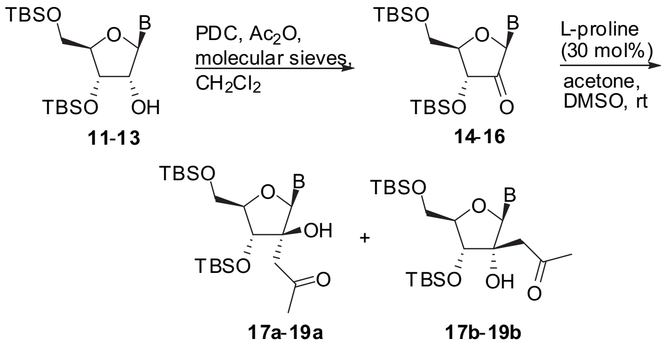
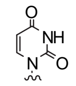
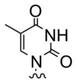
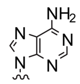


Fig. 1. Aldol transition state.

We then applied the proline-aldol reaction to 2′- and 3′-ketonucleosides towards the synthesis of spiro sugar-modified nucleosides. These compounds should represent good candidate as potent mimics of ATSAO[8a] derivatives or 2′-*C*-methyl cytidine with potential antiviral activities on the HIV-1 reverse transcriptase and the NS5B HCV polymerase, respectively.[15] The use of organocatalysis for aldolisation on nucleosides represent a soft quaternization method, especially for the 2′-ketonucleosides, which are known to be very sensitive and unstable due to the easy removal of the nucleic base.[12] 2′-Ketonucleosides **14**,[16] **15**[17] and **16**[17] were obtained using the classical PDC reagent for oxidation from nucleosides **11**, **12** and **13**, respectively. Using the proline-aldol condensation conditions, the 2′-*C*-branched-chain nucleosides were obtained with low yields (23%–44%) and weak selectivity except for nucleoside **15a**, which only gave the diastereoisomer **18a** in 26% yield (Table 2).

Table 2
2′-*C*-Branched-chain nucleosides synthesis[a]

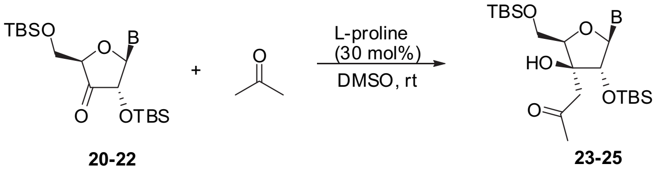


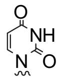
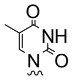
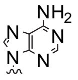
Entry	Substrate	B	Product (yield%)[b]	Ratio[c]
1	**14**		**17a**/**17b** (44%)	63/37
2	**15**		**18a** (26%)	100/0
3	**16**		**19a**/**19b** (23%)	76/24

[a] Reaction conditions: ulose (1 equiv), catalyst (30 mol %) in DMSO at room temperature for 24 h.
[b] Isolated yield after column chromatography.
[c] Determined by NMR.

Finally, we investigated the direct aldol reaction on the 3′-ketonucleosides. Starting from the known 3′-ketonucleosides uridine **20**[18] and thymidine **21**,[16] we were delighted to obtain stereoselectively the 3′-*C*-branched-chain nucleosides **23** and **24** in 72% and 90% yield, respectively (Table 3). In the same way, the purine adenosine **22**[19] led to the aldol derivative **25** in 87% yield.

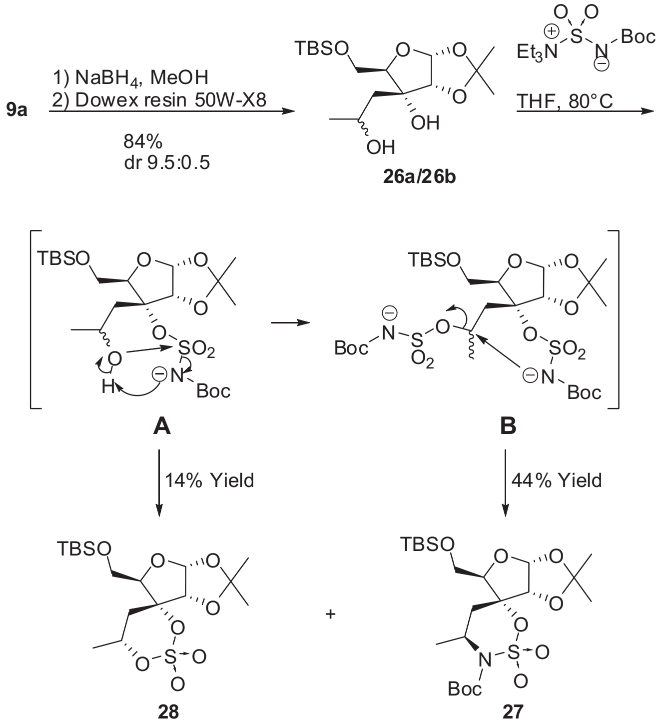
Table 3
3′-*C*-Branched-chain nucleosides synthesis[a]



Entry	Substrate	B	Product (yield%)[b]
1	**20**		**23** (72%)
2	**21**		**24** (90%)
3	**22**		**25** (87%)

[a] Reaction conditions: ulose (1 equiv), catalyst (30 mol %) in DMSO at room temperature for 24 h.

[b] Isolated yield after column chromatography.

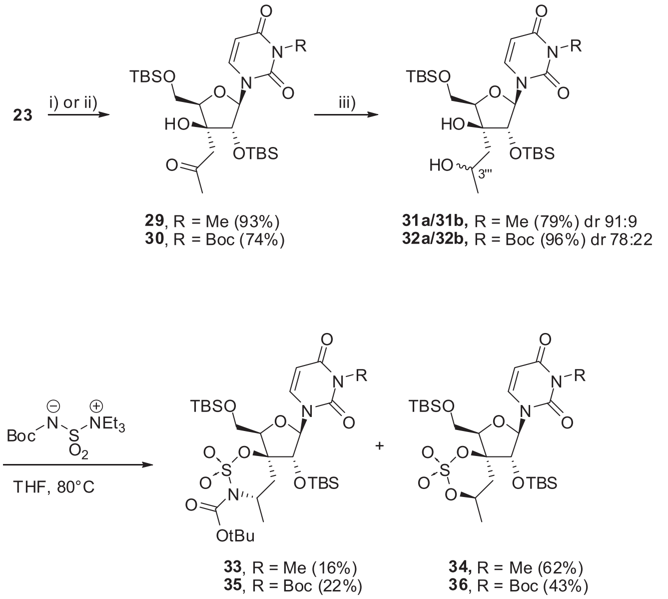


Scheme 2. Reactivity of Burgess reagent with 1,3-diol.

Cyclic sulfamidates represent synthetically versatile electrophiles. Their synthesis and reactivity have been described in detail.[20] Although the reactivity of cyclic sulfamidates is well known, especially in carbohydrate chemistry[21] where they were useful intermediates to synthesize various α- and β-glycosylamines, their application to nucleoside chemistry has received little attention[22] and to our knowledge, no spiro-sulfamidate of a pyrimidine nucleoside has been reported so far. In order to extend the molecular library of potent NNRTI (Non Nucleosidic Reverse Transcriptase Inhibitor) similar to ATSAO compounds, we decided to undertake the synthesis of these electrophile spiro derivatives.

Before synthesizing 3′-spiro nucleosides, we initially conducted the reaction in a monosaccharide series. Compound **9a** was chosen as model because of the presence of the 5-OTBS protecting group (Scheme 2). The carbonyl group was reduced using $NaBH_4$ in MeOH, which led to the mixture of diastereomers **26a**/**26b** in 84% yield (ratio 9.5/0.5). These latter were submitted to the *N*-Boc Burgess-type reagent (4 equiv) in THF. As expected, the sulfamidate **27** was obtained but, in a modest yield (44%) via the double alcohol activation of the 1,3-diol. Surprisingly, the sulfamidate was accompanied by a cyclic sulfate **28** in 14% yield. No spiro-derivatives were isolated from the minor diastereoisomer **26**. Cyclic sulfate byproducts have never been described using a Burgess reagent in literature. In-depth analysis of the ^{13}C NMR clearly shows that the carbon atom bearing the nitrogen atom in sulfamidate **27** presents a chemical shift at 52.5 ppm, whereas the same carbon atom in the sulfate **28** deshielded at 80.7 ppm. Moreover, the HRMS found for both compounds are in accordance with the expected calculated HRMS (See Experimental section. Compound **28**: $[M+H]^+$ $C_{17}H_{36}NO_8SiS$ calcd 442.1931, found 442.1946; Compound **27**: $[M+Na]^+$ $C_{22}H_{41}NO_9SiSNa$ calcd 546.2169, found 546.2183). The plausible mechanism to explain the competition between the formation of the cyclic sulfamidate and sulfate probably involved the initial formation of a mono-sulfonated intermediate **A**. Before the second addition of the Burgess reagent leading to intermediate **B**, the restricted conformation imposed by the glucidic scaffold could facilitate the concerted nucleophilic attack of the hydroxyl group on the SO_2 electrophilic centre and the alcohol deprotonation to afford **28**. Concurrently, the intermediate **A** could react one more time with the Burgess reagent to afford the expected sulfamidate **27** after an intramolecular displacement with inversion of configuration. This result clearly showed that this step is dependent on the steric constraint generated by the *N*-Boc Burgess reagent.

Considering this interesting result and in order to synthesize a 3′-spiro-sulfamidate nucleoside **33** and **35**, the aldol nucleoside **23** was first functionalized to avoid the reactivity between the nitrogen atom of the nucleic base and the Burgess reagent. Some attempts to directly use the Burgess reagent with the unprotected *N*-3 led to a complex mixture of compounds and degradation. The uridine **23** was either alkylated in presence of K_2CO_3 and MeI in acetone to afford **29** in 93% yield or protected with a Boc protecting group to afford **30** in 74% yield (Scheme 3). We choosed the Boc



Scheme 3. Burgess reagent reactivity with pyrimidine nucleosides. Reagents and conditions: (i) MeI, K_2CO_3, acetone; (ii) Boc_2O, pyridine, CH_2Cl_2; (iii) (a) $NaBH_4$, MeOH, (b) Dowex resin 50W-X8.

protecting group, known to be readily cleaved under mild conditions and in fact, probably compatible with the cyclic sulfate or cyclic sulfamidate moieties. After a reduction step with $NaBH_4$ in MeOH, a mixture of isomers 1,3-diols **31a**/**31b** (ratio 91/9) was obtained in 71% yield from **23** and **32a**/**32b** in 96% yield from **30**.

When the mixture of 1,3-diols **31a**/**b** was submitted to the *N*-Boc Burgess reagent (4 equiv) in refluxing THF, a mixture of two six-membered ring compounds were obtained. In a similar fashion, as observed with the monosaccharide **26a**/**b**, HPLC purification provided the sulfamidate **33** and the cyclic sulfate **34** in 16% and 62% yield, respectively. Increasing the equivalents in *N*-Boc Burgess reagent (6 equiv vs 4 equiv) led to **33** and **34** in 23% and 36% yield, respectively. Moreover, very recently, Hudlicky and co-workers[23] have studied the thermal stability by NMR experiments of several Burgess reagents. They observed that some Burgess reagents decomposed in less than an hour in refluxing THF and led us consequently, to use 4 equiv of Burgess reagent in this study. This interesting result emphasized a decrease in the overall yield (59% vs 78%) and a ratio increasing of **33** versus **34** (6 equiv: **34**/**33**=1.56; 4 equiv: **34**/**33**=3.8) and thus confirmed the previous proposed mechanism as well as the relationship between the bulky Burgess reagent's and the favoured mono or bis-sulfonated intermediate. The same conditions (4 equiv of Burgess reagent) applied to purified and isolated **32a** also led to sulfamidate **35** in 22% yield and sulfate **36** in 43% yield. These examples represent a direct method towards the synthesis of spiro-sulfate on nucleoside diol. Usually, cyclic sulfate were fused with the furanose ring.[24] The few examples[25] described in the literature were mostly used the two-step sequences: formation of the cyclic sulfite intermediate followed by a Sharpless oxidation.[26] Cyclic sulfates are useful intermediates in organic synthesis, one of their advantage consists in activating a position (here, C-4″) for nucleophilic attack and to generate an acyclic sulfate.[20b,27a]

The choice of Boc as protecting group proved to be suitable since conditions used for its cleavage preserves the cyclic sulfate and sulfamidate moieties for derivatives **35** and **36**. Using classical standard conditions (TFA, CH_2Cl_2), sulfamidate **35** led to deprotected compound **37** in 47% yield and *N*-Boc derivative **38** in 24% yield. Using the same conditions, sulfate **36** led to deprotected compound **39** in 40% yield and partially desilylated compound **40** (24%) (Scheme 4).

To confirm the configuration of the stereochemistry of C-4″ in the 1,3-diol **31a** (the major product obtained after reduction of the carbonyl group) and **34**, a NOESY experiment was realized on the cyclic sulfate **34** (Fig. 2). Two correlations were observed for H-4′/H-5″ and H-4′/H-4″, thereby ruling out the C-4′ configuration as well as the presence of the methylene group below the sugar ring.

