Synthesis and Chemoselective N- and O-Alkylation of Thiadiazolopyrimidine Nucleosides and Uridines

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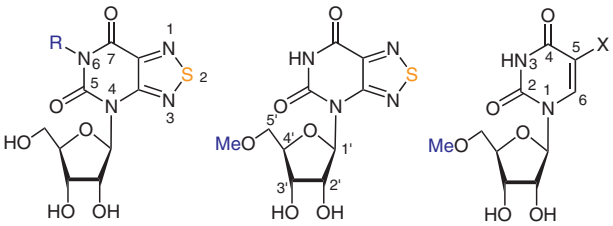
Abstract: A facile and selective N- or O-alkylation of 4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrmidine-5,7(4*H*,6*H*)-dione as well as uridines was accomplished via bimolecular base alkylation or bimolecular nucleophilic substitution reaction controlled by the reagents. In the presence of 18-crown-6 and anhydrous K_2CO_3, the highly chemoselective O-methylation was performed using dimethyl carbonate (DMC) in DMF at 22–25 °C, i.e. the 2′,3′-*O*-isopropylidene derivatives of 4-β-D-ribofurnosyl[1,2,5]thiadiazolo[3,4-*d*]pyrmidine-5,7(4*H*,6*H*)-dione, uridine, and 5-bromouridine, underwent only the primary alcoholic O-methylation reaction without affecting the NH group of the pyrimidne ring. The novel N-alkylated derivatives of 4-β-D-ribofurnosyl[1,2,5]thiadiazolo[3,4-*d*]pyrmidine-5,7(4*H*,6*H*)-dione were also prepared using the appropriate alkyl halides with a base.

Key words: ribofuranosylthiadiazolopyrimidines, uridines, chemoselectivity, alkylations, heterocycles

In the treatment of human viral diseases, purine nucleoside analogues have recently emerged as an important therapeutic agent.[1] The majority of purine nucleoside analogues are natural substrates with modifications in the heterocyclic base. Such base-modified analogues are perhaps the most obvious target due to the density of accessible hydrogen-bond donor and acceptor sites that reside on the heterocycle. These analogues have been used to comprehensively map the contribution of functional groups on conserved purines to hairpin ribozyme activity.[2] One of the simplest strategies for the alteration of a functional group is methylation. This has the effect of removing the hydrogen bond from nitrogen or oxygen for the purpose of introducing minimal steric perturbation. A new alkylated isopurine nucleoside has recently been isolated from the marine sponge *Tedania digitata* and identified as 1-methylisoguanosine.[3,4] The isolation of the same compound from the digestive glands of a nudibranch has also recently been reported,[5] and it has been shown to possess potent muscle-relaxant activity as well as exhibiting cardiovascular and anti-inflammatory properties.[5–8] Most of the naturally occurring purine nucleosides possess a ribofuranosyl moiety on the imidazole ring. Nevertheless, there has been increased interest in purine nucleosides with a ribofuranosyl moiety attached to a nitrogen atom of the pyrimidine ring, such as 3-β-D-ribofuranosyl-adenine and -xanthine, because of their potential biological activities[9] and their activity in enzyme-catalyzed reactions.[10] These results have aroused our continuing interest in the synthesis of isopurine nucleosides with a ribofuranosyl moiety residing on the pyrimidine ring, which would be useful in the treatment of neoplastic and viral diseases. However, although chemoselective alkylation is an effective method for the introduction of alkyl groups at different positions on nitrogen or oxygen,[11] the chemoselective alkylation of purine and pyrimidine nucleosides has not been studied intensively.

In this paper, we report a facile synthesis of 4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidines, which includes modifications at the level of heterocyclic base, such as 6-N-substituted derivatives (**I**), or of the ribofuranosyl moiety such as 5′-*O*-methyl derivative (**II**), as a new aspect of chemoselective methylation (Figure 1). These derivatives are structurally related to isoxanthosine and represent the first examples of these kinds of compounds. In addition, a chemoselective synthesis of 5′-*O*-methyluridine (**III**) and 5-bromo-5′-*O*-methyluridine (**IV**) is also reported.



