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Highly β-stereoselective nucleosidation from α-D-*xylo*- and α-D-*ribo*-furanose 1,2-thiocarbonates

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Abstract—Cyclic 1,2-thiocarbonates of α-D-*xylo*- and α-D-*ribo*-furanoses were found to be excellent glycosyl donors in mild NIS-mediated nucleophilic substitution reactions, affording β-nucleosides with complete stereoselectivity and moderate to high yields after treatment with persilylated pyrimidinic bases. The nucleophile is believed to open the thiocarbonate ring at the anomeric position presumably via an S_N2 mechanism. Participation of the nucleobase silylating agent [*N*,*O*-bis(trimethylsilyl)acetamide] in the mechanism of the nucleosidation step was shown, where a large excess of it has been proven to be necessary in order to achieve high yields. Absolute configurations at C-1′ were ascertained by chemical correlation synthesizing the corresponding 2,2′-*anhydro*-nucleosides.

1. Introduction

Cyclic 1,2-thiocarbonate sugars have been reported as substrates in nucleophilic substitution reactions owing to their properties: they are stable compounds, easily prepared and handled, and susceptible to regioselective nucleophilic openings under mild conditions. For instance, they have been employed as glycosyl donors in glycosidation reactions using a sulfur methylating agent as a promoter.[1] In the same manner, *vic*-diol cyclic thiocarbonates gave very good yields and regioselectivities in nucleophilic reactions using different nitrogen,[2] oxygen[2a] and sulfur nucleophiles.[2a]

On the other hand, cyclic 1,2-sulfite sugars latter have also been used as glycosyl donors in nucleoside synthesis using persilylated pyrimidinic bases with good yields and, in some cases, good stereoselectivities.[3] We have also previously reported the use of cyclic 1,2-thiocarbonate sugars as excellent starting materials for the synthesis of glycosyl azides and nucleosides,[4] the latter being an NIS-mediated process. We now report an extensive study on nucleoside synthesis using 3,5-di-*O*-benzyl-**1a**[1,4] and 3,5-di-*O*-benzoyl-α-D-*xylo*-furanose 1,2-thiocarbonates **1b**[5] as well as the *ribo* analogues **2a** and **2b** as starting materials. The nucleobases employed in each case were thymine, uracil and 5-fluorouracil, which were used as their persilylated derivatives.

2. Results and discussion

After the satisfactory results in the reaction of 1,2-thiocarbonates **1a** and **2a** with sodium azide to afford the corresponding glycosyl azides,[4] it was envisioned to carry out nucleosidation reactions under similar conditions. Experiments conducted using thymine/NaH or thymine/DBU in dimethylformamide afforded the expected products in less than 10% yield. Also, the use of persilylated thymine led to unsuccessful results owing to their moderate nucleophilic character. Finally, the reaction was performed with persilylated nucleobases using NIS as promoter, which acts by oxidizing the sulfur atom. A similar procedure has been reported for the nucleosidation of phenylthio glycosides by means of NBS.[6]

Early experiments, where dichloromethane was chosen as the solvent, showed low yields, complex reaction mixtures and longer reaction times than expected. In addition, the reaction between **1b** and persilylated thymine afforded a minor fraction considered as the α-nucleoside, as evidenced from ^{1}H NMR data. This fact could be explained based on neighbouring group

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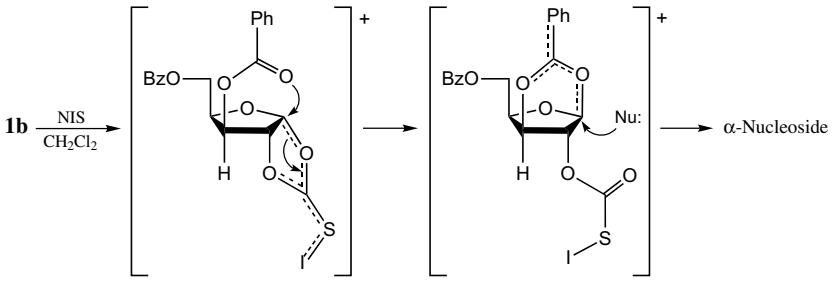


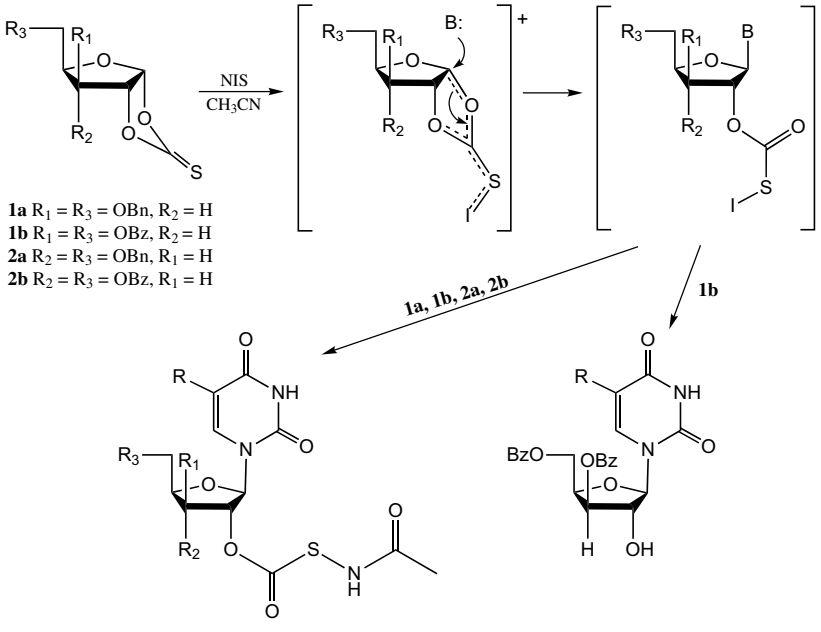
Scheme 1. Possible mechanism for the obtention of the α-anomer in the nucleosidation essays in dichloromethane.

participation that cannot take place in the other derivatives (Scheme 1).

On changing to acetonitrile as the solvent, yields were improved up to 90% and the reaction times were shortened to 10 min along with a complete consumption of the starting material. Furthermore, only the β-anomer was achieved independent of the sugar configuration (*xylo* or *ribo*). This fact suggests a possible S_N2 mechanism takes place on these compounds as suggested by Mukaiyama.[1a] A participation of the silylating agent was found in the reaction [persilylated nucleobases was previously obtained using a large excess of *N*,*O*-bis(trimethylsilyl)acetamide], performing the final step of the nucleosidation process. This excess has been demonstrated to be absolutely necessary in order to obtain high yields in the nucleosidation products (Scheme 2).[4]

In the case of **1b**, a side reaction leads to the corresponding 2′-O deprotected compounds **5bT**,[7] **5bU**[7] and **5bF**[8] to a considerable extent. It can be seen that better results were afforded for thymine, when benzyl was the sugar protecting group (compounds **3aT**[4] and **4aT**), and for uracil when benzoyl was (compounds **3bU**+**5bU** and **4bU**). Yields obtained are summarized in Table 1.