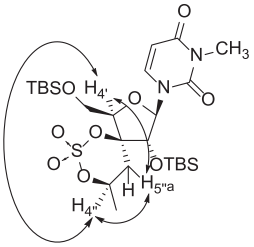
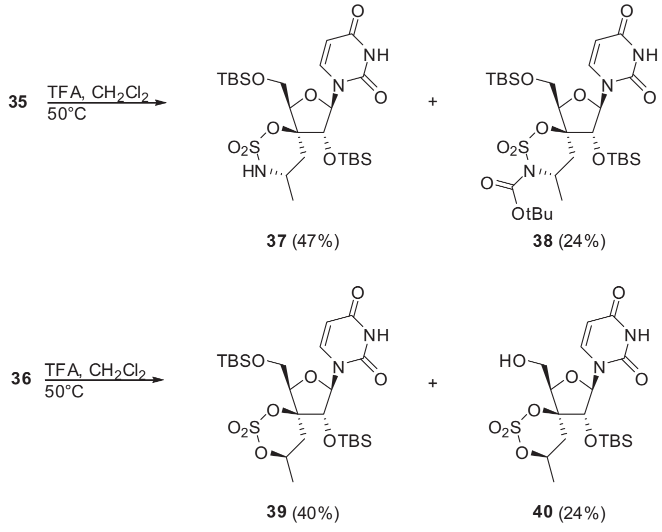
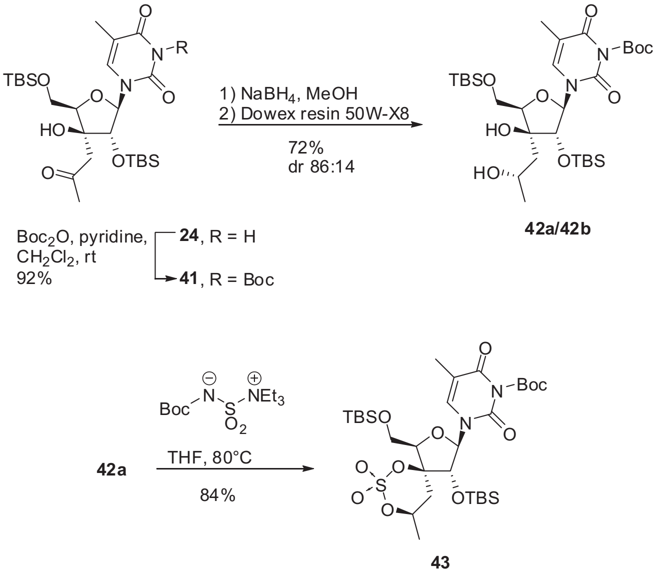


Fig. 2. NOESY experiment with spiro-sulfate **34**.



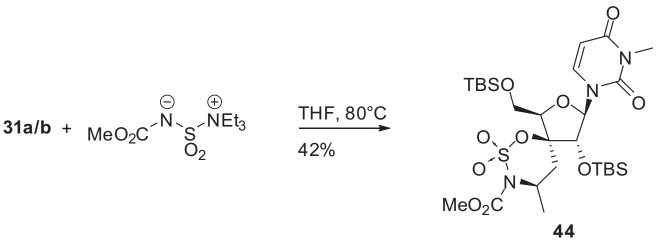
Scheme 4. Deprotection of uridine compounds.

The same result was also observed with the *N*-protected thymine derivative **41** obtained from compound **24** (Scheme 5). Compound **41** was obtained in 92% (Boc_2O, pyridine, CH_2Cl_2) and after a reduction step by $NaBH_4$, compound **42a** was separated and isolated from **42b** by HPLC for the next reaction step. Under the same reaction conditions used for the synthesis of **27**, the sole cyclic sulfate **43** was isolated in 84% yield. The cyclic sulfamidate derivative observed in the case of **33** has been scarcely detected by mass spectrometry in this case.



Scheme 5. Synthesis of spiro-sulfate.

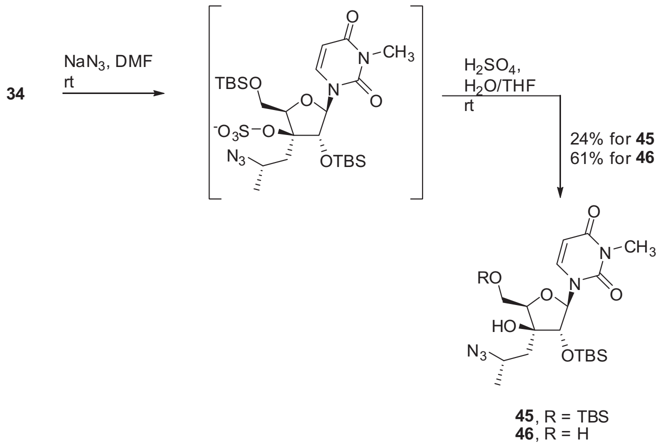
Finally, if we keep in mind that the formation of the cyclic sulfate was due to the bulkiness of the Burgess reagent, which preferentially attacks the alcoholic hydrogen than the S_N2 displacement, a less bulky Burgess reagent (Scheme 6), such as methyl *N*-(triethylammoniumsulfonyl)carbamate ($Et_3N{-}SO_2{-}NCO_2Me$) would lead preferentially to the sulfamidate ring. Remarkably, when the uridine derivative **31a**/**b** was submitted to the commercially available



Scheme 6. Chimioselectivity with Burgess reagent.

NCO_2Me Burgess reagent, we nicely isolated the sole sulfamidate derivative **44** in 42% yield.

To confirm the sulfate structures, we took advantage of the good electrophilic nature of the cyclic sulfate to open the ring with a nucleophile, such as sodium azide (Scheme 7). Firstly, the treatment of cyclic sulfate **34** with sodium azide in DMF at room temperature and subsequent aqueous H_2SO_4 hydrolysis of the generated acyclic sulfate gave the corresponding azidonucleosides **45** and **46** in 24% and 61% yield, respectively. Compound **46** was the result of the deprotection of the 5′-OTBS protecting group of compound **45**.



Scheme 7. Spiro-sulfate ring opening with NaN_3.

3. Conclusions

We have synthesized various branched-chain sugars and nucleosides under mild conditions using L-proline as catalyst. After a reduction step, the 1,3-diol has been easily converted into cyclic sulfamidate or sulfate. Their stabilities were proved in *N*-Boc acidic deprotection conditions. The activation of 1,3-diols via cyclic sulfamidate and sulfate would give rise to two types of compound: (a) a nucleophilic opening of cyclic sulfamidate on the C-3′ and (b) a nucleophilic ring opening of the cyclic sulfate on the C-4″. Similar studies on the 2′-position, variation of the nucleophiles and also the biological evaluation of the nucleosides is under investigation and will be reported in due course.

4. Experimental

4.1. Materials and methods

Melting points are uncorrected. Optical rotations were recorded in $CHCl_3$ solution. ^1H NMR (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in $CDCl_3$ (internal Me_4Si), respectively. ^1H assignments were deduced from 2D $^1H-^1H$ NMR COSY experiments. ^{13}C assignments were deduced from 2D $^{13}C-^1H$ NMR HSQC experiments. Stereochemical assignments were deduced by analysis of the corresponding NOESY graph (NOESY graph 2D homonuclear correlation via dipolar coupling. Dipolar coupling may be due to NOE or chemical exchange. Phase sensitive with gradient pulses in mixing time). TLC was performed on Silica F_{254} and detection by UV light at 254 nm or by charring with *p*-anisaldehyde−H_2SO_4−AcOH−EtOH reagent. FTIR spectra were obtained using ATR or NaCl and are reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a Q-TOF spectrometer. HPLC analysis was performed using a C18 5 μ (250mm×4.6 mm) column for the analytical part and a C18 5 μ (250mm×22 mm) column for HPLC preparative. Column chromatography was effected on Silica Gel 60 (230 mesh) or using an automatic flash chromatography apparatus. Cyclohexane and ethyl acetate were distilled before use.

4.2. Synthesis

*4.2.1. Methyl 3-O-benzyl-4,6-O-benzylidene-2-C-acetonyl-α-D-glucopyranose (**2**).* To a solution of compound **1** (916 mg, 2.47 mmol) in distilled CH_2Cl_2 (20 mL) at −78 °C was added DMSO (0.53 mL, 7.42 mmol) and oxalyl chloride (0.42 mL, 4.94 mmol). After stirring for 3 h, Et_3N (1.04 mL, 7.42 mmol) was added and the reaction was cooled at room temperature. After usual work-up, the crude ulose was dissolved in DMSO (20 mL) and acetone (5 mL) and L-proline (85 mg, 0.74 mmol) was added. After stirring for 40 h at room temperature, the reaction mixture was extracted with EtOAc and water. The organic phase was washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. After flash chromatography (EtOAc/cyclohexane, 20/80), compound **2** was isolated as a colourless syrup (1.03 g, 97% over two steps). $[\alpha]_D^{20}$ +50 (*c* 0.11, $CHCl_3$); IR (ATR) ν 3417, 2927, 2857, 1706, 1662, 1470, 1454, 1361, 1118, 1073, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.27 (m, 10H, 2× C_6H_5), 5.61 (s, 1H, C*H*Ph), 4.89 (s, 2H, OC*H*$_2$Ph), 4.79 (s, 1H, H-1), 4.33 (dd, 1H, $J_{5,6b}$=4 Hz, $J_{6a,6b}$=9.6 Hz, H-6a), 3.98 (d, 1H, $J_{3,4}$=9.9 Hz, H-3), 3.90 (dt, 1H, $J_{4,5}$=$J_{5,6b}$=9.5 Hz, $J_{5,6a}$=4.5 Hz, H-5), 3.82 (t, 1H, $J_{5,6b}$=$J_{6a,6b}$=9.5 Hz, H-6b), 3.64 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.5 Hz, H-4), 3.46 (s, 3H, OCH_3), 3.33 (d, 1H, $J_{A,B}$=15 Hz, H-A (CH_2CO)), 2.52 (d, 1H, $J_{A,B}$=15 Hz, H-B (CH_2CO)), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.9 (CO), 138.6, 137.7, 128.2–126.0 (2× C_6H_5), 101.9, 101.1 (C-1, *C*HPh), 80.8, 80.4 (C-4, C-3), 76.8 (C-2), 75.5 (O*C*H$_2$Ph), 69.0 (C-6), 62.9 (C-5), 55.5 (OCH_3), 43.3 (CH_2−), 32.7 (−CH_3). HRMS [MNa^+] $C_{24}H_{28}O_7Na$ calcd 451.1733, found 451.1729.

*4.2.2. Methyl 2-O-benzyl-4,6-O-benzylidene-3-C-acetonyl-α-D-gulopyranose (**4**).* To a solution of **3** (133 mg, 0.36 mmol) in DMSO (3 mL) and acetone (0.5 mL) was added L-proline (12.4 mg, 0.107 mmol). After stirring for 40 h at room temperature, water and EtOAc were added. The organic layer was separated by extraction and washed with a saturated solution of NaCl and water. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. After flash chromatography on silica gel (Cyclohexane/EtOAc, 15/85), compound **4** (100 mg, 65%) was successively isolated as a solid: mp=78–79 °C; $[\alpha]_D^{20}$ +120 (*c* 0.11, $CHCl_3$); IR (ATR) ν 3418, 3389, 2920, 2855, 1668, 1446, 1413, 1357, 1165, 1113, 1059, 1041, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.29 (m, 10H, 2× C_6H_5), 5.49 (s, 1H, C*H*Ph), 4.79 (d, 1H, $J_{A,B}$=12 Hz, H-A OCH_2Ph), 4.74 (s, 1H, H-1), 4.69 (d, 1H, $J_{A,B}$=12 Hz, H-B OCH_2Ph), 4.32 (d, 1H, $J_{6a,6b}$=12 Hz, H-6a), 4.24 (dd, 1H, $J_{4,5}$=6 Hz, $J_{5,6b}$=3 Hz, H-5), 4.10 (dd, 1H, H-6b), 3.91 (d, 1H, H-4), 3.69 (d, 1H, $J_{A,B}$=15 Hz, H-A (CH_2CO)), 3.68 (s, 1H, H-2), 3.48 (s, 3H, OCH_3), 2.64 (d, 1H, $J_{A,B}$=15 Hz, H-B (CH_2CO)), 2.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.5 (CO), 138.4, 137.9, 129.1–126.2 (2× C_6H_5), 103.3 (C-1), 101.1 (*C*HPh), 78.3 (C-4), 74.3 (C-3), 73.7 (C-5), 72.7 (O*C*H$_2$Ph), 69.3 (C-6), 61.9 (C-2), 55.8 (OCH_3), 44.3 (CH_2−), 32.1 (−CH_3). HRMS [MNa^+] $C_{24}H_{28}O_7Na$ calcd 451.1733, found 451.1729.

*4.2.3. 1,2:5,6-Di-O-isopropylidene-3-C-acetonyl-α-D-ribofuranose (**8a**) and 1,2:5,6-di-O-isopropylidene-3-C-acetonyl-α-D-xylofuranose (**8b**).* To a solution of **5** (100 mg, 0.39 mmol) in DMSO (4 mL) and acetone (1 mL) was added L-proline (0.0134 g, 0.12 mmol). After stirring for 24 h at room temperature, water (20 mL) was added. The aqueous phase was then extracted with EtOAc (3×15 mL) and the organic layers were combined, washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. After flash chromatography on silica gel (Cyclohexane/EtOAc, 8/2–7/3), compound **8b** (26.8 mg, 22%) was successively isolated as a syrup followed by compound **8a** (32.5 mg, 27%) as a syrup.

Compound **8a**: $[\alpha]_D^{20}$ +45 (*c* 0.105, $CHCl_3$); IR (ATR) ν 2998, 1708, 1374, 1205, 1045, 1011, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.59 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 4.44 (d, 1H, $J_{1,2}$=3.8 Hz, H-2), 3.95–3.87 (m, 2H, H-6a, H5), 3.77 (dd, 1H, $J_{4,6a}$=5.2 Hz, $J_{6a,6b}$=8.0 Hz, H-6a), 3.65 (dd, 1H, $J_{5,6b}$=5.2 Hz, $J_{6a,6b}$=8.0 Hz, H-6b), 3.65 (d, 1H, $J_{4,6a}$=8.1 Hz, H-4), 3.23 (br s, 1H, OH), 2.95 (d, 1H, $J_{3'a,3'b}$=15.0 Hz, H-3′a (CH_2CO)), 2.24 (d, 1H, $J_{3'a,3'b}$=15.0 Hz, H-3′b (CH_2CO)), 2.16 (s, 3H, CH_3), 1.44, 1.31, 1.23, 1.20 (s, 12H, 4× CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.2 (CO), 112.6, 109.8 [2× O*C*(CH_3)$_2$], 103.5 (C-1), 82.0 (C-4), 80.9 (C-2), 78.5 (C-3), 73.3 (C-5), 67.8 (C-6), 44.5 (CH_2CO), 32.5 (CH_3), 26.6, 26.5, 26.4, 25.2 (4× CH_3). HRMS [MNa^+] $C_{15}H_{24}O_7Na$ calcd 339.1420, found 339.1413. Compound **8b**: $[\alpha]_D{}^{20}$ +10 (*c* 0.085, $CHCl_3$); IR (ATR) ν 2987, 1700, 1372, 1213, 1165, 1063, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.70 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 4.36 (d, 1H, $J_{1,2}$=3.7 Hz, H-2), 4.20 (m, 1H, H-5), 4.02 (br s, 1H, OH), 3.93 (dd, 1H, $J_{5,6a}$=6.3 Hz, $J_{6a,6b}$=8.7 Hz, H-6a), 3.82 (dd, 1H, $J_{5,6b}$=5.3 Hz, $J_{6a,6b}$=8.7 Hz, H-6b), 3.49 (d, 1H, $J_{4,5}$=8.2 Hz, H-4), 2.88 (d, 1H, $J_{A,B}$=18.3 Hz, H-A (CH_2CO)), 2.79 (d, 1H, $J_{A,B}$=18.3 Hz, H-B (CH_2CO)), 2.07 (s, 3H, CH_3), 1.32, 1.18, 1.28, 1.12 (s, 12H, 4× CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.7 (CO), 112.0, 109.1 [2× O*C*(CH_3)$_2$], 104.6 (C-1), 85.4 (C-4), 82.8 (C-2), 79.3 (C-3), 72.2 (C-5), 67.4 (C-6), 43.7 (CH_2CO), 30.9 (CH_3), 26.9, 26.7, 26.3, 25.2 (4× CH_3). HRMS [MNa^+] $C_{15}H_{24}O_7Na$ calcd 339.1420, found 339.1412.