I II **III** X = H **IV** X = Br

Figure 1

The desired 4-β-D-ribofurnosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**5**) was synthesized according to the preliminary outlined procedure[12] with some modification (Scheme 1). Namely, the reaction of 5′,6-anhydro-6-hydroxy-2′,3′-*O*-isopropylideneuridine (**1**)[13] with liquid ammonia, in the presence of ammonium acetate at 50 °C, afforded 6-amino-2′,3′-*O*-isopropylideneuridine (**2**)[12] in 40% yield. This reaction was also carried out in the presence of ammonium chloride, but it was observed that the yield using ammonium acetate as the catalyst gave slightly better yield. Since this amination was carried out in sealed steel containers for extended times,

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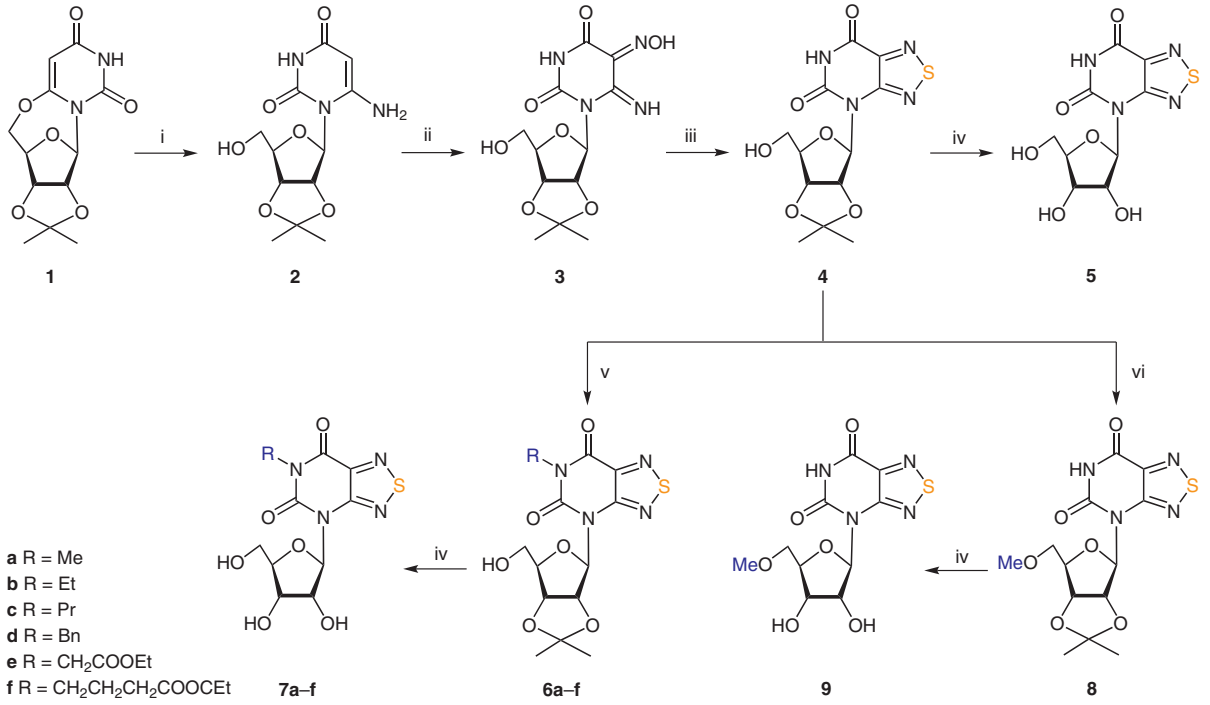


Scheme 1 *Reagents and conditions*: (i) liquid NH_3, NH_4Cl or $AcONH_4$, 50 °C, 1.5 d; (ii) amyl nitrite, HCl, EtOH–EtOAc, 25 min; (iii) $Na_2S_2O_3{\cdot}5H_2O$, 5% aq AcOH, r.t., 1 h; (iv) 0.5 M HCl, MeOH, 50 °C, 4–8 h; (v) alkyl halide (**a**, MeI; **b**, EtI; **c**, *n*-PrI; **d**, BnBr; **e**, $BrCH_2CO_2Et$; **f**, $BrCH_2CH_2CH_2CO_2Et$), K_2CO_3, anhyd DMF or acetone, 0 °C→r.t., 10 min→4 h; (vi) Me_2CO_3, 18-crown-6-ether, K_2CO_3, anhyd DMF, 22–25 °C, 1 d.

portions of the starting material decomposed. The reason for the lower yield of this reaction is presumably due to the decomposition of the ribose–pyrimidine linkage, since TLC showed the presence of another compound, which was not characterized, that ran around the base line on the TLC in addition to the amino product (**2**). Nitrosation of **2** was accomplished with amyl nitrite, in the presence of a catalytic amount of HCl in a mixture of ethanol and ethyl acetate, to give the 5-hydroxyimino-6-imino derivative **3** in an excellent yield of 89%. Direct conversion of **3** into 4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**4**) was carried out in good yield (73%) by reaction with $Na_2S_2O_3{\cdot}5H_2O$ in a 5% acetic acid solution at room temperature. Subsequent hydrolysis of **4** thus obtained, with HCl in methanol afforded the desired 4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**5**)[12] in 88% yield.