In order to remove the protecting group at C-2′, the obtained nucleosides can be treated under acidic (CF_3CO_2H/H_2O/dioxane) or basic (DABCO/dioxane or

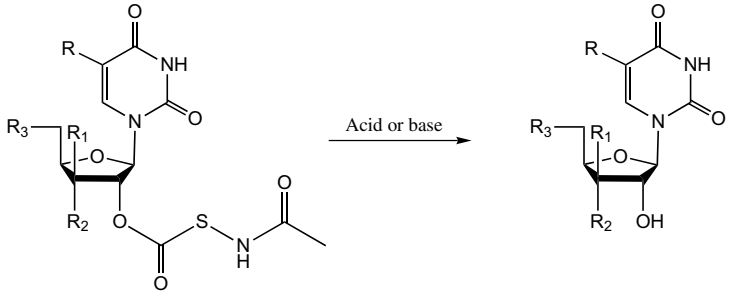


Scheme 2. Nucleosides afforded from thiocarbonates **1a**, **1b**, **2a** and **2b**.

Table 1. Yields achieved in the nucleosidation process

Starting thiocarbonate		Persilylated nucleobase	Nucleoside[a] (yield %)	2′-O deprotection (yield %)
xylo	**1a**	Thymine	**3aT** (90)	—
		Uracil	**3aU** (76)	—
		5-Fluorouracil	**3aF** (71)	—
	1b	Thymine	**3bT** (61)	**5bT** (32)
		Uracil	**3bU** (65)	**5bU** (33)
		5-Fluorouracil	**3bF** (51)	**5bF** (22)
ribo	**2a**	Thymine	**4aT** (90)	—
		Uracil	**4aU** (74)	—
		5-Fluorouracil	**4aF** (83)	—
	2b	Thymine	**4bT** (60)	—
		Uracil	**4bU** (92)	—
		5-Fluorouracil	**4bF** (68)	—

[a] Nemotecnic rules for numbering: (1) odd numbers: *xylo* sugars; even numbers: *ribo* sugars. (2) letter **a**: benzyl as O protecting group; letter **b**: benzoyl. (3) T: Thymine; U: Uracil; F: 5-fluorouracil.



3aT $R_1 = R_3 = OBn$, $R_2 = H$, R = Me
3aU $R_1 = R_3 = OBn$, $R_2 = H$, R = H
3aF $R_1 = R_3 = OBn$, $R_2 = H$, R = F
3bT $R_1 = R_3 = OBz$, $R_2 = H$, R = Me
3bU $R_1 = R_3 = OBz$, $R_2 = H$, R = H
3bF $R_1 = R_3 = OBz$, $R_2 = H$, R = F
4aT $R_2 = R_3 = OBn$, $R_1 = H$, R = Me
4aU $R_2 = R_3 = OBn$, $R_1 = H$, R = H
4aF $R_2 = R_3 = OBn$, $R_1 = H$, R = F
4bT $R_2 = R_3 = OBz$, $R_1 = H$, R = Me
4bU $R_2 = R_3 = OBz$, $R_1 = H$, R = H
4bF $R_2 = R_3 = OBz$, $R_1 = H$, R = F

5aT $R_1 = R_3 = OBn$, $R_2 = H$, R = Me
5aU $R_1 = R_3 = OBn$, $R_2 = H$, R = H
5aF $R_1 = R_3 = OBn$, $R_2 = H$, R = F
5bT $R_1 = R_3 = OBz$, $R_2 = H$, R = Me
5bU $R_1 = R_3 = OBz$, $R_2 = H$, R = H
5bF $R_1 = R_3 = OBz$, $R_2 = H$, R = F
6aT $R_2 = R_3 = OBn$, $R_1 = H$, R = Me
6aU $R_2 = R_3 = OBn$, $R_1 = H$, R = H
6aF $R_2 = R_3 = OBn$, $R_1 = H$, R = F

Scheme 3. 2′-O deprotection by means of acidic or basic conditions.

Table 2. Yields afforded in the deprotection reaction

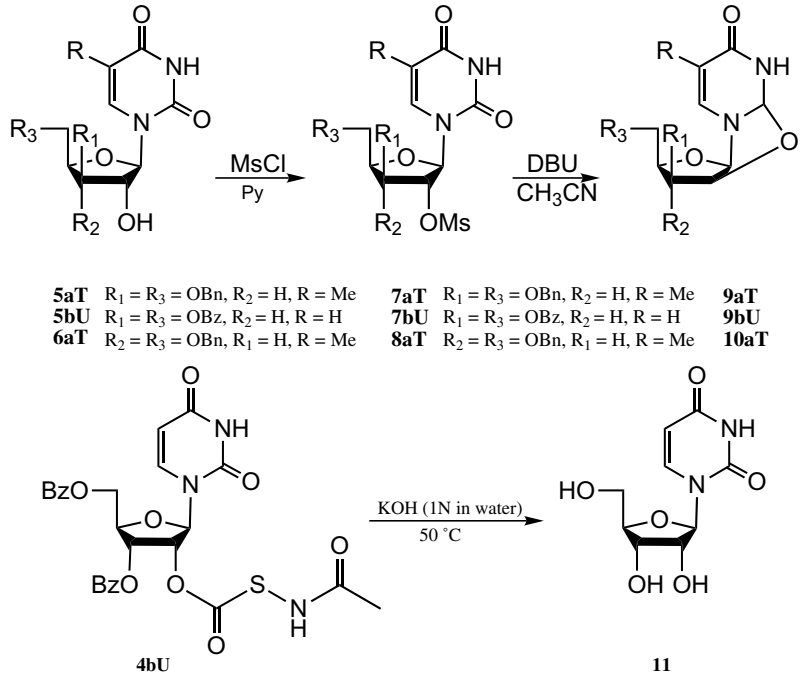
Starting nucleoside		2′-O deprotection (yield %)	Experimental conditions[a]
xylo	**3aT**	**5aT** (90)	KOH/water
	3aU	**5aU** (88)	KOH/water
	3aF	**5aF** (85)	KOH/water
	3bT	**5bT** (86)	CF_3CO_2H/water/dioxane
	3bU	**5bU** (85)	DABCO/dioxane
	3bF	**5bF** (90)	DABCO/dioxane
ribo	**4aT**	**6aT** (93)	KOH/water
	4aU	**6aU** (87)	KOH/water
	4aF	**6aF** (90)	KOH/water

[a] See experimental for a detailed description.