*4.2.4. 5-O-tert-Butyldimethylsilyl-1,2-O-isopropylidene-3-C-acetonyl-α-D-ribofuranose (**9a**) and 5-O-tert-butyldimethylsilyl-1,2-O-isopropylidene-3-C-acetonyl-α-D-xylofuranose (**9b**).* To a solution of **6** (2.00 g, 6.61 mmol) in DMSO (60 mL) and acetone (15 mL) was added L-proline (0.22 g, 1.98 mmol). After stirring for 24 h at room temperature, water and EtOAc were added. The organic layer was separated by extraction and washed with a saturated solution of NaCl and water. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. After flash chromatography on silica gel (Cyclohexane/EtOAc, 15/85), compound **9b** (112 mg, 5%) was successively isolated as a syrup followed by compound **9a** (1.33 g, 60%) as a syrup. Compound **9a**: $[\alpha]_D^{20}$ +41 (*c* 0.55, $CHCl_3$); IR (ATR) ν 2929, 1704, 1372, 1258, 1069, 1004, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.70 (d, 1H, $J_{1,2}$=6 Hz, H-1), 4.43 (d, 1H, $J_{1,2}$=6 Hz, H-2), 3.81 (dd, 1H, $J_{4,5a}$=6 Hz, $J_{5a,5b}$=9 Hz, H-5a), 3.74 (dd, 1H, $J_{4,5b}$=6 Hz, $J_{5a,5b}$=9 Hz, H-5b), 3.68 (t, 1H, $J_{4,5a}$=$J_{4,5b}$=6 Hz, H-4), 3.43 (br s, 1H, OH), 2.83 (d, 1H, $J_{A,B}$=15 Hz, H-A (CH_2CO)), 2.35 (d, 1H, $J_{A,B}$=15 Hz, H-B (CH_2CO)), 2.16 (s, 3H, CH_3), 1.49, 1.26 (s, 6H, 2× CH_3), 0.83 (s, 9H, *t*-Bu), 0.01 (s, 6H, 2× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.2 (CO), 112.4 [O*C*(CH_3)$_2$], 103.6 (C-1), 82.4 (C-4), 81.1 (C-2), 78.0 (C-3), 60.9 (C-5), 44.2 (CH_2CO), 32.3 (CH_3), 26.5 (2× CH_3), 25.8 (*t*-Bu), 18.1 (Cq *t*-Bu), −5.4 (2× $SiCH_3$). HRMS [$MNH_4{}^+$] $C_{17}H_{36}NO_6Si$ calcd 378.2312, found 378.2308. Compound **9b**: $[\alpha]_D{}^{20}$ +10 (*c* 0.165, $CHCl_3$); IR (ATR) ν 2929, 1706, 1374, 1251, 1098, 1004, 835, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.88 (d, 1H, $J_{1,2}$=3 Hz, H-1), 4.51 (d, 1H, $J_{1,2}$=3 Hz, H-2), 4.40 (s, 1H, OH), 4.01 (dd, 1H, $J_{4,5a}$=6 Hz, $J_{5a,5b}$=12 Hz, H-5a), 3.87 (dd, 1H, $J_{4,5b}$=6 Hz, $J_{5a,5b}$=12 Hz, H-5b), 3.82 (t, 1H, $J_{4,5a}$=$J_{4,5b}$=6 Hz, H-4), 2.96 (d, 1H, $J_{A,B}$=18 Hz, H-A (CH_2CO)), 2.89 (d, 1H, $J_{A,B}$=18 Hz, H-B (CH_2CO)), 2.23 (s, 3H, CH_3), 1.44, 1.30 (s, 6H, 2× CH_3), 0.90 (s, 9H, *t*-Bu), 0.03 (s, 6H, 2× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.6 (CO), 111.9 [O*C*(CH_3)$_2$], 104.4 (C-1), 85.6 (C-2), 81.4 (C-4), 79.7 (C-3), 60.5 (C-5), 44.4 (CH_2CO), 31.2 (CH_3), 26.9, 26.4 (2× CH_3), 25.8 (*t*-Bu), 18.2 (Cq *t*-Bu), -5.5 (2× $SiCH_3$). HRMS [$MNH_4{}^+$] $C_{17}H_{36}NO_6Si$ calcd 378.2312, found 378.2309.

*4.2.5. 1,2-O-Isopropylidene-3-C-acetonyl-5-O-trityl-α-D-ribofuranose (**10a**).* To a solution of **7** (0.1 g, 0.23 mmol) in DMSO (4 mL) and acetone (1 mL) was added L-proline (0.008 g, 0.07 mmol). After stirring for 24 h at room temperature, water (20 mL) was added. The aqueous phase was then extracted with EtOAc (3×15 mL) and the organic layers were combined, washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. After flash chromatography on silica gel (Cyclohexane/EtOAc, 1/0–7/3), compound **10a** (98.1 mg, 86%) was isolated as a white solid. Mp=67 °C; $[\alpha]_D^{20}$ +3 (*c* 0.10, $CHCl_3$); IR (ATR) ν 3299, 1706, 1372, 1213, 1050, 1002, 759, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.26 (m, 15H, 3× C_6H_5), 5.87 (d, 1H, $J_{1,2}$=3.9 Hz, H-1), 4.60 (d, 1H, $J_{1,2}$=3.9 Hz, H-2), 4.16 (t, 1H, $J_{4,5a}$=$J_{4,5b}$=5.3 Hz, H-4), 3.38 (m, 2H, H-5a, OH), 3.24 (dd, 1H, $J_{4,5b}$=4.9 Hz, $J_{5a,5b}$=10 Hz, H-5b), 2.65 (d, 1H, $J_{A,B}$=15 Hz, H-A (CH_2CO)), 2.25 (d, 1H, $J_{A,B}$=15 Hz, H-B (CH_2CO)), 2.14 (s, 3H, CH_3), 1.67, 1.42 (s, 6H, 2× CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.5 (CO), 143.7, 128.8–127.3 (C_6H_5), 112.7 [O*C*(CH_3)$_2$], 104.0 (C-1), 87.1 (Cq trityl), 81.1 (C-4), 80.9 (C-2), 78.4 (C-3), 61.7 (C-5), 43.9 (CH_2CO), 32.5 (CH_3), 26.7 (2× CH_3). HRMS [MNa^+] $C_{30}H_{32}O_6Na$ calcd 511.2097, found 511.2092.

*4.2.6. 1-(3′,5′-Bis-O-tert-butyldimethylsilyl-2′-C-acetonyl-β-D-lyxofuranosyl)uracil (**17a**) and 1-(3′,5′-bis-O-tert-butyldimethylsilyl-2′-C-acetonyl-β-D-ribofuranosyl)uracil (**17b**).* To a solution of **14** (1.71 g, 3.53 mmol) in DCM (25 mL) over molecular sieves (4 Å), was added PDC (0.929 g, 2.47 mmol) and Ac_2O (1.26 mL, 12.34 mmol). The reaction was allowed to stir at reflux for 2 h. EtOAc (50 mL) wad added, the mixture was filtered over a pad of silica gel and washed with EtOAc. The solvent was then removed at room temperature under reduced pressure. To a solution of this crude product (1.7 g, 3.53 mmol) in DMSO (35 mL) and acetone (10 mL) was added L-proline (122 mg, 1.06 mmol). After stirring for 48 h at room temperature, water (60 mL) was added. The aqueous phase was then extracted with EtOAc (3×50 mL) and the organic layers were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The residue was the purified by flash chromatography to afford 837 mg (44%) of a mixture of **17a** and **17b** (63/37 ratio). Pure fraction of separated **17a** and **17b** have been isolated for analysis. Compound **17a**: mp=155–156 °C; $[\alpha]_D^{20}$ +38 (*c* 0.12, $CHCl_3$); IR (ATR) ν 2955, 2929, 2857, 1712, 1675, 1474, 1464, 1280, 1251, 1095, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41 (s, 1H, H-6), 5.99 (s, 1H, H-1′), 4.30 (s, 1H, H-2′), 3.97–3.83 (m, 4H, H-3′, H-4′, H-5′a, H-5′b), 2.96 (d, 1H, $J_{2''a,2''b}$=18 Hz, H-2″a), 2.75 (d, 1H, $J_{2''a,2''b}$=18 Hz, H-2″b), 2.17 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 0.95, 0.90 (s, 18H, 2× *t*-Bu), 0.14, 0.13, 0.06 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.3 (CO), 164.1, 151.1 (C-4, C2), 138.0 (C-6), 109.1 (C-5), 87.2 (C-1′), 86.2 (C-4′), 80.3 (C-3′), 78.2 (C-2′), 63.4 (C-5′), 43.0 (C-2″), 31.0 (CH_3), 25.7 (2× *t*-Bu), 18.4, 17.8 (2× Cq *t*-Bu), 12.5 (CH_3), −4.3, −4.7, −5.3, −5.4 (4× $SiCH_3$). HRMS [MNa^+] $C_{25}H_{46}N_2O_7Si_2Na$ calcd 565.2741, found 565.2728. Compound **17b**: mp=64–65 °C; $[\alpha]_D{}^{20}$ +60 (*c* 0.09, $CHCl_3$); IR (ATR) ν 2955, 2929, 2857, 1685, 1471, 1253, 1128, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.12 (s, 1H, NH), 7.47 (s, 1H, H-6), 6.04 (s, 1H, H-1′), 5.00 (d, 1H, $J_{3',4'}$=7.0 Hz, H-3′), 4.46 (s, 1H, OH), 4.24 (dt, 1H, $J_{3',4'}$=7.0 Hz, $J_{4',5'a}$=3.7 Hz, H-4′), 3.94 (dd, 1H, $J_{5'a,5'b}$=11.2 Hz, $J_{5'a,4'}$=3.7 Hz, H-5′a), 3.85 (dd, 1H, $J_{5'a,5'b}$=11.2 Hz, $J_{5'b,4'}$=3.9 Hz, H-5′b), 2.91 (d, 1H, $J_{2''a,2''b}$=18 Hz, H-2″a), 2.77 (d, 1H, $J_{2''a,2''b}$=18 Hz, H-2″b), 2.24 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 0.97, 0.90 (s, 18H, 2× *t*-Bu), 0.19, 0.17, 0.13, 0.10 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.4 (CO), 164.1, 151.1 (C-4, C2), 137.6 (C-6), 109.2 (C-5), 86.8 (C-1′), 80.2 (C-4′), 76.7 (C-2′), 73.4 (C-3′), 62.0 (C-5′), 45.4 (C-2″), 31.7 (CH_3), 26.0, 25.9 (2× *t*-Bu), 18.4, 18.3 (2× Cq *t*-Bu), 12.7 (CH_3), −4.5, −4.7, −5.2, −5.3 (4× $SiCH_3$). HRMS [MNa^+] $C_{25}H_{46}N_2O_7Si_2Na$ calcd 565.2741, found 565.2730.

*4.2.7. 1-(3′,5′-Bis-O-tert-butyldimethylsilyl-2′-C-acetonyl-β-D-lyxofuranosyl)thymine (**18a**).* A solution of CrO_3 (4.23 g, 42.4 mmol) in pyridine (6.9 mL) was stirred for 20 min at −5 °C then CH_2Cl_2 (10 mL) was added and Ac_2O (4.2 mL, 44.52 mmol). After stirring for 5 min, compound **10** (6.26 g, 13.25 mmol) dissolved in CH_2Cl_2 (90 mL) was added. The reaction mixture was cooled at room temperature for 3 h. EtOAc (100 mL) was then added and the reaction mixture was filtered through a silica pad and eluate with EtOAc. After elimination of the solvent under reduced pressure, the ulose derivative was obtained (4.3 g, 69%) and used in the next step without further purification. To a solution of crude ulose (1.5 g, 3.19 mmol) in DMSO (25 mL) and acetone (10 mL) was added L-proline (0.110 g, 0.95 mmol). After stirring for 48 h at room temperature, water (50 mL) was added. The aqueous phase was then extracted with EtOAc (3×30 mL) and the organic layers were combined, washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and evaporated to dryness. After flash chromatography (Cyclohexane/EtOAc, 85/15), compound **18a** was isolated as a white solid (0.443 g, 26%). Mp=68 °C; $[\alpha]_D^{20}$ +5 (*c* 0.12, $CHCl_3$); IR (ATR) ν 2929, 1688, 1463, 1252, 1098, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.96 (br s, 1H, NH), 7.52 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.94 (s, 1H, H-1′), 5.62 (d, 1H, $J_{5,6}$=8.2 Hz, H-5), 4.61 (s, 1H, OH), 4.22 (s, 1H, H-3′), 3.92 (m, 1H, H-4′), 3.84 (dd, 1H, $J_{4',5'a}$=6.7 Hz, $J_{5'a,5'b}$=9.9 Hz, H-5′a), 3.76 (dd, 1H, $J_{4',5'b}$=4.3 Hz, $J_{5'a,5'b}$=9.9 Hz, H-5′b), 2.92 (d, 1H, $J_{2''a,2''b}$=18 Hz, H-2″a), 2.71 (d, 1H, $J_{2''a,2''b}$=18 Hz, H-2″b), 2.12 (s, 3H, CH_3), 0.87, 0.83 (s, 18H, 2× *t*-Bu), 0.06, 0.01 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.9 (CO), 163.9, (C-4), 151.3 (C-2), 142.4 (C-6), 101.1 (C-5), 87.7 (C-1′), 86.3 (C-4′), 80.5 (C-2′), 78.2 (C-3′), 63.4 (C-5′), 43.2 (C-2″), 31.2 (CH_3), 26.0, 25.8 (2× *t*-Bu), 18.5, 17.9 (2× Cq *t*-Bu), −4.3, −5.0, −5.3 (4× $SiCH_3$). HRMS [MNa^+] $C_{24}H_{44}N_2O_7Si_2Na$ calcd 551.2585, found 551.2590.