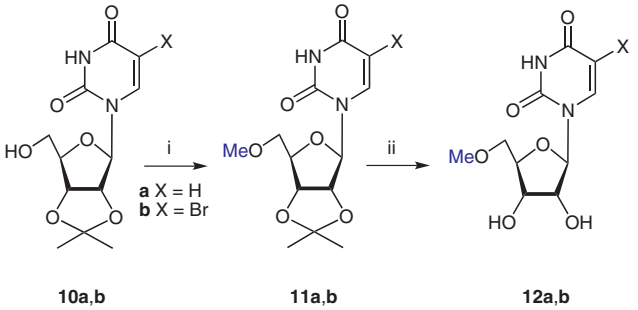
When compound **4** was treated with an appropriate alkyl halide, in the presence of anhydrous K_2CO_3 in anhydrous DMF at room temperature, the alkylation proceeded to afford the corresponding 6*N*-alkyl-2′,3′-*O*-isopropylidene nucleosides (**6a–f**). Subsequent treatment of **6a–f** with 0.5 M HCl in methanol at 50 °C gave the corresponding 6*N*-alkyl nucleosides (**7a–f**) in high yields after deprotection. On the other hand, when compound **4** was treated with dimethyl carbonate (DMC) in the presence of 18-crown-6 and anhydrous K_2CO_3, the alkylation proceeded on the hydroxy group at the 5′-position to yield the 5′-*O*-methyl-4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl) derivative **8** in 75% yield. In this case, the methylation occurred on the ribofuranosyl moiety instead of on the pyrimidine ring. The product **8** was easily deprotected by treatment with 0.5 M HCl in methanol at 50–60 °C to give the 5′-*O*-methyl-4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**9**) in 75% yield. Similarly, treatment of **4** with an appropriate alkyl halide (MeI, EtI, *n*-PrI, and BnBr) in the presence of 18-crown-6 did not give the 5′-*O*-alkyl nucleosides, but instead gave the usual 6-*N*-alkyl nucleosides only. Therefore, the presence of both 18-crown-6 and DMC is essential for selective methylation on the primary alcohol. All new compounds exhibited satisfactory elemental analyses and the IR, ^1H and ^{13}C NMR spectral data given in experimental part are consistent with the structures shown.

It is clear that, in case of alkylating agents such as alkyl halide, the alkylation preferentially occurred on the 6-*N*-position of the pyrimidine ring, whereas with DMC in the presence of 18-crown-6 and K_2CO_3, it took place chemoselectively on the 5′-hydroxy position of the ribofuranosyl moiety, without affecting the NH group of the pyrimidine base. Furthermore, methylation with DMC, in the presence of 18-crown-6, gave much better yields for the reaction.

A plausible mechanism for selective alkylation on the primary alcohol can be outlined in the following way. DMC is a versatile compound that enables phenolic mono-O-, mono-S-, and mono-N-methylation reactions and can react as a methylating agent in the presence of a nucleophile.[14] 18-Crown-6 is an organic compound that can

coordinate some metal ions in its central cavity. Especially, 18-crown-6 displays a particular affinity for the potassium cation.[15] The above chemoselectivity can be explained on the basis of the principle of hard and soft acids and bases (HSAB principle).[16] The chemoselective alkylation is due to the ambident character of DMC which, in the presence of 18-crown-6 and K_2CO_3, acts as a hard electrophile. In contrast, the hydroxy group at the 5′-position of ribofuranosyl moiety of compound **4** can convert into an alkoxy ion, which is a harder nucleophile due to the increased basicity of K_2CO_3 in the presence of 18-crown-6. Consequently, the DMC, as a hard nucleophile, reacts with the alkoxy ion, as a hard electrophile, rather than the imino ion at the 3-position of the pyrimidine moiety, which behaves as a soft nucleophile. In 1987, Hovinen reported that the alkylation of 2′,3′-*O*-isopropylideneuridine by methyl iodide, in the presence of excess sodium hydride in THF, afforded the 5′-*O*-methyl derivative, exclusively.[17] Later, Bessodes et al. also showed that 2′,3′-*O*-isopropylideneuridine can be preferentially methylated on the 5′-hydroxy group by methyl iodide in THF, in the presence of 18-crown-6 and potassium hydroxide at room temperature, in 55% yield along with the N-alkylated product at the 3-position.[18] It is worthwhile to report here that DMC is a well known, non-toxic reagent[19] and our methodology of chemoselective O-alkylation for the primary alcohol is widely applicable in nucleic acid chemistry and green chemistry.