KOH/water) conditions to yield the corresponding deprotected compounds (Scheme 3). Compounds **4bT**, **4bU** and **4bF** suffered either partial 3′-*O* → 2′-*O* migration of the benzoyl protecting group affording inseparable mixtures or full deprotection. Yields and experimental conditions are reported on Table 2.

Even though some of these nucleosides have been previously reported, they were poorly characterized. Hence, in order to demonstrate unequivocally the β-configuration at the anomeric position, compounds **5aT**,[9] **5bU** and **6aT**[10] were first treated with MsCl in pyridine obtaining the corresponding 2′-O-mesylated derivatives **7aT**,[11] **7bU** and **8aT**. Then, basic conditions (DBU/acetonitrile) initiated the expected intramolecular displacement that led to the already described 2,2′-*anhydro*-nucleosides **9aT**,[4,12] **9bU** [12b,13] and **10aT**[14] (Scheme 4).

In addition, compound **4bU** was treated with KOH/water in order to obtain the well known nucleoside uridine **11** (Scheme 1). With the ^1H NMR spectra, these results demonstrate unequivocally the β-configuration



5aT $R_1 = R_3 = OBn$, $R_2 = H$, R = Me
5bU $R_1 = R_3 = OBz$, $R_2 = H$, R = H
6aT $R_2 = R_3 = OBn$, $R_1 = H$, R = Me

7aT $R_1 = R_3 = OBn$, $R_2 = H$, R = Me
7bU $R_1 = R_3 = OBz$, $R_2 = H$, R = H
8aT $R_2 = R_3 = OBn$, $R_1 = H$, R = Me

9aT
9bU
10aT

4bU **11**

Scheme 4. Chemical correlation in order to ascertain the C-1′ configuration.

Table 3. Yields afforded in the chemical correlation steps

Starting nucleoside		Mesylation (yield %)	Anhydrization (yield %)	Full deprotection (yield %)
xylo	**5aT**	**7aT** (90)	**9aT** (85)	—
	5bU	**7bU** (85)	**9bU** (85)	—
ribo	**6aT**	**8aT** (86)	**10aT** (85)	—
	4bU	—	—	**11** (89)

of all the afforded nucleosides. Yields are summarized in Table 3.

3. Conclusions

In summary, we have reported a new method to prepare nucleosides from 1,2-thiocarbonate sugars. Thus, cyclic 1,2-thiocarbonates from α-D-*xylo*-and α-D-*ribo*-furanoses have been treated with different persilylated pyrimidinic bases along with NIS acting as promoter. Solvent election has been shown to be crucial since the reaction does not go in CH_2Cl_2 but it works very well in CH_3CN. Yields go from moderate to high, and reactions were performed under very mild conditions to achieve the expected nucleosides with complete β-stereoselectivity. This fact was ascertained by chemical correlation. It is expected that this new method of nucleosidation could be applied on other different systems in order to obtain a wide range of new products.

4. Experimental

Melting points were determined with a Gallenkamp Melting Point apparatus and were uncorrected. Optical rotations were performed in dichloromethane and concentrations were 1 g/100 mL (*c* 1), unless otherwise was indicated, and measured on JASCO DIP-370 and Perkin Elmer 141 polarimeters. IR spectra were recorded on Perkin Elmer 782 and Mattson Satellite FTIR spectrometers. NMR spectra were obtained from Brüker AM-300, AMX-300 and ARX-400 for solutions in $CDCl_3$ (Me_4Si as internal reference) unless otherwise was indicated. High-resolution mass spectra were measured on Fisons Mod. Platform II and VG Autospec-Q spectrometers. Column chromatography was performed on silica gel (Merck 7734) and thin layer chromatography (TLC) on precoated silica gel 60 F_{254} aluminium sheets. Usual workup means that the organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum.

4.1. General procedure for the synthesis of α-D-*ribo*-furanose 1,2-thiocarbonates 2a and 2b

1,1′-thiocarbonyl-diimidazole (196 mg, 1.1 mmol) was added to solutions of both the *ribo*-furanose 1,2-diol derivatives **1a** and **1b** (1 mmol) in dry CH_2Cl_2 (5 mL), stirring for 30 min at room temperature. Mixtures were diluted with CH_2Cl_2 (25 mL), washed with aq 10% HCl, water and brine. After usual workup, the residues were chromatographed using mixtures of ether–hexane to afford the corresponding 1,2-thiocarbonates **2a** and **2b**.

4.1.1. 3,5-Di-*O*-benzyl-1,2-*O*-thiocarbonyl-α-D-*ribo*-furanose 2a. 279 mg (75%); mp 75–76 °C; $[\alpha]_D^{23} = +200$; ν_{max} (KBr) 1290 cm^{-1}; ^1H NMR (300 MHz) δ 7.39–7.24 (10H, m), 6.25 (1H, d, $J = 4.8$ Hz), 5.04 (1H, t, $J = 4.6$ Hz), 4.72, 4.54 (2H, 2d, $J = 11.7$ Hz), 4.52, 4.47

(2H, 2d, $J = 12.0$ Hz), 4.15–4.07 (2H, m), 3.79 (1H, dd, $J = 1.6$, 11.4 Hz), 3.61 (1H, dd, $J = 2.9$ Hz); ^{13}C NMR (75 MHz) δ 190.5, 137.5, 136.6, 128.7, 128.6, 128.5, 128.3, 128.1, 127.9, 107.2, 81.7, 79.8, 75.9, 73.6, 73.0, 66.7; HRMS (LSIMS) 395.09289 $[M+Na]^+$, calcd for $C_{20}H_{20}O_5SNa$: 395.0929 (dev. 0.1 ppm).