*4.2.8. 1-(3′,5′-Bis-O-tert-butyldimethylsilyl-2′-C-acetonyl-β-D-ribofuranosyl)adenine (**19a**) and 1-(3′,5′-bis-O-tert-butyldimethylsilyl-2′-C-acetonyl-β-D-arabinofuranosyl)adenine (**19b**).* To a solution of **16** (1.3 g, 2.62 mmol) in DCM (20 mL) over molecular sieves (4 Å), was added PDC (0.690 g, 1.8 mmol) and Ac_2O (0.9 mL, 9.2 mmol). The reaction was allowed to stir at reflux for 2 h. EtOAc (50 mL) wad added, the mixture was filtered over a pad of silica gel and washed with EtOAc. The solvent was then removed at room temperature under reduced pressure. To a solution of this crude product (1.3 g, 2.62 mmol) in DMSO (20 mL) and acetone (10 mL) was added L-proline (90.6 mg, 7.9 mmol). After stirring for 48 h at room temperature, water (60 mL) was added. The aqueous phase was then extracted with EtOAc (3×50 mL) and the organic layers were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography to afford 0.34 g (23%) of a mixture of **19a** and **19b** (76/24). Pure fraction of separated **19a** and **19b** have been isolated for analysis. Compound **19a**: mp=92–93 °C; $[\alpha]_D^{20}$ +9 (*c* 0.13, $CHCl_3$); IR (ATR) ν 3304, 3159, 2953, 2929, 2856, 1706, 1633, 1597, 1471, 1250, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.30, 8.15 (s, 2H, H-2, H-6), 6.30 (br s, 2H, NH_2), 6.09 (s, 1H, H-1′), 4.85 (br s, 1H, OH), 4.45 (d, 1H, $J_{4',5'a}$=1.2 Hz, H-3′), 4.02 (m, 1H, H-4′), 3.94 (dd, 1H, $J_{4',5'a}$=5.7 Hz, $J_{5'a,5'b}$=10.4 Hz, H-5′a), 3.84 (dd, 1H, $J_{4',5'b}$=4.1 Hz, $J_{5'a,5'b}$=10.4 Hz, H-5′b), 3.02 (d, 1H, $J_{2''a,2''b}$=18.2 Hz, H-2″a (CH_2CO)), 2.49 (d, 1H, $J_{2''a,2''b}$=18.2 Hz, H-2″b (CH_2CO)), 2.05 (s, 3H, CH_3), 0.90, 0.89, 0.88, 0.87 (s, 18H, 2× *t*-Bu), 0.11, 0.10, 0.03 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.3 (CO), 155.7, 150.1, 119.1 (C-4, C-8, C-9), 153.0, 140.1 (C-2, C-6), 87.4 (C-1′), 86.6 (C-4′), 79.9 (C-2′), 78.1 (C-3′), 63.8 (C-5′), 42.9 (CH_2CO), 31.2 (CH_3), 26.1, 25.9 (2× *t*-Bu), 18.6, 18.0 (2× Cq *t*-Bu), −4.2, −4.9, −5.2, −5.3 (4× $SiCH_3$). HRMS [MNa^+] $C_{25}H_{45}N_5O_5Si_2Na$ calcd 574.2911, found 574.2836. Compound **19b**: mp=60–61 °C; $[\alpha]_D{}^{20}$ +49 (*c* 0.11, $CHCl_3$); IR (ATR) ν 3308, 3154, 2953, 2929, 2856, 1707, 1637, 1597, 1471, 1251, 1144, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.24, 8.16 (s, 2H, H-2, H-6), 6.31 (s, 1H, H-1′), 6.01 (br s, 2H, NH_2), 5.07 (d, 1H, $J_{3',4'}$=7.4 Hz, H-3′), 4.94 (br s, 1H, OH), 4.28 (m, 1H, H-4′), 3.91 (dd, 1H, $J_{4',5'a}$=3.2 Hz, $J_{5'a,5'b}$=11.1 Hz, H-5′a), 3.81 (dd, 1H, $J_{4',5'b}$=2.0 Hz, $J_{5'a,5'b}$=11.1 Hz, H-5′b), 2.73 (d, 1H, $J_{A,B}$=18.1 Hz, H-A (CH_2CO)), 2.67 (d, 1H, $J_{A,B}$=18.1 Hz, H-B (CH_2CO)), 2.17 (s, 3H, CH_3), 0.92, 0.90 (s, 18H, 2× *t*-Bu), 0.15, 0.12, 0.08, 0.04 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.2 (CO), 155.3, 150.1, 119.3 (C-4, C-8, C-9), 152.6, 140.8 (C-2, C-6), 86.1 (C-1′), 80.2 (C-4′), 76.2 (C-2′), 73.7 (C-3′), 62.0 (C-5′), 45.1 (CH_2CO), 31.6 (CH_3), 26.1, 25.9 (2× *t*-Bu), 18.5, 18.3 (2× Cq *t*-Bu), −4.4, −4.6, −5.2, −5.3 (4× $SiCH_3$). HRMS [MNa^+] $C_{25}H_{45}N_5O_5Si_2Na$ calcd 574.2911, found 574.2871.

*4.2.9. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-C-acetonyl-β-D-xylofuranosyl)uracil (**23**).* To a solution of **20** (5.00 g, 10.6 mmol) in DMSO (92 mL) and acetone (23 mL) was added L-proline (0.37 g, 3.18 mmol). After stirring for 24 h at room temperature, water (150 mL) was added. The aqueous phase was then extracted with EtOAc (3×100 mL) and the organic layers were combined, washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The residue was triturated in hexane and filtered to afford 4.04 g (72%) of compound **23** as a white solid. Mp=68 °C; $[\alpha]_D^{20}$ +5 (*c* 0.12, $CHCl_3$); IR (ATR) ν 2930, 1690, 1470, 1264, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.84 (d, 1H, $J_{5,6}$=9 Hz, H-5), 5.75 (s, 1H, H-1′), 5.68 (d, 1H, $J_{5,6}$=9 Hz, H-6), 4.33 (s, 1H, H-2′), 4.16–3.97 (m, 3H, H-4′, H-5′a, H-5′b), 3.01 (d, 1H, $J_{A,B}$=18 Hz, H-A (CH_2CO)), 2.91 (d, 1H, $J_{A,B}$=18 Hz, H-B (CH_2CO)), 2.21 (s, 3H, CH_3), 0.95, 0.90 (s, 18H, 2× *t*-Bu), 0.24, 0.15, 0.14, 0.08 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.2 (CO), 150.5 (C-2, C-4), 141.2 (C-6), 101.0 (C-5), 91.4 (C-1′), 84.5 (C-4′), 82.3 (C-2′), 79.5 (C-3′), 60.8 (C-5′), 44.2 (CH_2CO), 30.9 (CH_3), 25.9, 25.8 (2× *t*-Bu), 18.3, 17.9 (2× Cq *t*-Bu), −4.4, −5.4, −5.5, −5.6 (4× $SiCH_3$). HRMS [MH^+] $C_{24}H_{45}N_2O_7Si_2$ calcd 529.2765, found 529.2762.

*4.2.10. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-C-acetonyl-β-D-xylofuranosyl)thymine (**24**).* To a solution of **21** (2.00 g, 4.12 mmol) in DMSO (36 mL) and acetone (9 mL) was added L-proline (0.14 g, 1.24 mmol). After stirring for 24 h at room temperature, water (50 mL) was added. The aqueous phase was then extracted with EtOAc (3×50 mL) and the organic layers were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Hexane was added and after filtration, compound **24** was obtained as a white solid (2.02 g, 90%). Mp=69 °C; $[\alpha]_D^{20}$ −3.5 (*c* 0.335, $CHCl_3$); IR (ATR) ν 2929, 1683, 1471, 1257, 1105, 839, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.64 (s, 1H, H-6), 5.77 (d, 1H, $J_{1',2'}$=3 Hz, H-1′), 4.33 (br s, 1H, OH), 4.30 (d, 1H, $J_{1',2'}$=3 Hz, H-2′), 4.08 (dd, 1H, $J_{4',5'a}$=6 Hz, $J_{5'a,5'b}$=12 Hz, H-5′a), 3.96 (dd, 1H, $J_{4',5'b}$=6 Hz, $J_{5'a,5'b}$=12 Hz, H-5′b), 3.89 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=6 Hz, H-4′), 2.99 (d, 1H, $J_{A,B}$=18 Hz, H-A (CH_2CO)), 2.90 (d, 1H, $J_{A,B}$=18 Hz, H-B (CH_2CO)), 2.19 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 0.93, 0.82 (s, 18H, 2× *t*-Bu), 0.18, 0.13, 0.12, 0.03 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.3 (CO), 164.3, 150.6 (C-2, C-4), 137.0 (C-6), 109.6 (C-5), 91.1 (C-1′), 84.1 (C-4′), 82.4 (C-2′), 79.4 (C-3′), 60.9 (C-5′), 44.3 (CH_2CO), 30.9 (CH_3), 25.9, 25.8 (2× *t*-Bu), 17.8, 17.9 (2× Cq *t*-Bu), 12.6 (CH_3), −4.5, −4.4, −5.4, −5.5 (4× $SiCH_3$). HRMS [MH^+] $C_{25}H_{47}N_2O_7Si_2$ calcd 543.2922, found 543.2936.

*4.2.11. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-C-acetonyl-β-D-xylofuranosyl)adenine (**25**).* To a solution of **22** (2.30 g, 4.65 mmol) in DMSO (40 mL) and acetone (10 mL) was added L-proline (0.16 g, 1.39 mmol). After stirring for 24 h at room temperature, water (50 mL) was added. The aqueous phase was then extracted with EtOAc (3×50 mL) and the organic layers were combined, washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was triturated in hexane and filtered to afford 2.22 g (87%) of compound **25** as a white solid. Mp=164 °C; $[\alpha]_D^{20}$ −21(*c* 0.125, $CHCl_3$); IR (ATR) ν 2928, 1659, 1472, 1251, 1083, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.32, 8.19 (s, 2H, H-2, H-6), 5.99 (s, 1H, H-1′), 4.73 (s, 1H, H-2′), 4.15 (dd, 1H, $J_{4',5'a}$=6 Hz, $J_{5'a,5'b}$=9 Hz, H-5′a), 4.03 (t, 1H, $J_{4',5'b}$=9 Hz, $J_{5'a,5'b}$=9 Hz, H-5′b), 3.98 (dd, 1H, $J_{4',5'a}$=6 Hz, $J_{4',5'b}$=9 Hz, H-4′), 3.07 (d, 1H, $J_{A,B}$=18 Hz, H-A (CH_2CO)), 3.00 (d, 1H, $J_{A,B}$=18 Hz, H-B (CH_2CO)), 2.21 (s, 3H, CH_3), 0.92, 0.90 (s, 18H, 2× *t*-Bu), 0.20, 0.14, 0.13, 0.05 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 208.4 (CO), 155.3, 149.2, 119.3 (C-4, C-8, C-9), 152.5, 140.1 (C-2, C-6), 90.9 (C-1′), 85.2 (C-4′), 82.8 (C-2′), 79.5 (C-3′), 61.1 (C-5′), 44.9 (CH$_2$CO), 31.0 (CH$_3$), 25.9, 25.8 (2× *t*-Bu), 18.3, 17.8 (2× Cq *t*-Bu), −4.1, −5.3, −5.4 (4× SiCH$_3$). HRMS [MH$^+$] C$_{25}$H$_{46}$N$_5$O$_5$Si$_2$ calcd 552.3038, found 552.3029.

*4.2.12. 5-O-tert-Butyldimethylsilyl-1,2-O-isopropylidene-3-C-(2′-hydroxypropyl)-α-D-ribofuranose (**26a/26b**).* To a solution of compound **9a** (1.03 g, 3.10 mmol) in MeOH (10 mL) maintained between −5 and −10 °C was added portionwise NaBH$_4$ (234 mg, 6.20 mmol). After stirring for 1 h, the reaction mixture was neutralized with a Dowex 50W-X8 resin until pH 7. After filtration and elimination of the solvent under reduced pressure, 870 mg (84%) of a mixture of compound **26a/26b** (91/9 ratio) was isolated. The 1,3-diol was used in the next step without further purification. IR (NaCl) ν 3454, 2955, 2931, 2885, 2857, 1471, 1416, 1375, 1254, 1216, 1098, 1020, 998, 838 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.70 (d, 1H, $J_{1,2}$=6.0 Hz, H-1), 4.35 (d, 1H, $J_{1,2}$=6.0 Hz, H-2), 4.12 (m, 1H, −C*H*OH), 3.82 (m, 2H, H-4, H-5a), 3.68 (dd, 1H, $J_{4,5b}$=9.0 Hz, $J_{5a,5b}$=12.0 Hz, H-5b), 1.71 (d, 1H, $J_{A,B}$=12.0 Hz, H-A (C*H*$_2$CH)), 1.66 (d, 1H, $J_{A,B}$=12.0 Hz, H-B (C*H*$_2$CH)), 1.52, 1.30 (s, 6H, 2× CH$_3$), 1.13 (d, 3H, $J_{CH,CH3}$=6.0 Hz, CH$_3$), 0.83 (s, 9H, *t*-Bu), 0.02 (s, 6H, 2× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 112.4 [O*C*(CH$_3$)$_2$], 103.6 (C-1), 83.0 (C-4), 80.6 (C-2), 79.9 (C-3), 64.5 (−CHOH), 61.3 (C-5), 37.9 (−CH$_2$−), 25.8 (2× CH$_3$), 25.6 (*t*-Bu), 23.9 (CH$_3$), 18.2 (Cq *t*-Bu), −5.3, −5.4 (2× SiCH$_3$). HRMS [MNa$^+$] C$_{17}$H$_{34}$O$_6$SiNa calcd 385.2022, found 385.2010.