The method of this chemoselective alkylation was also applicable to uridine derivatives. Namely, the 2′,3′-*O*-isopropylidene derivatives of uridine (**10a**)[20] and 5-bromouridine (**10b**)[21] were similarly methylated by treatment with DMC, in the presence of 18-crown-6 and K_2CO_3 in anhydrous DMF, to afford the corresponding 5′-*O*-methyl-2′,3′-*O*-isopropylideneuridine (**11a**)[22] and its 5-bromo derivative **11b**[21] with yields of 57% and 61%, respectively (Scheme 2). Predominately, the methylation occurred on the 5′-hydroxy group of the ribofuranosyl moiety.



10a,**b** **11a**,**b** **12a**,**b**

Scheme 2 *Reagents and conditions*: (i) Me_2CO_3, 18-crown-6, K_2CO_3, anhyd DMF, 22–25 °C, 1 d; (ii) 0.5 M HCl, MeOH, 50 °C, 5–7 h.

In conclusion, we have demonstrated the first general synthesis of [1,2,5]thiadiazolo[3,4-*d*]pyrimidine nucleosides, namely, 6-N- or 5′-O-substituted 4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidines, as a new class of cardiovascular and anti-inflammatory agents. In addition, the combination of DMC with 18-crown-6 and potassium carbonate made it possible to set up the chemoselective alkylation of 2′,3′-*O*-isopropylidene derivatives of 4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine **4**, uridine **10a** and 5-bromouridine **10b**. Under the investigated conditions in the presence of 18-crown-6, DMC is far superior for chemoselective alkylation of such compounds as **4**, **10a**, and **10b**. The conditions lead to only primary alcoholic O-methylation without affecting the NH group of the pyrimidine base, whereas the alkylation of **4** with alkyl halide gave only 6-N-alkylation without affecting the primary hydroxy group of the ribofuranosyl moiety. Further synthetic and mechanistic investigations as well as biological evaluation of the [1,2,5]thiadiazolo[3,4-*d*]pyrimidine nucleoside analogs are in progress, and will be reported in detail shortly.

Melting points were determined using a Yanagimoto micro-melting point hot-stage apparatus and are uncorrected. IR spectra were recorded using a Jasco FT/IR-200 spectrophotometer as Nujol mulls. Mass spectra were recorded at 70 eV ionizing voltage with FAB ionization using VG-70SE spectrometer and glycerol as a matrix. NMR spectra were obtained with a Varian VXR 300 MHz spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (ppm) based on internal TMS (δ = 0.00 pm) in $CDCl_3$ or DMSO-d_6. ^{13}C NMR chemical shifts are expressed in ppm based on solvent signal of $CDCl_3$. The coupling constants (*J* values) are given in Hz. UV spectra were recorded in EtOH with a Beckman DU-600 spectrophotometer and absorption values in italics refer to wavelengths at which shoulders or inflexions occur in the absorption. Specific rotation was recorded in H_2O or dioxane with a DIP-1000 digital polarimeter. Elemental analyses were measured by a Yanako CHN Corder MT-5 apparatus. All reagents were of commercial quality from freshly opened containers and were used without further purification. Reaction progress was monitored by analytical thin layer chromatograph (TLC) on precoated glass plates (silica gel 60 F_{254}, Merck) and products were visualized by UV light. Column chromatography was accomplished on Daisogel IR-60 (63/210 μm, Daiso Co.). The reaction temperatures are indicated as the temperature of the oil bath. Anhydrous DMF was stored over activated 4 Å molecular sieves and all other solvents were dried and freshly distilled prior to use.

6-Amino-2′,3′-*O*-isopropylideneuridine (2)

A mixture of 5′,6-anhydro-6-hydroxy-2′,3′-*O*-isopropylideneuridine[13] (**1**; 5.0 g, 17.73 mmol), $AcONH_4$ (0.96 g, 12.46 mmol) or NH_4Cl (0.66 g, 12.45 mmol) and liquid NH_3 (~50 mL) in a sealed steel tube was heated at 50 °C (20 kg/cm^2) for 1.5 d. The ammonia was removed and the residue was purified by column chromatography on silica gel (EtOAc–EtOH, 10:1) to give the product **2**.

Yield: 2.1 g (40%); colorless powdery crystals; mp 229–231 °C (EtOAc–EtOH) (Lit.[12] 229–230 °C); R_f = 0.43 (EtOAc–EtOH, 4:1).