4.1.2. 3,5-Di-*O*-benzoyl-1,2-*O*-thiocarbonyl-α-D-*ribo*-furanose 2b. 300 mg (75%); mp 111–112 °C; $[\alpha]_D^{23} = +170$; ν_{max} (KBr) 1725, 1269 cm^{-1}; ^{1}H NMR (300 MHz) δ 8.15–7.98, 7.64–7.52, 7.48–7.37 (10H, 3m), 6.43 (1H, d, $J = 4.7$ Hz), 5.59 (1H, t, $J = 5.1$ Hz), 5.24 (1H, dd, $J = 9.0$ Hz), 4.78 (1H, dd, $J = 3.0$, 12.2 Hz), 4.65–4.59 (1H, m), 4.55 (1H, dd, $J = 4.8$ Hz); ^{13}C NMR (100 MHz) δ 189.7, 165.9, 165.5, 134.2, 133.6, 130.2, 129.8, 129.2, 128.7, 128.6, 128.0, 106.6, 80.9, 77.0, 71.8, 61.7; HRMS (LSIMS) 423.05194 $[M+Na]^+$, calcd for $C_{20}H_{16}O_7SNa$: 423.05144 (dev. −1.2 ppm).

4.2. General procedure for the nucleosidation process

N,*O*-Bis(trimethylsilyl)acetamide (1.5 mL, 6 mmol) was added to a stirred suspension of the corresponding pirimidine (thymine, uracil, or 5-fluorouracil, 2 mmol) in CH_3CN (15 mL). Once the pirimidine was dissolved (15 min), compounds **1a**, **1b** or **2a**, **2b** (1 mmol) and NIS (450 mg, 2 mmol) were added. The solution was stirred at room temperature until the starting material disappeared (10 min). The crude was evaporated, the residue was dissolved in CH_2Cl_2 (25 mL), and the solution was successively washed with $NaHCO_3$ saturated aqueous solution, water, 10% $Na_2S_2O_3$ solution, and water. After usual workup, the residue was purified by column chromatography (CH_2Cl_2–MeOH 25:1) to achieve **3a**,**b** (**T**,**U**,**F**)–**4a**,**b** (**T**,**U**,**F**) and **5b** (**T**,**U**,**F**). For a complete description of compounds **3aT**, **3aU** and **3aF** see Ref. 4.

4.2.1. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzoyl-β-D-*xylo*-furanosyl)thymine 3bT. 355 mg (61%); $[\alpha]_D^{23} = +164$; ν_{max} (KBr) 1713, 1694 cm^{-1}; ^{1}H NMR (400 MHz) δ 10.25 (1H, s), 8.25 (1H, s), 7.97–7.91, 7.60–7.51, 7.44–7.34 (10H, 3m), 7.42 (1H, s), 6.08 (1H, d, $J = 2.2$ Hz), 5.73 (1H, dd, $J = 1.2$, 3.1 Hz), 5.48 (1H, bs), 4.75–4.66 (3H, m), 2.14 (3H, s), 1.75 (3H, s); ^{13}C NMR (100 MHz)δ 172.0, 169.7, 166.0, 164.5, 163.8, 150.9, 134.5, 134.2, 133.5, 129.8, 129.7, 129.1, 128.8, 128.5, 128.2, 111.8, 88.6, 82.7, 79.1, 74.8, 61.3, 23.0, 12.4; HRMS (LSIMS) 606.11619 $[M+Na]^+$, calcd for $C_{27}H_{25}N_3O_{10}SNa$: 606.11583 (dev. −0.6 ppm).

4.2.2. 1-(3′,5′-Di-*O*-benzoyl-β-D-*xylo*-furanosyl)thymine 5bT.[7] 149 mg (32%); mp 102–103 °C; $[\alpha]_D^{23} = +52$ (*c* 1, MeOH); ν_{max} (KBr) 3385, 1720, 1690 cm^{-1}; ^{1}H NMR (300 MHz) δ 10.34 (1H, br s), 7.97, 7.86, 7.56, 7.38 (10H, 4m), 7.69 (1H, s), 5.87 (1H, s), 5.61 (1H, d, $J = 3.3$ Hz), 5.56 (1H, br s), 5.02–4.97 (1H, m), 4.85 (1H, dd, $J = 6.2$, 12.1 Hz), 4.69 (1H, dd, $J = 4.2$ Hz), 4.50 (1H, s), 1.85 (3H, s); ^{13}C NMR (80 MHz) δ 166.3, 165.0, 164.4, 150.8, 135.6, 134.0, 133.4, 129.8, 129.6, 129.4, 128.8, 128.6, 128.5, 110.5, 93.1, 80.6, 80.0, 76.9, 61.7, 12.5; HRMS (LSIMS) 489.12765 $[M+Na]^+$, calcd for $C_{24}H_{22}N_2O_8Na$: 489.12738 (dev.−0.6 ppm).

4.2.3. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzoyl-β-D-*xylo*-furanosyl)uracil 3bU. 370 mg (65%); mp 140–141 °C; $[\alpha]_D^{23} = +147$; ν_{max} (KBr) 1722, 1694 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.13 (1H, s), 8.79 (1H, s), 8.06–8.03, 7.97–7.92, 7.67–7.60, 7.52–7.45 (10H, 4m), 7.93 (1H, d, $J = 8.2$ Hz), 6.14 (1H, d, $J = 2.3$ Hz), 5.88 (1H, br d), 5.80 (1H, br s), 5.66 (1H, dd, $J = 2.0$ Hz), 4.97 (1H, dt, $J = 3.8$, 5.5 Hz), 4.80 (2H, d), 2.11 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 171.2, 170.0, 166.3, 165.4, 163.4, 151.1, 140.5, 134.6, 134.1, 130.6, 130.5, 130.3, 129.8, 129.5, 129.4, 103.0, 89.4, 83.1, 79.9, 75.9, 62.5, 22.8; HRMS (LSIMS) 592.10057 $[M+Na]^+$, calcd for $C_{26}H_{23}N_3O_{10}SNa$: 592.10018 (dev. −0.7 ppm).

4.2.4. 1-(3′,5′-Di-*O*-benzoyl-β-D-*xylo*-furanosyl)uracil 5bU.[7] 149 mg (33%); mp 69–70 °C; $[\alpha]_D^{23} = +56$; ν_{max} (KBr) 3232, 1711 cm^{-1}; ^{1}H NMR (300 MHz) δ 10.43 (1H, s), 7.96, 7.86, 7.58, 7.41 (10H, 4m), 7.93 (1H, d, $J = 8.3$ Hz), 5.87 (1H, s), 5.72 (1H, d), 5.64 (1H, d, $J = 3.2$ Hz), 5.02 (1H, q), 4.86 (1H, dd, $J = 6.5$, 12.3 Hz), 4.73 (1H, dd, $J = 4.2$ Hz), 4.56 (1H, s); ^{13}C NMR (75 MHz) δ 166.2, 165.1, 163.9, 151.0, 139.9, 134.0, 133.4, 129.8, 129.7, 129.3, 128.7, 128.5, 128.4, 101.9, 93.2, 80.9, 79.9, 77.0, 61.7; HRMS (LSIMS) 475.11195 $[M+Na]^+$, calcd for $C_{23}H_{20}N_2O_8Na$: 475.11173 (dev. −0.5 ppm).