*4.2.13. 1,2-O-Isopropylidene-5-O-tert-butyldimethylsilyl-β-D-ribofuranosyl-3-spiro-6′-(4′-R-methyl-1′,3′,2′-dioxathiane-2′,2′-dioxide) (**28**) and 1,2-O-isopropylidene-5-O-tert-butyldimethylsilyl-β-D-ribofuranosyl-3-spiro-6′-(3′-N-tert-butoxycarbonyl-4′-S-methyl-1′,2′,3′-oxathiazinone-2′,2′-dioxide) (**27**).* To a solution of alcohol **26a/b** (333 mg, 0.92 mmol) in anhydrous THF (20 mL) was added *tert*-butyl *N*-(triethyl-ammoniumsulfonyl)carbamate (1.04 g, 3.70 mmol) at room temperature in a single portion. The resulting solution was placed immediately in an oil bath at 75 °C and stirred for 2 days. Upon completion of the reaction, the solvent was removed under reduced pressure and the residue was diluted in CH$_2$Cl$_2$, then washed with saturated aqueous NH$_4$Cl. The organic phase was dried (Na$_2$SO$_4$) and concentrated. The crude orange oil was purified by flash chromatography using first as eluent CH$_2$Cl$_2$ to afford the sulfate **28** as a clear oil (57 mg, 14.5%), then a mixture of CH$_2$Cl$_2$/EtOAc (30/1) to afford 212 mg (44%) of the sulfamidate **27** as a pale yellow oil. Compound **28**: $[\alpha]_D^{20}$ +34.9 (*c* 1.0, CHCl$_3$); IR (NaCl) ν 2955, 2931, 2858, 1721, 1397, 1257, 1168, 1099, 1016, 929, 838 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.74 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 5.13–5.27 (m, 1H, C*H*−CH$_3$), 4.42 (d, 1H, $J_{1,2}$=3.8 Hz, H-2), 4.37–4.41 (m, 1H, H-4), 4.21 (dd, 1H, $J_{4,5a}$=1.4 Hz, $J_{5a,5b}$=12.8 Hz, H-5a), 4.01 (dd, 1H, $J_{4,5b}$=3.4 Hz, $J_{5a,5b}$=12.8 Hz, H-5b), 2.51 (dd, 1H, $J_{CH,A}$=1.9 Hz, $J_{A,B}$=14.4 Hz, H-A C*H*$_2$CH), 1.98 (d, 1H, CH$_2$, $J_{CH,B}$=11.8 Hz, $J_{A,B}$=14.4 Hz, H-B C*H*$_2$CH), 1.59 (s, 3H, CH$_3$), 1.48, 1.46 (s, 3H, CH$_3$), 1.36 (s, 3H, C*H*$_3$), 0.88 (s, 9H, *t*-Bu), 0.08, 0.07 (s, 6H, 2× SiCH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 114.4 (Cq *C*(CH$_3$)$_2$), 102.3 (C-1), 90.7 (C-3), 86.1 (C-2), 80.7 [*C*H(CH$_3$)], 79.4 (C-4), 60.7 (C-5), 33.5 (CH$_2$), 27.0, 26.7 [O*C*(CH$_3$)$_2$], 25.9 (*t*-Bu), 21.1 (CH$_3$), 18.4 (Cq *t*-Bu), −5.1, −5.5 (2× SiCH$_3$). HRMS [MH$^+$] C$_{17}$H$_{36}$NO$_8$SiS calcd 442.1931, found 442.1946. Compound **27**: $[\alpha]_D{}^{20}$ +28.7 (*c* 1.0, CHCl$_3$); IR (NaCl) ν 2956, 2933, 2858, 1731, 1385, 1312, 1218, 1146, 878 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.89 (d, 1H, $J_{1,2}$=4.4 Hz, H-1), 4.63 (t, 1H, $J_{4,5}$=2.3 Hz), 4.48–4.58 (m, 2H, H-2, C*H*CH$_3$), 3.75–3.86 (m, 2H, H-5a, H-5b), 2.72 (dd, 1H, $J_{CH,A}$=4.3 Hz, $J_{A,B}$=15.2 Hz H-A −C*H*$_2$CH), 2.15 (dd, 1H, $J_{CH,B}$=5.03 Hz, $J_{A,B}$=15.2 Hz, H-A −C*H*$_2$CH), 1.58 (s, 3H, CH$_3$), 1.51 (s, 9H, *t*-Bu), 1.49 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_3$), 0.87 (s, 9H, *t*-Bu), 0.05, 0.06 (s, 6H, 2× SiCH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 150.2 (CO), 115.4 [O*C*(CH$_3$)$_2$], 105.1 (C-1), 91.2 (Cq *t*-Bu), 87.0 (C-2), 85.4 (C-4), 84.9 (C-3), 62.3 (C-5), 52.5 (*C*H(CH$_3$)), 33.2 (CH$_2$), 28.0 (*t*-Bu), 27.9, 26.9 (2× CH$_3$), 25.9 (*t*-Bu), 19.6 (CH$_3$), 18.17 (Cq *t*-Bu), -5.39, -5.55 (2× SiCH$_3$). HRMS [MNa$^+$] C$_{22}$H$_{41}$NO$_9$SiSNa calcd 546.2169, found 546.2183.

*4.2.14. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-C-acetonyl-β-D-xylofuranosyl)-3-N-methyluracil (**29**).* To a solution of compound **23** (1.0 g, 1.89 mmol) in acetone (100 mL) was added K$_2$CO$_3$ (523 mg, 3.78 mmol) and methyl iodide (1.17 mL, 18.9 mmol). After stirring for 4 h under reflux, the reaction mixture was cooled at room temperature then filtered and the solvent eliminated under reduced pressure. Hexane was added to precipitate the potassium carbonate residue. After filtration and elimination of the solvent, compound **29** was obtained as a white solid (950 mg, 93%). Mp=105–106 °C; $[\alpha]_D^{20}$ +6 (*c* 0.15, CHCl$_3$); IR (ATR) ν 3440, 2929, 2856, 1710, 1700, 1664, 1655, 1470, 1250, 1100, 1076 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.80 (d, 1H, $J_{5,6}$=8.1 Hz, H-5), 5.75 (d, 1H, $J_{1',2'}$=0.9 Hz, H-1′), 5.70 (d, 1H, $J_{5,6}$=8.1 Hz, H-6), 4.31 (d, 1H, $J_{1',2'}$=0.9 Hz, H-2′), 4.10 (dd, 1H, $J_{4',5'a}$=5.1 Hz, $J_{5'a',5'b}$=10.2 Hz, H-5′a), 3.98 (m, 2H, H-4′, H-5′b), 3.34 (s, 3H, NCH$_3$), 2.99 (d, 1H, $J_{A,B}$=18 Hz, H-A (CH$_2$CO)), 2.89 (d, 1H, $J_{A,B}$=18 Hz, H-B (CH$_2$CO)), 2.19 (s, 3H, CH$_3$), 0.89, 0.86 (s, 18H, 2× *t*-Bu), 0.23, 0.15, 0.13, 0.08 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 209.1 (CO), 163.1, 151.1 (C-2, C-4), 138.9 (C-6), 100.3 (C-5), 91.9 (C-1′), 84.4 (C-4′), 82.3 (C-2′), 79.5 (C-3′), 60.8 (C-5′), 44.2 (CH$_2$CO), 30.9 (CH$_3$), 27.5 (NCH$_3$), 25.9, 25.8 (2× *t*-Bu), 18.2, 17.9 (2× Cq *t*-Bu), −4.3, −5.4, −5.5, −5.6 (4× SiCH$_3$). HRMS [MNa$^+$] C$_{25}$H$_{46}$N$_2$O$_7$Si$_2$Na calcd 565.2741, found 565.2747.

*4.2.15. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-C-acetonyl-β-D-xylofuranosyl)-3-N-tert-butoxycarbonyluracil (**30**).* To a solution of **23** (1.14 g, 2.15 mmol) in 20 mL of a mixture of pyridine/CH$_2$Cl$_2$ (8/2) was added Boc$_2$O (1.88 g, 8.62 mmol). The reaction mixture was stirred at room temperature for overnight. After elimination of the solvent under reduced pressure and flash chromatography, compound **30** was isolated as a white solid (1.0 g, 74%). Mp=51–52 °C; $[\alpha]_D^{20}$+20 (*c* 0.49, CH$_2$Cl$_2$); IR (ATR) ν 2930, 2857, 1786, 1718, 1678, 1445, 1371, 1252, 1149, 1113, 1086, 837 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.84 (d, 1H, $J_{5,6}$=8.3 Hz, H-6), 5.76 (d, 1H, $J_{1',2'}$=1.2 Hz, H-1′), 5.70 (d, 1H, H-5), 4.30 (d, 1H, H-2′), 4.10 (dd, 1H, $J_{4',5'a}$=5.3 Hz, $J_{5'a,5'b}$=10.5 Hz, H-5′a), 4.01–3.92 (m, 2H, H-4′, H-5′b), 3.01 (d, 1H, $J_{A,B}$=18.2 Hz, H-A C*H*$_2$CO), 2.89 (d, 1H, $J_{A,B}$=18.2 Hz, H-B C*H*$_2$CO), 2.21 (s, 3H, CH$_3$), 1.63 (s, 9H, *t*-Bu), 0.95, 0.91 (s, 18H, 2× *t*-Bu), 0.20, 0.16, 0.12, 0.07 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 208.8 (CO), 160.1, 147.9, 147.3 (C-2, C-4, CO), 139.9 (C-6), 100.2 (C-5), 90.8 (C-1′), 86.4 (Cq *t*-Bu), 83.8 (C-4′), 81.9 (C-2′), 79.0 (C-3′), 60.4 (C-5′), 43.7 (CH$_2$CO), 30.5 (CH$_3$), 27.5, 25.6 (3× *t*-Bu), 17.7, 17.0 (2× Cq *t*-Bu), −4.9, −5.9, −6.0, −6.1 (4× SiCH$_3$). HRMS [MNa$^+$] C$_{29}$H$_{52}$N$_2$O$_9$Si$_2$Na calcd 651.3109, found 651.3088.

*4.2.16. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-(S)-C-isopropanoyl-β-D-xylofuranosyl)-3′-N-methyluracil (**31a**) and 1-(2′,5′-bis-O-tert-butyldimethylsilyl-3′-(R)-C-isopropanoyl-β-D-xylofuranosyl)-3′-N-methyluracil (**31b**).* To a solution of compound **29** (950 mg, 1.75 mmol) in MeOH (20 mL) maintained between −5 and −10 °C was added portionwise NaBH$_4$ (132 mg, 3.5 mmol). After stirring for 1 h, the reaction mixture was neutralized with a Dowex 50W-X8 resin until pH 7. After filtration and elimination of the solvent under reduced pressure, the crude was triturated in hexane then filtered to afford 750 mg (79%) of a mixture of compound **31a/31b** (91/9 ratio). Separation by HPLC (CH$_3$CN, 20 mL/min, 254 nm, prevail C18 5 μ) afforded, respectively, compound **31a** and **31b** as white solid. Compound **31a**: mp=164–165 °C; $[\alpha]_D^{20}$ +33 (*c* 0.14, CHCl$_3$); IR (ATR) ν 3577, 3422, 2956, 2931, 2856, 1706, 1661, 1470, 1462, 1247, 1114, 1108, 1075 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.89 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.73 (d, 1H, $J_{1',2'}$=2.3 Hz, H-1′), 5.70 (d, 1H, H-5), 4.24 (dd, 1H, $J_{4',5'a}$=2.3 Hz, $J_{5'a,5'b}$=12.0 Hz, H-5′a), 4.20 (m, 1H, H-3‴), 4.12 (d, 1H, $J_{1',2'}$=2.3 Hz, H-2′), 4.08 (dd, 1H, $J_{4',5'b}$=2.3 Hz, $J_{5'a,5'b}$=12.0 Hz, H-5′b), 3.99 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=2.3 Hz, H-4′), 2.00 (dd, 1H, $J_{3''a,3'''}$=10.2 Hz, $J_{3''a,3''b}$=14.8 Hz, H-3″a), 1.65 (dd, 1H, $J_{3''b,3'''}$=2.5 Hz, $J_{3''a,3''b}$=14.8 Hz, H-3″b), 1.27 (d, 3H, $J_{CH,3'''}$=6.2 Hz, CH$_3$), 0.92, 0.89 (s, 18H, 2× *t*-Bu), 0.18, 0.17, 0.15, 0.10 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 163.2, 151.1 (C-2, C-4), 138.6 (C-6), 100.3 (C-5), 90.7 (C-1′), 83.6, 83.1 (C-4′, C-2′), 81.3 (C-3′), 64.9 (C-3‴), 62.7 (C-5′), 39.5 (C-3″), 27.5 (NCH$_3$), 25.8, 24.3 (2× *t*-Bu), 24.3 (CH$_3$), 18.1, 18.0 (2× Cq *t*-Bu), −4.7, −5.0, −5.5, −5.6 (4× SiCH$_3$). HRMS [MNa$^+$] $C_{25}H_{48}N_2O_7Si_2Na$ calcd 567.2898, found 567.2920. Compound **31b**: mp=104–105 °C; $[\alpha]_D^{20}$ +65 (*c* 0.07, CHCl$_3$); IR (ATR) ν 3359, 2955, 2929, 2857, 1705, 1655, 1462, 1251, 1102 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.90 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.71 (d, 1H, $J_{5,6}$=8.2 Hz, H-5), 5.70 (s, 1H, H-1′), 4.29 (dd, 1H, $J_{4',5'a}$=2.9 Hz, $J_{5'a,5'b}$=12.0 Hz, H-5′a), 4.25 (s, 1H, H-2′), 4.15 (dd, 1H, $J_{4',5'b}$=2.9 Hz, $J_{5'a,5'b}$=12.0 Hz, H-5′b), 4.14 (m, 1H, H-3‴), 3.94 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=2.9 Hz, H-4′), 3.37 (s, 3H, CH$_3$), 1.93 (dd, 1H, $J_{3''a,3'''}$=0.7 Hz, $J_{3''a,3''b}$=14.2 Hz, H-3″a), 1.60 (dd, 1H, $J_{3''b,3'''}$=10.3 Hz, $J_{3''a,3''b}$=14.2 Hz, H-3″b), 1.23 (d, 3H, $J_{CH,3'''}$=6.1 Hz, CH$_3$), 0.95, 0.94 (s, 18H, 2× *t*-Bu), 0.32, 0.19, 0.18, 0.14 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 163.3, 151.0 (C-2, C-4), 138.7 (C-6), 100.0 (C-5), 92.5 (C-1′), 83.4 (C-3′), 83.4 (C-4′), 81.2 (C-2′), 66.1 (C-3‴), 61.9 (C-5′), 38.4 (C-3″), 27.5 (NCH$_3$), 25.8, 25.7 (2× *t*-Bu), 23.9 (CH$_3$), 18.1, 17.9 (2× Cq *t*-Bu), −3.7, −5.5, −5.7, −5.8 (4× SiCH$_3$). HRMS [MNa$^+$] $C_{25}H_{48}N_2O_7Si_2Na$ calcd 567.2898, found 567.2918.