IR (Nujol): 3405 (OH), 3300, 3260, 3210 (NH), 1735, 1665 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 3.76–3.88 (m, 2 H, 5′-H_2), 4.08–4.13 (m, 1 H, 4′-H), 4.87 (s, 1 H, 5-H), 4.94 (dd, $J_{2',3'}$ = 6.9 Hz, $J_{3',4'}$ = 4.2 Hz, 1 H, 3′-H), 5.13 (dd, $J_{1',2'}$ = 4.2 Hz, $J_{2',3'}$ = 6.9 Hz, 1 H, 2′-H), 5.18 (dd, *J* = 4.2, 3.6 Hz, 1 H, 5′-OH, D_2O exch.), 6.32 (s, 2 H, NH_2, D_2O exch.), 6.52 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, 1′-H), 9.57 (s, 1 H, NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = 271 nm (4.52).

5-Hydroxyimino-6-imino-2′,3′-*O*-isopropylidene-5,6-dihydrouridine (3)

Compound **2** (0.5 g, 1.67 mmol) was dissolved in a mixture of EtOH (10 mL) and EtOAc (10 mL) by warming. After cooling to r.t., amyl nitrite (1.2 mL) was added to the solution dropwise with stirring over 15 min. After one drop of concd HCl was added to the solution, purple crystals deposited immediately. The mixture was stirred at r.t. for 15 min more then kept in a refrigerator for several hours. The solid deposit was filtered and washed with EtOAc to afford the product **3**.

Yield: 0.49 g (89%); purple powdery crystals; mp >300 °C (EtOAc–EtOH) (Lit.[12] >300 °C); R_f = 0.54 (EtOAc–AcOH, 4:1).

IR (Nujol): 3335 (OH), 3200, 3150, 3090 (NH), 1740, 1700 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.28 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 3.51–3.60 (m, 2 H, 5′-H_2), 4.07 (m, 1 H, 4′-H), 4.78 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 3.9 Hz, 1 H, 3′-H), 5.16 (dd, $J_{1',2'}$ = 4.2 Hz, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 5.36 (br s, 1 H, 5′-OH, D_2O exch.), 6.16 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, 1′-H), 9.58 (br s, 1 H, =NOH, D_2O exch.), 11.65 (s, 1 H, 3-NH, D_2O exch.), 13.84 (br s, 1 H, =NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = 316 nm (4.55).

4-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (4)

A mixture of 5-hydroxyimino-6-imino-2′,3′-*O*-isopropylidene-5,6-dihydorouridine (**3**; 0.5 g, 1.52 mmol) and 5% AcOH (10 mL) was stirred at r.t., and to the solution was added $Na_2S_2O_3{\cdot}5H_2O$ (0.70 g, 2.82 mmol) in portions. Stirring was continued until the color of the solution changed completely from purple to colorless. When the reaction was complete, the solution was evaporated to dryness in vacuo at low temperature. To the residue was added H_2O (15 mL) and the solution was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhyd $MgSO_4$, and evaporated to dryness. After trituration of the residue with *n*-hexane, the resulting precipitate was collected by filtration and washed with *n*-hexane to isolate the product **4**.

Yield: 0.38 g (73%); colorless powdery crystals; mp 126–127 °C (EtOAc) (Lit.[12] 126–127 °C); R_f = 0.52 (EtOAc).

IR (Nujol): 3450 (OH), 3200 (NH), 1720 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 2.93 (br s, 1 H, 5′-OH, D_2O exch.), 3.82 [br d (dd after addition of D_2O, $J_{4',5'a}$ = 3.9 Hz, J_{gem} = 12.3 Hz), 1 H, 5′-H_a], 3.92 (ddd, $J_{4',5'b}$ = 2.7 Hz, $J_{5'b,OH}$ = 3.6 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H_b), 4.33 (ddd, $J_{3',4'} = J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 2.7 Hz, 1 H, 4′-H), 5.07 (dd, $J_{2',3'}$ = 6.6 Hz, $J_{3',4'}$ = 3.9 Hz, 1 H, 3′-H), 5.32 (dd, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 6.6 Hz, 1 H, 2′-H), 6.54 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, 1′-H), 9.03 (br s, 1 H, NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = *248* (3.73), 314 nm (4.13).

4-β-D-Ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (5)

A solution of **4** (0.5 g, 1.46 mmol) in a mixture of MeOH (50 mL) and 0.5 M HCl (20 mL) was heated at 50 °C for 7 h. After cooling to r.t., the solution was neutralized with Et_3N and evaporated in vacuo. Finally, the solution was co-evaporated with EtOH to complete dryness and the dry residue was treated with absolute EtOH. The insoluble material was filtered off, the filtrate was evaporated in vacuo and the residue was purified by column chromatography (EtOAc) to give the product **5**.

Yield: 0.39 g (88%); colorless powdery crystals; mp 115–116 °C (amorphous, EtOAc) (Lit.[12] 115 °C); R_f = 0.27 (EtOAc).

IR (Nujol): 3385 (OH), 3190 (NH), 1720 (C=O).