4.2.5. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzoyl-β-D-*xylo*-furanosyl)-5-fluorouracil 3bF. 300 mg (51%); mp 154–155 °C; $[\alpha]_D^{23} = +156$; ν_{max} (KBr) 1721, 1694 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.58 (1H, s), 8.80 (1H, s), 8.08 (1H, d, $J = 6.7$ Hz), 8.03 (2H, d, $J = 7.4$ Hz), 7.95 (2H, d, $J = 7.4$ Hz), 7.64, 7.60 (2H, d, $J = 7.4$ Hz), 7.46, 7.44 (4H, 2t), 6.14 (1H, s), 5.86 (1H, d, $J = 3.5$ Hz), 5.82 (1H, s), 4.96–4.93 (1H, m), 4.87 (1H, dd, $J = 6.0$, 12.0 Hz), 4.81 (1H, dd, $J = 4.6$ Hz), 2.09 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 171.3, 169.9, 166.4, 165.4, 157.5 (d, $J = 27.0$ Hz), 149.6, 141.5 (d, $J = 231.5$ Hz), 134.6, 134.1, 130.6, 130.5, 130.2, 129.8, 129.5, 129.4, 124.8 (d, $J = 35.0$ Hz) 89.4, 83.0, 80.1, 75.8, 62.5, 22.8; HRMS (LSIMS) 610.09146 $[M+Na]^+$, calcd for $C_{26}H_{22}N_3O_{10}FSNa$: 610.09076 (dev. −1.1 ppm).

4.2.6. 1-(3′,5′-Di-*O*-benzoyl-β-D-*xylo*-furanosyl)-5-fluorouracil 5bF.[8] 103 mg (22%); $[\alpha]_D^{23} = +96$ (*c* 1, MeOH); ν_{max} (KBr) 3429, 1711 cm^{-1}; ^{1}H NMR (300 MHz) δ 10.29 (1H, s), 7.99 (1H, d, $J = 6.0$ Hz), 7.97–7.79, 7.56–7.50, 7.42–7.33 (10H, 3m), 7.93 (1H, d, $J = 8.3$ Hz), 5.83 (1H, s), 5.59 (1H, d, $J = 3.2$ Hz), 5.02 (1H, d, $J = 3.5$ Hz), 4.98–4.93 (1H, m), 4.87 (1H, dd, $J = 6.2$, 12.2 Hz), 4.68 (1H, dd, $J = 4.1$ Hz), 4.50 (1H, br s); ^{13}C NMR (75 MHz) δ 166.3, 165.1, 157.1 (d, $J = 26.3$ Hz), 149.3, 140.5 (d, $J = 236.7$ Hz), 134.2, 133.5, 129.7, 129.6, 129.2, 129.0, 128.9, 128.6, 124.3 (d, $J = 34.9$ Hz), 92.8,

80.7, 80.0, 77.0, 61.6; HRMS (LSIMS) 493.10226 [M+Na]$^+$, calcd for $C_{23}H_{19}N_2O_8FNa$ 493.10223 (dev. +0.1 ppm).

4.2.7. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzyl-β-D-*ribo*-furanosyl)thymine 4aT. 500 mg (90%); $[\alpha]_D^{23} = +67$; ν_{max} (KBr) 3238, 1692 cm^{-1}; ^{1}H NMR (400 MHz) δ 9.83 (1H, s), 7.88 (1H, s), 7.48 (1H, s), 7.34–7.19 (10H, m), 6.10 (1H, d, $J = 4.3$ Hz), 5.41 (1H, t, $J = 4.5$ Hz), 4.70, 4.44 (2H, 2d, $J = 11.9$ Hz), 4.51, 4.45 (2H, 2d, $J = 11.7$ Hz), 4.25–4.16 (2H, m), 3.79 (1H, d, $J = 10.4$ Hz), 3.49 (1H, d), 2.13 (3H, s), 1.51 (3H, s); ^{13}C NMR (100 MHz) δ 171.8, 170.3, 164.1, 150.9, 137.2, 137.1, 135.6, 128.7, 128.6, 128.5, 128.2, 128.1, 127.7, 111.4, 87.3, 82.3, 78.0, 75.0, 73.6, 73.3, 68.6, 23.1, 12.1; HRMS (LSIMS) 578.15630 [M+Na]$^+$, calcd for $C_{27}H_{29}N_3O_8SNa$: 578.15730 (dev. +1.8 ppm).

4.2.8. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzyl-β-D-*ribo*-furanosyl)uracil 4aU. 400 mg (74%); $[\alpha]_D^{23} = +92$; ν_{max} (KBr) 3215, 1692 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.95 (1H, s), 7.92 (1H, s), 7.73 (1H, d, $J = 8.2$ Hz), 7.38–7.20 (10H, m), 6.07 (1H, d, $J = 3.8$ Hz), 5.42 (1H, br s), 5.36 (1H, d), 4.70, 4.42 (2H, 2d, $J = 11.8$ Hz), 4.43 (2H, s), 4.22 (2H, br s), 3.80 (1H, d, $J = 10.6$ Hz), 3.52 (1H, d), 2.14 (3H, s); ^{13}C NMR (75 MHz) δ 171.8, 170.2, 163.6, 150.6, 140.0, 137.1, 137.0, 128.6, 128.5, 128.2, 128.2, 128.0, 127.9, 102.5, 87.6, 82.2, 77.7, 75.3, 73.6, 73.2, 68.3, 23.0; HRMS (LSIMS) 564.14125 [M+Na]$^+$, calcd for $C_{26}H_{27}N_3O_8SNa$: 564.14165 (dev. +0.7 ppm).

4.2.9. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzyl-β-D-*ribo*-furanosyl)-5-fluorouracil 4aF. 464 mg (83%); $[\alpha]_D^{23} = +98$; ν_{max} (KBr) 3233, 1708 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.90 (1H, s), 7.98 (1H, d, $J = 6.2$ Hz), 7.75 (1H, s), 7.38–7.24 (10H, m), 6.10 (1H, d, $J = 3.5$ Hz), 5.43 (1H, br s), 4.70, 4.43 (2H, 2d, $J = 11.8$ Hz), 4.52, 4.45 (2H, 2d, $J = 11.5$ Hz), 4.23 (2H, s), 3.80 (1H, d, $J = 10.8$ Hz), 3.47 (d, 1H), 2.15 (3H, s); ^{13}C NMR (100 MHz) δ 171.8, 170.3, 157.2 (d, $J = 28.0$ Hz), 149.4, 140.7 (d, $J = 252.0$ Hz), 137.0, 136.6, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 124.0 (d, $J = 36.8$ Hz), 87.5, 82.7, 77.7, 75.5, 73.8, 73.3, 68.1, 23.0; HRMS (LSIMS) 582.13230 [M+Na]$^+$, calcd for $C_{26}H_{26}N_3O_8FSNa$: 582.13223 (dev.−0.1 ppm).