*4.2.17. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-(S)-C-isopropanoyl-β-D-xylofuranosyl)-3-N-tert-butoxycarbonyluracil (**32a**) and 1-(2′,5′-bis-O-tert-butyldimethylsilyl-3′-(R)-C-isopropanoyl-β-D-xylofuranosyl)-3-N-tert-butoxycarbonyluracil (**32b**).* To a solution of **30** (930 mg, 1.48 mmol) in MeOH (15 mL) maintained between −5 and −10 °C was added portionwise NaBH$_4$ (56 mg, 1.48 mmol). After stirring for 1 h, the reaction mixture was neutralized with a Dowex 50W-X8 resin until pH 7. After filtration and elimination of the solvent under reduced pressure, the crude was triturated in hexane then filtered to afford 895 mg (96%) of a mixture of compound **32a**/**32b** (78/22 ratio). Purification by HPLC (CH$_3$CN, 20 mL/min, 254 nm) afforded **32a** as an incolor liquid. $[\alpha]_D^{20}$ +25 (*c* 0.40, CH$_2$Cl$_2$); IR (ATR) ν 3390, 2930, 2858, 1786, 1719, 1670, 1452, 1372, 1253, 1148, 1062, 837 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.90 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.70 (d, 1H, $J_{1',2'}$=2.9 Hz, H-1′), 5.67 (d, 1H, H-5), 4.20 (m, 2H, H-3‴, H-5′a), 4.10 (d, 1H, H-2′), 4.06 (dd, 1H, $J_{4',5'b}$=2.4 Hz, $J_{5'a,5'b}$=11.8 Hz, H-5′a), 3.99 (t, 1H, $J_{4',5'b}$=$J_{4',5'a}$=2.4 Hz, H-4′), 2.00 (dd, 1H, $J_{3''a,3'''}$=10.2 Hz, $J_{3''a,3''b}$=14.9 Hz, H-3″a), 1.66 (m, 1H, H-3″b), 1.60 (s, 9H, *t*-Bu), 1.27 (d, 3H, $J_{CH,CH3}$=6.2 Hz, CH$_3$), 0.95, 0.91 (s, 18H, 2× *t*-Bu), 0.17, 0.16, 0.15, 0.14 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 160.1, 147.9, 147.3 (C-2, C-4, CO), 139.5 (C-6), 100.3 (C-5), 89.1 (C-1′), 86.0 (Cq *t*-Bu), 83.4, 83.1 (C-2′, C-4′), 80.7 (C-3′), 64.3 (C-3‴), 62.3 (C-5′), 39.0 (C-3″), 26.9, 25.3, 25.2 (3× *t*-Bu), 23.9 (CH$_3$), 17.6, 17.5 (2× Cq *t*-Bu), −5.0, −5.5, −6.1, −6.2 (4× SiCH$_3$). HRMS [MNa$^+$] $C_{29}H_{54}N_2O_9Si_2Na$ calcd 653.3266, found 653.3238.

*4.2.18. 1-[(2′,5′-Bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)-3-N-methyluracil]-3′-spiro-6″-(3″-N-tert-butoxycarbonyl-4″-R-methyl-1″,2″,3″-oxathiazinone-2″,2″-dioxide) (**33**) and 1-[(2′,5′-bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)-3-N-methyluracil]-3′-spiro-6″-(4″-R-methyl-1″,3″,2″-dioxathiane-2″,2″-dioxide) (**34**).* To a solution of **31a**/**31b** (300 mg, 0.55 mmol) in distilled THF (15 mL) was added Burgess reagent (620 mg, 2.2 mmol). After stirring overnight at 80 °C under a nitrogen atmosphere, the solvent was eliminated under reduced pressure and the crude was purified by flash chromatography (EtOAc/cyclohexane, 10/90) to afford 266 mg of an unseparable mixture of **34** (62%) and **33** (16%) (3.4/1 ratio). The mixture was separated by HPLC (CH$_3$CN, 20 mL/min, 254 nm). Compound **33**: mp=59–60 °C; $[\alpha]_D^{20}$ +25 (*c* 0.13, CHCl$_3$); IR (ATR) ν 2954, 2930, 2858, 1732, 1709, 1664, 1461, 1409, 1291, 1253, 1146, 1109 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.61 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.81 (d, 1H, $J_{5,6}$=8.2 Hz, H-5), 5.76 (d, 1H, $J_{1',2'}$=1.6 Hz, H-1′), 4.66 (d, 1H, $J_{1',2'}$=1.6 Hz, H-2′), 4.63 (m, 1H, C*H*CH$_3$), 4.19 (dd, 1H, $J_{4',5'a}$=5.4 Hz, $J_{4',5'b}$=4.4 Hz, H-4′), 4.13 (dd, 1H, $J_{4',5'a}$=5.4 Hz, $J_{5'a,5'b}$=10.9 Hz, H-5′a), 4.03 (dd, 1H, $J_{4',5'b}$=4.4 Hz, $J_{5'a,5'b}$=10.9 Hz, H-5′b), 3.35 (s, 3H, NCH$_3$), 2.58 (dd, 1H, $J_{A,CH}$=6.7 Hz, $J_{A,B}$=15.0 Hz, H-A (C*H*$_2$CH)), 2.49 (dd, 1H, $J_{B,CH}$=8.3 Hz, $J_{A,B}$=15.0 Hz, H-B (C*H*$_2$CH)), 1.51 (s, 3H, CH$_3$), 1.40 (d, 3H, $J_{CH,CH3}$=6.5 Hz, CH$_3$), 0.95, 0.94 (s, 18H, 2× *t*-Bu), 0.26, 0.22, 0.17, 0.16 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 162.8, 151.2, 149.4 (C-2, C-4, CO), 137.1 (C-6), 101.2 (C-5), 93.7 (C-3′), 90.9 (C-1′), 85.4 (C-4′), 79.0 (C-2′), 60.1 (C-5′), 52.0 (−CH−CH$_2$), 28.9 (CH$_2$−CH−), 27.8 (*t*-Bu), 27.5 (NCH$_3$), 25.8, 25.7 (2× *t*-Bu), 20.7 (CH$_3$), 18.3, 17.9 (2× Cq *t*-Bu), −4.1, −5.4, −5.5, −5.7 (4× SiCH$_3$). HRMS [MNa$^+$] $C_{30}H_{55}N_3O_{10}Si_2SNa$ calcd 728.3044, found 728.3064. Compound **34**: mp=59–60 °C; $[\alpha]_D^{20}$ +13 (*c* 0.1, CHCl$_3$); IR (ATR) ν 2955, 2930, 2857, 1708, 1665, 1458, 1403, 1253, 1203, 1093 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.40 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.83 (d, 1H, $J_{5,6}$=8.2 Hz, H-5), 5.78 (s, 1H, H-1′), 5.19 (s, 1H, H-2′), 4.93 (ddq, 1H, $J_{CH,A}$=12.4 Hz, $J_{CH,B}$=2.3 Hz, $J_{CH,CH3}$=6.2 Hz, −C*H*−CH$_2$), 4.22 (dd, 1H, $J_{4',5'a}$=7.6 Hz, $J_{4',5'b}$=5.0 Hz, H-4′), 4.06 (dd, 1H, $J_{4',5'a}$=7.6 Hz, $J_{5'a',5'b}$=10.3 Hz, H-5′a), 3.98 (dd, 1H, $J_{4',5'b}$=5.0 Hz, $J_{5'a',5'b}$=10.3 Hz, H-5′b), 2.45 (dd, 1H, $J_{CH,A}$=12.5 Hz, $J_{A,B}$=15 Hz, H-A C*H*$_2$CH−), 2.33 (d, 1H, $J_{CH,B}$=2.3 Hz, $J_{A,B}$=15 Hz, H-B C*H*$_2$CH−), 1.49 (m, 3H, $J_{CH,CH3}$=6.2 Hz, C*H*$_3$CH−), 0.95, 0.94 (s, 18H, 2× *t*-Bu), 0.30, 0.22, 0.16, 0.15 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 162.7, 151.0 (C-2, C-4), 136.7 (C-6), 101.5 (C-5), 96.1 (C-3′), 92.0 (C-1′), 83.9 (C-4′), 79.8 (−*C*HCH$_3$), 77.2 (C-3′), 59.4 (C-5′), 29.6 (*C*H$_2$CH−), 27.9 (NCH$_3$), 25.9, 25.7 (2× *t*-Bu), 20.6 (CH$_3$), 18.2, 17.9 (2× Cq *t*-Bu), −4.2, −5.5, −5.6 (4× SiCH$_3$). HRMS [MNa$^+$] $C_{25}H_{46}N_2O_9SSi_2Na$ calcd 629.2360, found 629.2358.

*4.2.19. 1-[(2′,5′-Bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)-3-N-tert-butoxycarbonyluracil]-3′-spiro-6″-(3″-N-tert-butoxycarbonyl-4″-R-methyl-1″,2″,3″-oxathiazinone-2″,2″-dioxide) (**35**) and 1-[(2′,5′-bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)-3-N-tert-butoxycarbonyluracil]-3′-spiro-6″-(4″-R-methyl-1″,3″,2″-dioxathiane-2″,2″-dioxide) (**36**).* To a solution of **32a** (400 mg, 0.63 mmol) in distilled THF (15 mL) was added Burgess reagent (708 mg, 2.52 mmol). After stirring overnight at 80 °C under a nitrogen atmosphere, the solvent was eliminated under reduced pressure and the crude was purified by flash chromatography (EtOAc/cyclohexane, 10/90) to afford 300 mg of an unseparable mixture of sulfate **36** (43%) and sulfamidate **35** (22%) (1.7/1 ratio). The mixture was separated by HPLC (CH$_3$CN, 20 mL/min, 254 nm). Compound **35**: mp=79–80 °C; $[\alpha]_D^{20}$ +36 (*c* 0.15, CH$_2$Cl$_2$); IR (ATR) ν 2932, 2858, 1787, 1726, 1680, 1442, 1388, 1371, 1253, 1147, 837 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.54 (d, 1H, $J_{5,6}$=8.3 Hz, H-6), 5.62 (d, 1H, $J_{1',2'}$=2.8 Hz, H-1′), 5.60 (d, 1H, H-5), 4.44 (m, 2H, C*H*CH$_3$, H-2′), 3.98 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=4.3 Hz, H-4′), 3.92 (dd, 1H, $J_{5'a,5'b}$=11.2 Hz, H-5′a), 3.86 (dd, 1H, H-5′b), 2.41 (dd, 1H, $J_{A,CH}$=6.6 Hz, $J_{A,B}$=15.0 Hz, H-A (C*H*$_2$CH)), 2.34 (dd, 1H, $J_{B,CH}$=8.8 Hz, $J_{A,B}$=15.0 Hz, H-B (C*H*$_2$CH)), 1.43, 1.36 (s, 18H, 2× *t*-Bu), 1.22 (d, 3H, $J_{CH,CH3}$=6.4 Hz, CH$_3$), 0.78, 0.75 (s, 18H, 2× *t*-Bu), 0.02, 0.01, −0.01, −0.02 (s, 12H, 4× SiCH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 159.7, 148.9, 148.0, 147.0 (C-2, C-4, 2× CO), 138.3 (C-6), 101.3 (C-5), 92.6 (C-3′), 89.0 (C-1′), 86.0 (Cq *t*-Bu), 84.7 (C-4′), 78.7 (C-2′), 60.0 (C-5′), 51.6 (−CH−CH$_2$), 29.2 (*C*H$_2$−CH−), 27.3, 26.9, 25.3,25.2 (4× *t*-Bu), 20.2 (CH$_3$), 17.8, 17.4 (2× Cq *t*-Bu), −4.9, −5.8, −6.1 (4× SiCH$_3$). HRMS [MNa$^+$] $C_{34}H_{61}N_3O_{12}Si_2SNa$ calcd 814.3412, found 814.3406. Compound **36**: mp=67–68 °C; $[\alpha]_D^{20}$ +28 (*c* 0.16, CH$_2$Cl$_2$); IR (ATR) ν 2931, 2858, 1787, 1719, 1679, 1442, 1405, 1252, 1205, 1149, 1101, 870 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.40 (d, 1H, $J_{5,6}$=9.0 Hz, H-6), 5.80 (m, 2H, H-5, H-1′), 5.14 (d, 1H, $J_{1',2'}$=1.4 Hz, H-2′), 4.94 (ddq, 1H, $J_{CH,A}$=12.3 Hz, $J_{CH,B}$=2.2 Hz, $J_{CH,CH3}$=6.1 Hz, −C*H*−CH$_2$), 4.17 (dd, 1H, $J_{4',5'a}$=7.4 Hz,

$J_{4',5'b}$=4.9 Hz, H-4′), 4.04 (dd, 1H, $J_{4',5'a}$=7.4 Hz, $J_{5'a',5'b}$=10.4 Hz, H-5′a), 3.96 (dd, 1H, $J_{4',5'b}$=4.9 Hz, $J_{5'a',5'b}$=10.4 Hz, H-5′b), 2.46 (dd, 1H, $J_{CH,A}$=11.8 Hz, $J_{A,B}$=15.0 Hz, H-A CH_2CH–), 2.31 (d, 1H, $J_{CH,B}$=2.2 Hz, $J_{A,B}$=15.0 Hz, H-B CH_2CH–), 1.60 (s, 9H, *t*-Bu), 1.48 (d, 3H, $J_{CH,CH3}$=6.2 Hz, CH_3CH–), 0.94, 0.91 (s, 18H, 2× *t*-Bu), 0.24, 0.20, 0.14, 0.13 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.6, 147.9, 146.9 (C-2, C-4, CO), 137.7 (C-6), 101.6 (C-5), 95.6 (C-3′), 90.9 (C-1′), 86.0 (Cq *t*-Bu), 83.2 (C-4′), 79.4 (–$CHCH_3$), 77.1 (C-2′), 58.9 (C-5′), 29.2 (CH_2CH–), 26.9, 25.3, 25.1 (3× *t*-Bu), 20.1 (CH_3), 17.7, 17.4 (2× Cq *t*-Bu), −4.9, −6.0, −6.1 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{29}H_{52}N_2O_{11}SSi_2Na$ calcd 715.2728, found 715.2729.