^{1}H NMR (DMSO-d_6): δ = 3.47 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 6.0 Hz, J_{gem} = 11.7 Hz), $J_{4',5'a}$ = 6.0 Hz, $J_{5'a,OH}$ = 5.7 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a], 3.65 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 4.2 Hz, J_{gem} = 11.7 Hz), $J_{4',5'b}$ = 4.5 Hz, $J_{5'b,OH}$ = 5.7 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b], 3.78 (ddd, $J_{3',4'}$ = 5.7 Hz, $J_{4',5'a}$ = 6.0 Hz, $J_{4',5'b}$ = 4.5 Hz, 1 H, 4′-H), 4.18 [q (dd after addition of D_2O, $J_{2',3'}$ = 5.7 Hz, $J_{3',4'}$ = 5.4 Hz), *J* = 5.7 Hz, 1 H, 3′-H], 4.60 (t, *J* = 5.7 Hz, 1 H, 5′-OH, D_2O exch.), 4.67 [q (dd after addition of D_2O, $J_{1',2'}$ = 4.8 Hz, $J_{2',3'}$ = 5.7 Hz), *J* = 5.4 Hz, 1 H, 2′-H], 5.03 (d, $J_{3',OH}$ = 6.0 Hz, 1 H, 3′-OH, D_2O exch.), 5.17 (d, $J_{2',OH}$ = 5.1 Hz, 1 H, 2′-OH, D_2O exch.), 6.12 (d, $J_{1',2'}$ = 4.5 Hz, 1 H, 1′-H), 12.03 (s, 1 H, NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = *249* (3.71), 315 nm (4.09).

Formation of 6-N-Alkylated [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione Nucleosides 6a–f; General Procedure

To a cooled mixture of 4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione (**4**; 0.34g, 1.0 mmol) and anhyd K_2CO_3 (0.207 g, 1.5 mmol) in dried DMF (4–5 mL) at 0 °C, was added an appropriate alkyl halide (1.5 mmol), and the mixture was stirred vigorously at 0 °C to r.t. for between 10 min and 4 h. The reaction mixture was poured into H_2O (10 mL) and the resulting solution was extracted with EtOAc (2 × 8 mL). The organic layer was dried over anhyd $MgSO_4$ and evaporated in vacuo to yield either a colorless oil or a white solid. The crude product was purified by column chromatography (EtOAc–*n*-hexane) to afford the corresponding compounds **6a–f** as colorless powdery crystals.

6-Methyl-4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (6a)

Yield: 0.18 g (54%); $[\alpha]_D^{20}$ –24.95 (*c* 1.00, dioxane); mp 72–74 °C; R_f = 0.76 (EtOAc).

IR (Nujol): 1685, 1720 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 2.86 (dd, $J_{5'a,OH}$ = 9.0 Hz, $J_{5'b,OH}$ = 3.3 Hz, 1 H, 5′-OH, D_2O exch.), 3.49 (s, 3 H, NCH_3), 3.82 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 3.6 Hz, J_{gem} = 12.3 Hz), $J_{4',5'a}$ = 3.6 Hz, $J_{5'a,OH}$ = 9.0 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H_a], 3.92 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 2.7 Hz, J_{gem} = 12.3 Hz), $J_{4',5'b}$ = 3.0 Hz, $J_{5'b,OH}$ = 3.3 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H_b], 4.33 (ddd, $J_{3',4'} = J_{4',5'a}$ = 3.6 Hz, $J_{4',5'b}$ = 3.0 Hz, 1 H, 4′-H), 5.10 (dd, $J_{2',3'}$ = 6.6 Hz, $J_{3',4'}$ = 3.6 Hz, 1 H, 3′-H), 5.31 (dd, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 6.6 Hz, 1 H, 2′-H), 6.61 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, 1′-H).

^{13}C NMR ($CDCl_3$): δ = 25.57 and 27.55 [C(CH_3)$_2$], 29.27 (NCH_3), 63.03 ($C_{5'}$), 80.55 ($C_{3'}$), 82.36 ($C_{2'}$), 86.63 ($C_{4'}$), 92.09 ($C_{1'}$), 114.85 [$C(CH_3)_2$], 137.84 (C_{7a}), 150.00 (C_{3a}), 153.51 (C_5), 154.29 (C_7).

UV (EtOH): λ_{max} (log ε) = 250 (3.70), 312 nm (4.04).

Anal. Calcd for $C_{13}H_{16}N_4O_6S$: C, 43.82; H, 4.53; N, 15.72. Found: C, 43.97; H, 4.57; N, 15.59.