4.2.10. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzoyl-β-D-*ribo*-furanosyl)thymine 4bT. 350 mg (60%); $[\alpha]_D^{23} = -59$; ν_{max} (KBr) 3259, 1713, 1692 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.73 (1H, s), 8.04–8.02, 7.60–7.53, 7.48–7.39 (10H, 3m), 7.74 (1H, s), 7.12 (1H, s), 6.14 (1H, d, $J = 5.5$ Hz), 5.78 (1H, dd, $J = 5.8$, 3.9 Hz), 5.64 (1H, t), 4.81 (1H, dd, $J = 3.6$, 13.2 Hz), 4.61–4.56 (2H, m), 2.06 (3H, s), 1.56 (3H, s); ^{13}C NMR (75 MHz) δ 171.6, 170.4, 166.1, 165.5, 163.8, 150.7, 135.0, 134.0, 133.8, 130.1, 129.7, 129.2, 128.9, 128.8, 128.4, 112.3, 87.8, 80.3, 76.3, 70.6, 63.5, 23.0, 12.2; HRMS (LSIMS) 606.11644 [M+Na]$^+$, calcd for $C_{27}H_{25}N_3O_{10}SNa$: 606.11583 (dev. −1.0 ppm).

4.2.11. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzoyl-β-D-*ribo*-furanosyl)uracil 4bU. 523 mg (92%); mp 171–172 °C; $[\alpha]_D^{23} = -43$; ν_{max} (KBr) 1713, 1694 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.2 (1H, s), 8.73 (1H, s), 8.09–7.99, 7.69–7.60, 7.56–7.46 (10H, 3m), 7.75 (1H, d, $J = 8.1$ Hz), 6.08 (1H, d, $J = 3.4$ Hz), 6.02–5.96 (2H, m), 5.59 (1H, d), 4.79–4.64 (3H, m), 2.04 (3H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 170.4, 169.6, 165.7, 165.0, 162.6, 150.3, 141.4, 133.7, 133.3, 130.0, 129.9, 129.6, 129.1, 128.8, 128.6, 102.4, 90.0, 79.4, 76.5, 70.2, 63.3, 22.0; HRMS (LSMIS) 592.10064 [M+Na]$^+$, calcd for $C_{26}H_{23}N_3O_{10}SNa$: 592.10018 (dev. −0.8 ppm).

4.2.12. 1-(2′-*O*-Acetamidomercaptocarbonyl-3′,5′-di-*O*-benzoyl-β-D-*ribo*-furanosyl)-5-fluorouracil 4bF. 400 mg (68%); mp 202–203 °C; $[\alpha]_D^{23} = -32$; ν_{max} (KBr) 1713 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.68 (1H, s), 8.75 (1H, s), 8.08–8.06, 7.69–7.61, 7.56–7.45 (10H, 3m), 7.98 (1H, d, $J = 6.6$ Hz), 6.11 (1H, d, $J = 3.4$ Hz), 6.00–5.91 (1H, m), 4.81–4.70 (3H, m), 2.04 (3H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 170.4, 169.6, 165.7, 164.9, 156.7 (d, $J = 28.7$ Hz), 149.0, 140.8 (d, $J = 248.1$ Hz), 133.7, 133.4, 130.0, 129.8, 129.6, 129.1, 128.8, 128.6, 125.2 (d, $J = 36.2$ Hz), 89.4, 79.7, 76.5, 70.1, 63.3, 22.0; HRMS (LSIMS) 610.09071 [M+Na]$^+$, calcd for $C_{26}H_{22}N_3O_{10}FSNa$: 610.09076 (dev. +0.1 ppm).

4.3. General procedures in order to remove the 2′-*O*-acetamidomercaptocarbonyl group

Method A: Nucleosides **3a**(**T**,**U**,**F**)–**4a**(**T**,**U**,**F**) (0.5 mmol) were added to an aqueous solution of KOH (1 N, 10 mL). The mixture was stirred and heated at 50 °C until consumption of the starting product was observed (TLC, ether). The reaction mixture was diluted with EtOH (25 mL) and neutralized with Amberlite IR 120. The solvent was evaporated and the residue was purified by column chromatography (CH_2Cl_2–MeOH 20:1) to give nucleosides **5a**(**T**,**U**,**F**)–**6a** (**T**,**U**,**F**).

Method B: Nucleosides **3bU** and **3bF** (0.5 mmol) were deprotected with DABCO in dioxane under reflux. The reaction mixture was finished after 12 h, the solvent was removed, and the residue was partitioned into CH_2Cl_2–H_2O. The organic layer was successively washed with a diluted solution of HCl and water. After usual workup, the residue was purified by column chromatography (CH_2Cl_2–MeOH 20:1) to afford the already described pure **5bU** (192 mg, 85%) and **5bF** (212 mg, 90%).

Method C: Nucleoside **3bT** (122 mg, 0.21 mmol) was treated with CF_3CO_2H (500 μl) in water–dioxane 2:1 (3 mL) at 60 °C. After 12 h the mixture was neutralized with a solution of $NaHCO_3$. The solvent was evaporated and the residue was partitioned into CH_2Cl_2–H_2O. After usual workup, the residue was chromatographed

(CH_2Cl_2–MeOH 20:1) to afford the already described nucleoside **5bT** (84 mg, 86%).

4.3.1. 1-(3′,5′-Di-*O*-benzyl-β-D-*xylo*-furanosyl)thymine 5aT.[9] 197 mg (90%); $[\alpha]_D^{23} = -24$; ν_{max} (KBr) 3380, 3207, 1695 cm^{-1}; ^1H NMR (300 MHz) δ 10.58 (1H, s), 7.47 (1H, s), 7.40–7.30 (10H, m), 5.90 (1H, s), 5.48 (1H, br s), 4.68, 4.62 (2H, 2d, $J = 12.0$ Hz), 4.69 (1H, m), 4.56, 4.47 (2H, 2d, $J = 11.3$ Hz), 4.46 (1H, s), 4.06 (1H, d, $J = 3.6$ Hz), 3.93 (1H, dd, $J = 5.2$, 10.9 Hz), 3.90 (1H, dd, $J = 4.2$ Hz), 1.68 (3H, s); ^{13}C NMR (80 MHz) δ 164.6, 151.2, 137.8, 137.1, 136.8, 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 109.8, 92.8, 82.5, 82.2, 78.3, 73.5, 72.0, 67.6, 12.3; HRMS (LSIMS) 461.16866 $[M+Na]^+$, calcd for $C_{24}H_{26}N_2O_6Na$: 461.16885 (dev. +0.4 ppm).