*4.2.20. 1-[(2′,5′-Bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)uracil]-3′-spiro-6″-(4″-R-methyl-1″,2″,3″-oxathiazinone-2″,2″-dioxide) (**37**) and 1-[(2′,5′-bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl) uracil]-3′-spiro-6″-(3″-N-tert-butoxycarbonyl-4″-R-methyl-1″,2″,3″-oxathiazinone-2″,2″-dioxide) (**38**).* To a solution of **35** (52 mg, 0.066 mmol) in CH_2Cl_2 (10 mL) was added TFA (97.6 μL, 1.31 mmol). After stirring at 50 °C overnight, the solvent was eliminated under reduced pressure and the crude was purified by flash chromatography (EtOAc/cyclohexane, 30/70) to afford 29 mg of an unseparable mixture of **37** and **38**. The mixture was separated by HPLC (CH_3CN, 20 mL/min, 254 nm) to afford successively **37** (18 mg, 47%) and **38** (11 mg, 24%). Compound **37**: mp=108–109 °C; $[\alpha]_D^{20}$ +25 (*c* 0.14, CH_2Cl_2); IR (ATR) ν 2930, 2857, 1683, 1462, 1376, 1255, 1099, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.81 (d, 1H, H-5), 5.77 (d, 1H, $J_{1',2'}$=0.8 Hz, H-1′), 5.21 (d, 1H, H-2′), 4.94 (ddq, 1H, $J_{CH,CH3}$=6.1 Hz, $J_{CH,A}$=12.3 Hz, $J_{CH,B}$=2.3 Hz, –$CHCH_3$), 4.23 (dd, 1H, $J_{4',5'a}$=7.6 Hz, $J_{4',5'b}$=5.0 Hz, H-4′), 4.07 (dd, 1H, $J_{5'a,5'b}$=10.3 Hz, H-5′a), 3.99 (dd, 1H, H-5′b), 2.46 (dd, 1H, $J_{A,B}$=14.9 Hz, H-A CH_2CH–), 2.33 (dd, 1H, H-B CH_2CH–), 1.49 (d, 3H, CH_3), 0.96, 0.93 (s, 18H, 2× *t*-Bu), 0.30, 0.21, 0.16, 0.14 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6, 149.7 (C-2, C-4), 138.5 (C-6), 101.7 (C-5), 95.6 (C-3′), 91.0 (C-1′), 83.4 (C-4′), 79.3 (–$CHCH_3$), 76.1 (C-2′), 58.9 (C-5′), 29.1 (–$CHCH_2$), 25.3, 25.2 (3× *t*-Bu), 20.1 (CH_3), 17.7, 17.4 (2× Cq *t*-Bu), −4.7, −6.0 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{24}H_{45}N_3O_8SSi_2Na$ calcd 614.2364, found 614.2358. Compound **38**: Mp=81–82 °C; $[\alpha]_D{}^{20}$ +24 (*c* 0.09, CH_2Cl_2); IR (ATR) ν 2931, 2858, 1728, 1686, 1462, 1392, 1296, 1258, 1186, 1147, 1120, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.81 (d, 1H, H-5), 5.79 (d, 1H, $J_{1',2'}$=0.8 Hz, H-1′), 5.24 (d, 1H, H-2′), 4.96 (ddq, 1H, $J_{CH,CH3}$=6.2 Hz, $J_{CH,A}$=12.4 Hz, $J_{CH,B}$=2.0 Hz, –$CHCH_3$), 4.30 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=5.7 Hz, H-4′), 4.09 (d, 2H, H-5′a, H-5′b), 2.41 (dd, 1H, $J_{A,B}$=14.9 Hz, H-A CH_2CH–), 2.22 (dd, 1H, H-B CH_2CH–), 1.53 (d, 3H, CH_3), 0.94 (s, 9H, *t*-Bu), 0.31, 0.22 (s, 6H, 2× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.0, 150.1 (C-2, C-4), 139.1 (C-6), 102.1 (C-5), 96.6 (C-3′), 91.6 (C-1′), 84.5 (C-4′), 79.9 (–$CHCH_3$), 77.1 (C-2′), 59.4 (C-5′), 29.6 (–$CHCH_2$), 25.6 (*t*-Bu), 20.6 (CH_3), 17.9 (Cq *t*-Bu), −4.2, −5.5 (2× $SiCH_3$). HRMS [MNa$^+$] $C_{29}H_{53}N_3O_{10}SSi_2Na$ calcd 714.2888, found 714.2911.

*4.2.21. 1-[(2′,5′-Bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)uracil]-3′-spiro-6″-(4″-R-methyl-1″,3″,2″-dioxathiane-2″,2″-dioxide) (**39**) and 1-[(2′-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)uracil]-3′-spiro-6″-(4″-R-methyl-1″,3″,2″-dioxathiane-2″,2″-dioxide) (**40**).* To a solution of **36** (73 mg, 0.105 mmol) in CH_2Cl_2 (15 mL) was added TFA (0.15 mL, 2.10 mmol). After stirring at 50 °C overnight, the solvent was eliminated under reduced pressure and the crude was purified by flash chromatography (EtOAc/cyclohexane, 30/70) to afford 59 mg of an unseparable mixture of **39** and **40**. The mixture was separated by HPLC (CH_3CN, 20 mL/min, 254 nm) to afford successively **40** (12 mg, 24%) and **39** (25 mg, 40%). Compound **39**: mp=85–87 °C; $[\alpha]_D^{20}$ +19 (*c* 0.17, CH_2Cl_2); IR (ATR) ν 2930, 2858, 1685, 1458, 1405, 1254, 1205, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.50 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.80 (dd, 1H, $J_{5,6}$=8.2 Hz, $J_{5,NH}$=1.9 Hz, H-5), 5.74 (s, 1H, H-1′), 5.24 (s, 1H, H-2′), 4.21 (dd, 1H, $J_{4',5'a}$=7.1 Hz, $J_{4',5'b}$=5.1 Hz, H-4′), 4.08 (dd, 1H, $J_{5'a,5'b}$=10.6 Hz, H-5′a), 3.97 (dd, 1H, H-5′b), 3.75 (m, 1H, –$CHCH_3$), 2.24 (dd, 1H, $J_{A,B}$=14.7 Hz, $J_{CH,A}$=2.4 Hz, H-A CH_2CH–), 1.90 (dd, 1H, $J_{CH,B}$=2.4 Hz, H-B CH_2CH–), 1.31 (d, 3H, $J_{CH3,CH}$=6.5 Hz, CH_3), 0.97, 0.95 (s, 9H, *t*-Bu), 0.31, 0.22, 0.16 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.1, 150.1 (C-2, C-4), 139.5 (C-6), 101.6 (C-5), 95.4 (C-3′), 91.9 (C-1′), 84.7 (C-4′), 77.1 (C-2′), 59.6 (C-5′), 48.9 (–$CHCH_3$), 30.0 (–$CHCH_2$), 25.7 (2× *t*-Bu), 20.9 (CH_3), 18.2, 17.9 (2× Cq *t*-Bu), −4.2, −5.4, −5.5 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{24}H_{44}N_2O_9SSi_2Na$ calcd 615.2204, found 615.2194. Compound **40**: mp=103–104 °C; $[\alpha]_D{}^{20}$ +16 (*c* 0.11, CH_2Cl_2); IR (ATR) ν 2933, 2859, 1685, 1458, 1399, 1263, 1204, 1122, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.77 (dd, 1H, $J_{5,6}$=8.2 Hz, $J_{5,NH}$=1.7 Hz, H-5), 5.75 (d, 1H, $J_{1',2'}$=1.7 Hz, H-1′), 4.71 (d, 1H, H-2′), 4.67 (m, 1H, –$CHCH_3$), 4.20 (dd, 1H, $J_{4',5'a}$=5.3 Hz, $J_{4',5'b}$=4.5 Hz, H-4′), 4.14 (dd, 1H, $J_{5'a,5'b}$=11.0 Hz, H-5′a), 4.04 (dd, 1H, H-5′b), 2.59 (dd, 1H, $J_{A,B}$=15.0 Hz, $J_{CH,A}$=6.7 Hz, H-A CH_2CH–), 2.48 (dd, 1H, $J_{CH,B}$=8.2 Hz, H-B CH_2CH–), 1.54 (s, 9H, *t*-Bu), 1.42 (d, 3H, $J_{CH3,CH}$=6.5 Hz, CH_3), 0.97, 0.95 (s, 18H, 2× *t*-Bu), 0.25, 0.22, 0.18, 0.17 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.7, 150.1, 149.4 (C-2, C-4, CO), 139.5 (C-6), 101.8 (C-5), 93.6 (C-3′), 90.3 (C-1′), 85.5, 85.4 (C-4′, Cq *t*-Bu), 78.9 (C-2′), 60.1 (C-5′), 52.0 (–$CHCH_3$), 29.0 (–$CHCH_2$), 27.8, 25.8, 25.7 (3× *t*-Bu), 20.7 (CH_3), 18.3, 17.9 (2× Cq *t*-Bu), −4.2, −5.3, −5.5, −5.6 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{18}H_{30}N_2O_9SSi_2Na$ calcd 501.1339, found 501.1329.

*4.2.22. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-C-acetonyl-β-D-xylofuranosyl)-3-N-tert-butoxycarbonylthymine (**41**).* To a solution of **24** (1.80 g, 3.33 mmol) in 50 mL of a mixture of pyridine/CH_2Cl_2 (8/2) was added Boc_2O (1.45 g, 6.67 mmol). The reaction mixture was stirred at room temperature for overnight. After elimination of the solvent under reduced pressure and flash chromatography, compound **41** was isolated as a white solid (1.98 g, 92%). Mp=55–56 °C; $[\alpha]_D^{20}$ ±5 (*c* 0.12, $CHCl_3$); IR (ATR) ν 2954, 2929, 2857, 2359, 1785, 1710, 1665, 1462, 1442, 1370, 1255, 1235, 1140, 1109, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.63 (s, 1H, H-6), 5.77 (s, 1H, H-1′), 4.33 (br s, 1H, OH), 4.24 (s, 1H, H-2′), 4.05 (dd, 1H, $J_{4',5'a}$=5.0 Hz, $J_{5'a,5'b}$=10.8 Hz, H-5′a), 3.94 (dd, 1H, $J_{4',5'b}$=5.0 Hz, $J_{5'a,5'b}$=10.8 Hz, H-5′b), 3.86 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=5.0 Hz, H-4′), 2.97 (d, 1H, $J_{A,B}$=18 Hz, H-A (CH_2CO)), 2.87 (d, 1H, $J_{A,B}$=18 Hz, H-B (CH_2CO)), 2.18 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.59 (s, 9H, *t*-Bu), 0.92, 0.85 (s, 18H, 2× *t*-Bu), 0.16, 0.12, 0.08, 0.01 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 209.3 (CO), 161.4, 148.4, 147.9 (C-2, C-4, CO), 136.3 (C-6), 109.3 (C-5), 91.0 (C-1′), 86.2 (Cq *t*-Bu), 83.9 (C-4′), 82.6 (C-3′), 79.4 (C-2′), 60.9 (C-5′), 44.1 (CH_2CO), 30.8 (CH_3), 27.4, 25.8, 25.7 (3× *t*-Bu), 18.2, 17.8 (2× Cq *t*-Bu), 12.5 (CH_3), −4.5, −5.4, −5.5, −5.6 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{30}H_{54}N_2O_9Si_2Na$ calcd 665.3266, found 665.3281.