6-Ethyl-4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (6b)

Yield: 0.25 g (68%); $[\alpha]_D^{20}$ –26.19 (*c* 1.00, dioxane); mp 55–57 °C; R_f = 0.77 (EtOAc).

IR (Nujol): 1682, 1730 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3CH$_2$), 1.38 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 2.87 (dd, $J_{5'a,OH}$ = 9.0 Hz, $J_{5'b,OH}$ = 3.3 Hz, 1 H, 5′-OH, D_2O exch.), 3.87 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 3.6 Hz, J_{gem} = 12.3 Hz), $J_{4',5'a}$ = 3.6 Hz, $J_{5'a,OH}$ = 9.0 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H_a], 3.93 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 2.7 Hz, J_{gem} = 12.3 Hz), $J_{4',5'b}$ = 2.7 Hz, $J_{5'b,OH}$ = 3.3 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H_b], 4.14 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2), 4.34 (ddd, $J_{3',4'} = J_{4',5'a}$ = 3.6 Hz, $J_{4',5'b}$ = 2.7 Hz, 1 H, 4′-H), 5.09 (dd,

$J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 3.6 Hz, 1 H, 3′-H), 5.32 (dd, $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 6.61 (d, $J_{1',2'}$ = 3.3 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 253 (3.59), 311 nm (4.01).

Anal. Calcd for $C_{14}H_{18}N_4O_6S$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.59; H, 4.74; N, 15.21.

6-Propyl-4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (6c)
Yield: 0.27 g (71%); $[\alpha]_D^{20}$ –27.77 (*c* 1.00, dioxane); mp 60–62 °C; R_f = 0.75 (EtOAc).

IR (Nujol): 1684, 1730 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.00 (t, *J* = 7.2 Hz, 3 H, CH_3CH$_2$CH$_2$), 1.38 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.67–1.75 (m, 2 H, CH$_3$CH_2CH$_2$), 2.86 (dd, $J_{5'a,OH}$ = 9.0 Hz, $J_{5'b,OH}$ = 3.3 Hz, 1 H, 5′-OH, D_2O exch.), 3.81 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 3.6 Hz, J_{gem} = 12.3 Hz), $J_{4',5'a}$ = 3.6 Hz, $J_{5'a,OH}$ = 9.0 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H$_a$], 3.93 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 2.7 Hz, J_{gem} = 12.3 Hz), $J_{4',5'b}$ = 3.0 Hz, $J_{5'b,OH}$ = 3.3 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H$_b$], 4.00–4.05 (m, 2 H, CH$_3$CH$_2$CH_2N), 4.34 (ddd, $J_{3',4'}$ = $J_{4',5'a}$ = 3.6 Hz, $J_{4',5'b}$ = 3.0 Hz, 1 H, 4′-H), 5.09 (dd, $J_{2',3'}$ = 6.6 Hz, $J_{3',4'}$ = 3.6 Hz, 1 H, 3′-H), 5.32 (dd, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 6.6 Hz, 1 H, 2′-H), 6.60 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 253 (3.72), 313 nm (4.06).

Anal. Calcd for $C_{15}H_{20}N_4O_6S$: C, 46.87; H, 5.24; N, 14.57. Found: C, 46.90; H, 5.64; N, 14.60.

6-Benzyl-4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (6d)
Yield: 0.32 g (74%); $[\alpha]_D^{20}$ –25.20 (*c* 1.00, dioxane); mp 165–167 °C; R_f = 0.78 (EtOAc).

IR (Nujol): 1680, 1726 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 2.77 (dd, $J_{5'a,OH}$ = 9.0 Hz, $J_{5'b,OH}$ = 3.3 Hz, 1 H, 5′-OH, D_2O exch.), 3.78 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 3.6 Hz, J_{gem} = 12.3 Hz), $J_{4',5'a}$ = 3.6 Hz, $J_{5'a,OH}$ = 9.0 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H$_a$], 3.90 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 2.7 Hz, J_{gem} = 12.3 Hz), $J_{4',5'b}$ = 3.0 Hz, $J_{5'b,OH}$ = 3.3 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H$_b$], 4.30 (ddd, $J_{3',4'}$ = $J_{4',5'a}$ = 3.6 Hz, $J_{4',5'b}$ = 3.0 Hz, 1 H, 4′-H), 5.09 (dd, $J_{2',3'}$ = 6.6 Hz, $J_{3',4'}$ = 3.6 Hz, 1 H, 3′-H), 5.24 (s, 2 H, CH_2Ph), 5.29 (dd, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 6.6 Hz, 1 H, 2′-H), 6.59 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, 1′-H), 7.28–7.35 (m, 3 H, *m*,*p*-HPh), 7.50–7.53 (m, 2 H, *o*-HPh).