4.3.2. 1-(3′,5′-Di-*O*-benzyl-β-D-*xylo*-furanosyl)uracil 5aU.[3a] 186 mg (88%); mp 80–81 °C; $[\alpha]_D^{23} = -4$ (*c* 14, CH_2Cl_2); ν_{max} (KBr) 3573, 3177, 1694, 1682 cm^{-1}; ^1H NMR (300 MHz) δ 10.74 (1H, s), 7.64 (1H, d, $J = 8.1$ Hz), 7.36-7.14 (10H, m), 5.85 (1H, s), 5.53 (1H, d), 5.45 (1H, br s), 4.67 (1H, m), 4.64, 4.58 (2H, 2d, $J = 12.1$ Hz), 4.55, 4.44 (2H, 2d, $J = 11.5$ Hz), 4.45 (1H, s), 4.04 (1H, d, $J = 3.5$ Hz), 3.87 (2H, d, $J = 5.7$ Hz); ^{13}C NMR (75 MHz) δ 164.3, 151.3, 141.0, 137.9, 137.2, 128.6, 128.5, 128.3, 128.2, 127.9, 127.8, 101.3, 93.2, 82.8, 82.0, 78.3, 73.6, 72.2, 67.7; HRMS (LSIMS) 447.15310 $[M+Na]^+$, calcd for $C_{23}H_{24}N_2O_6Na$: 447.15320 (dev. +0.2 ppm).

4.3.3. 1-(3′,5′-Di-*O*-benzyl-β-D-*xylo*-furanosyl)-5-fluorouracil 5aF. 188 mg (85%); mp 103–104 °C; $[\alpha]_D^{23} = -4$ (*c* 6, CH_2Cl_2); ν_{max} (KBr) 3417, 3184, 1713 cm^{-1}; ^1H NMR (300 MHz) δ 10.70 (1H, s), 7.78 (1H, d, $J = 6.3$ Hz), 7.36–7.17 (10H, m), 5.81 (1H, s), 5.04 (1H, br s), 4.64, 4.59 (2H, 2d, $J = 11.9$ Hz), 4.61 (1H, m), 4.58, 4.50 (2H, 2d, $J = 11.6$ Hz), 4.43 (1H, s), 4.05 (1H, d, $J = 3.6$ Hz), 3.86 (2H, d, $J = 5.5$ Hz); ^{13}C NMR (75 MHz) δ 157.6 (d, $J = 26.0$ Hz), 149.6, 140.0 (d, $J = 235.1$ Hz), 137.6, 136.9, 128.6, 128.5, 128.2, 128.0, 127.9, 127.7, 125.5 (d, $J = 35.0$ Hz), 92.8, 82.8, 81.7, 78.4, 73.6, 72.3, 67.5; HRMS (LSIMS) 465.14406 $[M+Na]^+$, calcd for $C_{23}H_{23}N_2O_6FNa$ 465.14378 (dev. −0.6 ppm).

4.3.4. 1-(3′,5′-Di-*O*-benzyl-β-D-*ribo*-furanosyl)thymine 6aT.[10] 203 mg (93%); $[\alpha]_D^{23} = +8$ (*c* 4, CH_2Cl_2); ν_{max} (KBr) 3405, 3188, 1693 cm^{-1}; ^1H NMR (300 MHz) δ 9.61 (1H, s), 7.50 (1H, s), 7.38–7.22 (10H, m), 5.98 (1H, d, $J = 4.5$ Hz), 4.72, 4.60 (2H, 2d, $J = 11.9$ Hz), 4.54, 4.49 (2H, 2d, $J = 11.7$ Hz), 4.30–4.26 (2H, m), 4.11 (1H, t, $J = 4.9$ Hz), 3.90 (1H, br s), 3.82 (1H, dd, $J = 2.4$, 10.7 Hz), 3.55 (1H, dd, $J = 2.2$ Hz), 1.54 (3H, s); ^{13}C NMR (75 MHz) δ 163.3, 150.3, 136.6, 136.4, 135.1, 127.9, 127.8, 127.4, 127.1, 127.0, 126.9, 110.2, 88.9, 81.5, 76.9, 74.1, 73.6, 72.7, 68.5, 11.3; HRMS (LSIMS) 461.16822 $[M+Na]^+$, calcd for $C_{24}H_{26}N_2O_6Na$: 461.16885 (dev. +1.4 ppm).

4.3.5. 1-(3′,5′-Di-*O*-benzyl-β-D-*ribo*-furanosyl)uracil 6aU.[15] 184 mg (87%); mp 74–75 °C; $[\alpha]_D^{23} = +30$; ν_{max} (KBr) 3405, 3061, 1693 cm^{-1}; ^1H NMR (300 MHz) δ 9.65 (1H, s), 7.74 (1H, d, $J = 8.2$ Hz), 7.39–7.22 (10H, m), 5.94 (1H, d, $J = 4.1$ Hz), 5.34 (1H, d), 4.69, 4.57 (2H, 2d, $J = 11.9$ Hz), 4.47 (2H, s), 4.28–4.22 (2H, m), 4.08 (1H, t, $J = 5.0$ Hz), 3.82 (1H, dd, $J = 2.4$, 10.7 Hz), 3.76 (1H, br s), 3.56 (1H, dd, $J = 2.0$ Hz); ^{13}C NMR (75 MHz) δ 163.5, 150.9, 140.3, 137.3, 137.1, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 102.3, 90.1, 81.5, 76.7, 74.0, 73.7, 72.7, 69.1; HRMS (LSIMS) 447.15260 $[M+Na]^+$, calcd for $C_{23}H_{24}N_2O_6Na$: 447.15320 (dev. +1.4 ppm).