*4.2.23. 1-(2′,5′-Bis-O-tert-butyldimethylsilyl-3′-(S)-C-isopropanoyl-β-D-xylofuranosyl)-3′-N-tert-butoxycarbonylthymine (**42a**) and 1-(2′,5′-bis-O-tert-butyldimethylsilyl-3′-(R)-C-isopropanoyl-β-D-xylofuranosyl)-3′-N-tert-butoxycarbonylthymine (**42b**).* To a solution of compound **41** (720 mg, 1.12 mmol) in MeOH (10 mL) maintained between −5 and −10 °C was added portionwise $NaBH_4$ (43 mg, 1.12 mmol). After stirring for 1 h, the reaction mixture was neutralized with a Dowex 50W-X8 resin until pH 7. After filtration and elimination of the solvent under reduced pressure, the crude was triturated in hexane then filtered to afford 518 mg (72%) of a mixture of compound **42a**/**42b** (84/16 ratio). Separation by HPLC (CH_3CN, 20 ml/min, 254 nm) afforded, respectively, compound **42a** and **42b** as white solid. Compound **42a**: mp=179–180 °C; $[\alpha]_D^{20}$ +25 (*c* 0.12, $CHCl_3$); IR (ATR) ν 3562, 3436, 2958, 2931, 2856, 1780, 1707, 1649, 1464, 1369, 1254, 1152, 1137, 1114, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60 (s, 1H, H-6), 5.77 (d, 1H, $J_{1',2'}$=3.7 Hz, H-1′), 4.20 (m, 1H, H-3‴), 4.19 (dd, 1H, $J_{4',5'a}$=2.6 Hz, $J_{5'a,5'b}$=11.7 Hz, H-5′a), 4.06 (dd, 1H, $J_{4',5'b}$=2.6 Hz, $J_{5'a,5'b}$=11.7 Hz, H-5′b), 4.04 (d, 1H,

$J_{1',2'}$=3.7 Hz, H-2′), 3.95 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=2.6 Hz, H-4′), 2.00 (dd, 1H, $J_{3''a,3'''}$=10.2 Hz, $J_{3''a,3''b}$=15.0 Hz, H-3″a), 1.95 (s, 3H, CH_3), 1.66 (dd, 1H, $J_{3''b,3'''}$=2.2 Hz, $J_{3''a,3''b}$=15.0 Hz, H-3″b), 1.64 (s, 9H, *t*-Bu), 1.28 (d, 3H, $J_{CH,3'''}$=6.2 Hz, CH_3), 0.98, 0.92 (s, 18H, 2× *t*-Bu), 0.19, 0.14, 0.11 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.3, 148.6, 148.5 (C-2, C-4, CO), 135.5 (C-6), 109.9 (C-5), 88.7 (C-1′), 86.4 (Cq *t*-Bu), 83.4, 82.6 (C-2′, C-4′), 81.3 (C-3′), 64.8 (C-3‴), 62.9 (C-5′), 39.9 (C-3″), 27.4, 25.9 (2× *t*-Bu), 24.4 (CH_3), 18.1, 18.0 (2× Cq *t*-Bu), 12.5 (CH_3), −4.6, −4.9, −5.4, −5.5 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{30}H_{56}N_2O_9Si_2Na$ calcd 667.3422, found 667.3395. Compound **42b**: mp=184–185 °C; $[\alpha]_D^{20}$ +48 (*c* 0.07, $CHCl_3$); IR (ATR) ν 3485, 2956, 2929, 2857, 1779, 1707, 1662, 1463, 1370, 1256, 1152, 1143, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H, H-6), 5.74 (s, 1H, H-1′), 5.51 (s, 1H, OH), 4.23 (dd, 1H, $J_{4',5'a}$=3.0 Hz, $J_{5'a,5'b}$=12.0 Hz, H-5′a), 4.19 (s, 1H, H-2′), 4.18 (m, 1H, H-3‴), 4.14 (dd, 1H, $J_{4',5'b}$=3.0 Hz, $J_{5'a,5'b}$=12.0 Hz, H-5′b), 3.84 (t, 1H, $J_{4',5'a}$=$J_{4',5'b}$=3.0 Hz, H-4′), 1.93 (m, 4H, H-3″a, CH_3), 1.64 (s, 10H, H-3″b, *t*-Bu), 1.24 (d, 3H, $J_{CH,3'''}$=6.3 Hz, CH_3), 0.96, 0.91 (s, 18H, 2× *t*-Bu), 0.23, 0.18, 0.17, 0.16 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.5, 148.5, 148.0 (C-2, C-4, CO), 136.4 (C-6), 109.0 (C-5), 91.8 (C-1′), 86.4 (Cq *t*-Bu), 83.2 (C-3′), 82.9 (C-4′), 81.7 (C-2′), 66.1 (C-3‴), 61.8 (C-5′), 38.3 (C-3″), 27.5, 25.8 (2× *t*-Bu), 24.0 (CH_3), 18.1, 17.8 (2× Cq *t*-Bu), 12.6 (CH_3), −3.9, −5.4, −5.5, −5.6 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{30}H_{56}N_2O_9Si_2Na$ calcd 667.3422, found 667.3442.

*4.2.24. 1-[(2′,5′-Bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)-3-N-tert-butoxycarbonylthymine]-3′-spiro-6″-(4″-R-methyl-1″,3″,2″-dioxathiane-2″,2″-dioxide) (**43**).* To a solution of **42a** (200 mg, 0.31 mmol) in distilled THF (15 mL) was added Burgess reagent (349 mg, 1.24 mmol). After stirring overnight at 80 °C under a nitrogen atmosphere, the solvent was eliminated under reduced pressure and the crude was purified by flash chromatography (EtOAc/cyclohexane, 10/90) to afford **43** (184 mg, 84%) as a white solid. Mp=75–76 °C; $[\alpha]_D^{20}$ +11 (*c* 0.12, $CHCl_3$); IR (ATR) ν 2950, 2931, 2858, 1787, 1713, 1669, 1440, 1405, 1371, 1250, 1204, 1148, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 (s, 1H, H-6), 5.87 (d, 1H, $J_{1',2'}$=1.8 Hz, H-1′), 5.10 (d, 1H, $J_{1',2'}$=1.8 Hz, H-2′), 4.96 (m, 1H, $CHCH_3$), 4.10 (dd, 1H, $J_{4',5'a}$=7.4 Hz, $J_{4',5'b}$=4.2 Hz, H-4′), 4.05 (m, 1H, H-5′a), 3.95 (dd, 1H, $J_{4',5'b}$=4.2 Hz, $J_{5'a,5'b}$=9.4 Hz, H-5′b), 2.48 (dd, 1H, $J_{A,CH}$=12.1 Hz, $J_{A,B}$=14.9 Hz, H-A (CH_2CH)), 2.31 (dd, 1H, $J_{B,CH}$=1.9 Hz, $J_{A,B}$=14.9 Hz, H-B (CH_2CH)), 1.99 (s, 3H, CH_3), 1.60 (s, 9H, *t*-Bu), 1.49 (d, 3H, $J_{CH,CH3}$=6.2 Hz, CH_3), 0.95, 0.92 (s, 18H, 2× *t*-Bu), 0.20, 0.18, 0.15, 0.14 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.0, 148.5 (C-2, C-4), 147.6 (CO), 134.2 (C-6), 111.2 (C-5), 96.5 (C-3′), 91.0 (C-1′), 86.6 (Cq *t*-Bu), 83.2 (C-4′), 80.2 (−CH−CH_2), 77.7 (C-2′), 59.5 (C-5′), 29.8 (CH_2−CH−), 27.8, 25.8, 25.6 (3× *t*-Bu), 20.6 (CH_3), 18.2, 17.8 (2× Cq *t*-Bu), 12.8 (CH_3), −4.4, −5.4, −5.5 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{30}H_{54}N_2O_{11}SSi_2Na$ calcd 729.2885, found 729.2897.

*4.2.25. 1-[(2′,5′-Bis-O-tert-butyldimethylsilyl-β-D-xylofuranosyl)-3-N-methyluracil]-3′-spiro-6″-(3″-N-methoxycarbonyl-4″-R-methyl-1″,2″,3″-oxathiazinone-2″,2″-dioxide) (**44**).* To a solution of **31a**/**b** (512 mg, 0.94 mmol) in distilled THF (20 mL) was added Burgess reagent (898 mg, 3.77 mmol). After stirring overnight at 80 °C under a nitrogen atmosphere, the solvent was eliminated under reduced pressure and the crude was purified by flash chromatography (EtOAc/cyclohexane, 10/90) to afford 262 mg (42%) of **44** as a solid. Mp=59–60 °C; $[\alpha]_D^{20}$ +13 (*c* 0.16, $CHCl_3$); IR (ATR) ν 2955, 2930, 2857, 1738, 1708, 1666, 1461, 1047, 1291, 1254, 1181, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (d, 1H, $J_{5,6}$=8.2 Hz, H-6), 5.80 (d, 1H, $J_{5,6}$=8.2 Hz, H-5), 5.77 (d, 1H, $J_{1',2'}$=1.8 Hz, H-1′), 4.69 (m, 1H, $CHCH_3$), 4.67 (d, 1H, $J_{1',2'}$=1.7 Hz, H-2′), 4.21 (m, 1H, H-4′), 4.15 (dd, 1H, $J_{4',5'a}$=5.5 Hz, $J_{5'a,5'b}$=11.0 Hz, H-5′a), 4.05 (dd, 1H, $J_{4',5'b}$=4.2 Hz, $J_{5'a,5'b}$=11.0 Hz, H-5′b), 3.91 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 2.68 (dd, 1H, $J_{A,CH}$=6.7 Hz, $J_{A,B}$=15.1 Hz, H-A (CH_2CH)), 2.56 (dd, 1H, $J_{B,CH}$=8.2 Hz, $J_{A,B}$=15.1 Hz, H-B (CH_2CH)), 1.43 (d, 3H, $J_{CH,CH3}$=6.5 Hz, CH_3), 0.96, 0.95 (s, 18H, 2× *t*-Bu), 0.27, 0.21, 0.17, 0.16 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.0, 151.8, 151.4 (C-2, C-4, CO), 137.3 (C-6), 101.6 (C-5), 94.5 (C-3′), 91.0 (C-1′), 85.4 (C-4′), 79.4 (C-2′), 60.3 (C-5′), 55.0 (OCH_3), 29.1 (CH_2−CH−), 27.8 (CH_3), 26.1, 25.9 (2× *t*-Bu), 20.8 (CH_3), 18.5, 18.2 (2× Cq *t*-Bu), −4.0, −5.2, −5.4, −5.6 (4× $SiCH_3$). HRMS [MNa$^+$] $C_{27}H_{49}N_3O_{10}Si_2SNa$ calcd 686.2575, found 686.2579.

*4.2.26. 1-[2′,5′-Bis-O-tert-butyldimethylsilyl-3′-(S)-C-(2-(R)-hydroxypropyl)-β-D-xylofuranosyl]-3′-N-methyluracil (**45**) and 1-[2′-O-tert-butyldimethylsilyl-3′-(S)-C-(2-(R)-hydroxypropyl)-β-D-xylofuranosyl]-3′-N-methyluracil (**46**).* To a solution of **34** (81.3 mg, 0.13 mmol) in anhydrous DMF (1.2 mL) was added NaN_3 (17 mg, 0.27 mmol). After 24 h at room temperature, another 2 equiv of NaN_3 were added and the solution was allowed to stir at room temperature for an additional 24 h. DMF was then removed under reduced pressure and the resulting mixture was dissolved into THF (5 mL) and 0.5 mL of a solution of H_2SO_4 (220 μL) and H_2O (70 μL) in THF (5 mL) was added. The solution was allowed to stir at room temperature for 30 min, then DCM (10 mL) was added and the organic phase was washed by a saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to dryness. After flash chromatography on silica gel (Cyclohexane/EtOAc, 1/0–6/4), compound **45** (20.6 mg, 24%) was isolated as a syrup, and compound **46** (36.2 mg, 61%) as a white solid. Compound **45**: mp=54–55 °C; $[\alpha]_D^{20}$ −13 (*c* 0.08, $CHCl_3$); IR (ATR) ν 3333, 2955, 2929, 2857, 2113, 1702, 1656, 1470, 1249, 1110, 1088 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (d, 1H, $J_{5,6}$=8.1 Hz, H-5), 5.64 (d, 1H, H-1′), 5.63 (d, 1H, $J_{5,6}$=8.1 Hz, H-6), 4.23 (dd, 1H, $J_{5'a,5'b}$=12.2 Hz, $J_{4',5'a}$=2.5 Hz, H-5′a), 4.16 (s, 1H, H-2′), 4.06 (dd, 1H, $J_{4',5'b}$=2.0 Hz, H-5′b), 3.90 (m, 1H, −CHOH), 3.85 (t, 1H, $J_{4',5'b}$=$J_{4',5'b}$=2.0 Hz, H-4′), 3.31 (s, 3H, NCH_3), 1.96 (dd, 1H, $J_{A,CH}$=9.4 Hz, $J_{A,B}$=14.4 Hz, H-A (CH_2CH)), 1.66 (br s, 1H, OH), 1.46 (dd, 1H, $J_{B,CH}$=4.4 Hz, $J_{A,B}$=14.4 Hz, H-B (CH_2CH)), 1.35 (d, 3H, $J_{CH3,CH}$=6.5 Hz, CH_3CH−), 0.90 (s, 18H, 2× *t*-Bu), 0.24, 0.18, 0.14, 0.13 (s, 12H, 4× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.5, 150.7 (C-2, C-4), 138.9 (C-6), 100.2 (C-5), 92.4 (C-1′), 83.1 (C-2′), 81.7 (C-4′), 81.2 (C-3′), 62.4 (C-5′), 53.8 (−CH−CH_3), 37.4 (CH_2−CH−), 27.7 (NCH_3), 26.2, 25.9 (2× *t*-Bu), 20.5 (CH_3), 18.2 (2× Cq *t*-Bu), −3.7, −5.5, −5.6 (4× $SiCH_3$). HRMS [MH$^+$] $C_{25}H_{47}N_5O_6Si_2Na$ calcd 592.2963, found 592.2968. Compound **46**: mp=143–144 °C; $[\alpha]_D^{20}$ −23 (*c* 0.085, $CHCl_3$); IR (ATR) ν 3282, 2953, 2929, 2096, 1698, 1649, 1470, 1292, 1250, 1198, 1111, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, 1H, $J_{5,6}$=8.1 Hz, H-5), 5.71 (d, 1H, H-1′), 5.61 (d, 1H, $J_{5,6}$=8.1 Hz, H-6), 4.44 (s, 1H, H-2′), 4.23 (dd, 1H, $J_{5'a,5'b}$=12.9 Hz, $J_{4',5'a}$=2.7 Hz, H-5′a), 4.15 (dd, 1H, $J_{4',5'b}$=2.4 Hz, H-5′b), 4.04 (m, 1H, −CHOH), 4.00 (t, 1H, $J_{4',5'b}$=$J_{4',5'b}$=2.5 Hz, H-4′), 3.34 (s, 3H, NCH_3), 2.02 (dd, 1H, $J_{A,CH}$=10.7 Hz, $J_{A,B}$=14.4 Hz, H-A (CH_2CH)), 1.60 (dd, 1H, $J_{B,CH}$=3.4 Hz, $J_{A,B}$=14.4 Hz, H-B (CH_2CH)), 1.44 (d, 3H, $J_{CH3,CH}$=6.5 Hz, CH_3CH−), 0.98 (s, 9H, *t*-Bu), 0.32, 0.29 (s, 6H, 2× $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.5, 150.8 (C-2, C-4), 140.2 (C-6), 99.4 (C-5), 92.5 (C-1′), 84.5 (C-4′), 81.7 (C-3′), 81.4 (C-2′), 61.4 (C-5′), 53.9 (−CH−CH_3), 36.8 (CH_2−CH−), 27.7 (NCH_3), 26.2 (*t*-Bu), 20.5 (CH_3), 18.3 (Cq *t*-Bu), −3.8, −5.3 (2× $SiCH_3$). HRMS [MNa$^+$] $C_{19}H_{33}N_5O_6SiNa$ calcd 478.2098, found 478.2078.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.030.

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