4.3.6. 1-(3′,5′-Di-*O*-benzyl-β-D-*ribo*-furanosyl)-5-fluorouracil 6aF. 200 mg (90%); $[\alpha]_D^{23} = +19$; ν_{max} (KBr) 3429, 3063, 1712 cm^{-1}; ^1H NMR (300 MHz) δ 9.97 (1H, s), 8.00 (1H, d, $J = 6.4$ Hz), 7.38–7.24 (10H, m), 5.98 (1H, dd, $J = 4.3$, 1.3 Hz), 4.67, 4.57 (2H, 2d, $J = 11.8$ Hz), 4.55, 4.47 (2H, 2d, $J = 11.6$ Hz), 4.31–4.24 (2H, m), 4.09 (1H, t, $J = 4.9$ Hz), 3.81 (1H, dd, $J = 2.3$, 10.9 Hz), 3.50 (1H, dd, $J = 1.7$ Hz); ^{13}C NMR (75 MHz) δ 157.1 (d, $J = 28.2$ Hz), 149.6, 140.6 (d, $J = 251.4$ Hz), 137.1, 136.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 124.5 (d, $J = 37.0$ Hz), 89.9, 81.7, 76.8, 74.1, 73.8, 72.7, 68.7; HRMS (LSIMS) 465.14374 $[M+Na]^+$, calcd for $C_{23}H_{23}N_2O_6FNa$ 465.14378 (dev. +0.1 ppm).

4.4. Synthesis of the 2′-*O*-mesyl derivatives 7aT,7bU and 8aT

Mesylation of **5aT**, **5bU** and **6aT** (0.5 mmol) with mesyl chloride (78 μL, 1 mmol) in dry pyridine (2 mL) was worked up as usually. The crude was purified by column chromatography (Cl_2CH_2–MeOH 25:1) to give **7aT**, **7bU** and **8aT**, respectively.

4.4.1. 1-(3′,5′-Di-*O*-benzyl-2′-*O*-mesyl-β-D-*xylo*-furanosyl)thymine 7aT.[11] 232 mg (90%); mp 127–128 °C; $[\alpha]_D^{23} = +8$ (*c* 3.5, CH_2Cl_2); ν_{max} (KBr) 3032, 1697 cm^{-1}; ^1H NMR (300 MHz) δ 9.39 (1H, br s), 7.38–7.20 (11H, m), 5.99 (1H, s), 5.06 (1H, s), 4.67, 4.61 (2H, 2d, $J = 12.0$ Hz), 4.64, 4.57 (2H, 2d, $J = 11.7$ Hz), 4.54 (1H, m), 4.26 (1H, d, $J = 3.3$ Hz), 3.88 (2H, d, $J = 5.2$, 5.7 Hz), 3.28 (3H, s), 1.74 (3H, s); ^{13}C NMR (75 MHz) δ 163.4, 150.7, 137.6, 136.5, 135.3, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 110.6, 89.0, 84.1, 82.1, 80.5, 73.6, 72.6, 66.9, 38.8, 12.4; HRMS (LSIMS) 539.14676 $[M+Na]^+$, calcd for $C_{25}H_{28}N_2O_8SNa$ 539.14640 (dev. −0.7 ppm).

4.4.2. 1-(3′,5′-Di-*O*-benzoyl-2′-*O*-mesyl-β-D-*xylo*-furanosyl)uracilo 7bU. 225 mg (85%); mp 63–64 °C; $[\alpha]_D^{23} = +64$ (*c* 1, acetone); ν_{max} (KBr) 3196, 2967, 1723, 1692 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.12 (1H, s), 8.04–7.95, 7.68–7.59, 7.50–7.44 (10H, 3m), 8.00 (1H, d), 6.16 (1H, d, $J = 1.7$ Hz), 5.93 (1H, dd, $J = 1.4$, 3.8 Hz), 5.65 (1H, d, $J = 8.2$ Hz), 5.61 (1H, t), 5.02 (1H, dt), 4.88 (1H, dd, $J = 5.8$, 12.1 Hz), 4.84 (1H, dd, $J = 5.2$ Hz),

3.38 (3H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.6, 164.7, 162.7, 150.7, 139.6, 133.9, 133.4, 129.9, 129.8, 129.5, 128.9, 128.7, 128.6, 101.9, 89.6, 84.5, 79.7, 75.5, 61.7, 37.9; HRMS (LSIMS) 553.08989 $[M+Na]^+$, calcd for $C_{24}H_{22}N_2O_{10}SNa$: 553.08928 (dev. −1.1 ppm).

4.4.3. 1-(3′,5′-Di-*O*-benzyl-2′-*O*-mesyl-β-D-*ribo*-furanosyl)thymine 8aT. 222 mg (86%); $[\alpha]_D^{23} = +88$; ν_{max} (KBr) 3063, 1693 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.22 (1H, s), 7.65 (1H, s), 7.38–7.19 (10H, m), 6.02 (1H, d, $J = 2.1$ Hz), 5.22 (1H, t, $J = 2.2$ Hz), 4.84, 4.46 (2H, 2d, $J = 11.6$ Hz), 4.50, 4.44 (2H, 2d, $J = 11.8$ Hz), 4.27 (2H, d), 3.94 (1H, d, $J = 11.0$ Hz), 3.62 (1H, dd, $J = 2.2$ Hz), 3.25 (3H, s), 1.45 (3H, s); ^{13}C NMR (75 MHz) δ 163.2, 150.0, 136.4, 136.2, 134.2, 128.7, 128.6, 128.4, 128.3, 128.3, 127.9, 110.5, 87.5, 81.3, 80.1, 73.8, 73.6, 73.0, 66.6, 38.4, 11.2; HRMS (LSIMS) 517.16393 $[M+H]^+$, calcd for $C_{25}H_{29}N_2O_8SNa$: 517.16446 (dev. +1.0 ppm).

4.5. Synthesis of the 2,2′-*anhydro*-nucleosides 9aT,[4,12] 9bU,[12b,13] 10aT[14]

DBU (34 μL, 0.23 mmol) was added to different solutions of **7aT**, **7bU** and **8aT** (0.2 mmol) in CH_3CN (3 mL) at room temperature. TLC (CH_2Cl_2–MeOH 25:1) showed after 15 min the absence of the starting nucleosides, and the presence of slower-running compounds corresponding to the 2,2′-*anhydro* derivatives. The mixture was neutralized with acetic acid, concentrated and purified by column chromatography (CH_2Cl_2–MeOH 40:1) to give, respectively, the previously reported compounds **9aT**, **9bU** and **10aT** (85% in all cases).

4.6. Conversion of 4bU in uridine 11

4bU (285 mg, 0.5 mmol) were added to an aqueous solution of KOH (1 N,10 mL). The mixture was stirred and heated at 50 °C until consumption of the starting product was observed (TLC, ether). The reaction mixture was diluted with EtOH (25 mL) and neutralized with Amberlite IR 120. The solvent was evaporated and the residue was crystallized in ethanol affording uridine (**11**, 109 mg, 89%).

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