UV (EtOH): λ_{max} (log ε) = 247 (3.61), 312 nm (4.05).

Anal. Calcd for $C_{19}H_{20}N_4O_6S$: C, 52.77; H, 4.66; N, 12.96. Found: C, 52.96; H, 5.00; N, 13.00.

Ethyl 2-{4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dion-6-yl}acetate (6e)
Yield: 0.24 g (56%); $[\alpha]_D^{20}$ –21.04 (*c* 1.00, dioxane); mp 59–61 °C; R_f = 0.74 (EtOAc).

IR (Nujol): 1687, 1734 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3 H, CH_3CH$_2$O), 1.37 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 2.71 (dd, $J_{5'a,OH}$ = 9.0 Hz, $J_{5'b,OH}$ = 3.0 Hz, 1 H, 5′-OH, D_2O exch.), 3.78 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 3.9 Hz, J_{gem} = 12.3 Hz), $J_{4',5'a}$ = 3.9 Hz, $J_{5'a,OH}$ = 9.0 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H$_a$], 3.91 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 2.7 Hz, J_{gem} = 12.3 Hz), $J_{4',5'b}$ = 3.0 Hz, $J_{5'b,OH}$ = 3.0 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H$_b$], 4.25 (q, *J* = 7.2 Hz, 2 H, CH$_3$CH_2O), 4.31 (ddd, $J_{3',4'}$ = $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 3.0 Hz, 1 H, 4′-H), 4.79 (br s, 2 H, CH_2N), 5.07 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 3.9 Hz, 1 H, 3′-H), 5.30 (dd, $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 6.60 (d, $J_{1',2'}$ = 3.3 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 248 (3.59), 312 nm (4.01).

Anal. Calcd for $C_{16}H_{20}N_4O_8S$: C, 44.86; H, 4.71; N, 13.08. Found: C, 45.15; H, 4.69; N, 12.96.

Ethyl 4-{4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dion-6-yl}butanoate (6f)
Yield: 0.34 g (74%); $[\alpha]_D^{20}$ –28.21 (*c* 1.00, dioxane); mp 52–54 °C; R_f = 0.72 (EtOAc).

IR (Nujol): 1682, 1732 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H, CH_3CH$_2$O), 1.38 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 2.04 (quin, *J* = 7.2 Hz, 2 H, OCCH$_2$CH_2CH$_2$N), 2.41 (t, *J* = 7.2 Hz, 2 H, OCCH_2CH$_2$CH$_2$N), 2.87 (dd, $J_{5'a,OH}$ = 8.4 Hz, $J_{5'b,OH}$ = 3.3 Hz, 1 H, 5′-OH, D_2O exch.), 3.81 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 3.9 Hz, J_{gem} = 12.3 Hz), $J_{4',5'a}$ = 3.6 Hz, $J_{5'a,OH}$ = 8.4 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H$_a$], 3.91 [br d (dd after addition of D_2O, $J_{4',5'b}$ = 2.7 Hz, J_{gem} = 12.3 Hz), J_{gem} = 12.3 Hz, 1 H, 5′-H$_b$], 4.09 (q, *J* = 7.2 Hz, 2 H, CH$_3$CH_2O), 4.14 (t, *J* = 6.9 Hz, 2 H, CH_2N), 4.33 (ddd, $J_{3',4'}$ = $J_{4',5'a}$ = 3.6 Hz, $J_{4',5'b}$ = 3.0 Hz, 1 H, 4′-H), 5.08 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 3.6 Hz, 1 H, 3′-H), 5.31 (dd, $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 6.60 (d, $J_{1',2'}$ = 3.3 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 255 (3.66), 312 nm (4.03).

MS (FAB, glycerol matrix): *m*/*z* = 457 [MH^+].

Formation of 5′-Methoxy Derivatives of Thiadiazolopyrimidine and Uridine Nucleosides 8, 11a and 11b; General Procedure
A mixture of either **4**, **10a** or **10b** (1.0 mmol), anhyd K_2CO_3 (2.5 mmol), 18-crown-6 (1 mmol) and anhyd DMF (6 mL) was cooled at 22 °C. Me_2CO_3 (DMC; 1.5 mmol) was added to the mixture, and the mixture was stirred at 22–25 °C for 1 d. After the reaction was complete, the reaction mixture was poured into H_2O (8 mL) and neutralized with 10% HCl to yield a white solid. The resulting solid was collected by filtration and purified by column chromatography (EtOAc–*n*-hexane, 1:1) to afford the corresponding pure products **8**, **11a** and **11b** as colorless powdery crystals.

5′-*O*-Methyl-4-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*, 6*H*)-dione (8)
Yield: 0.27 g (75%); $[\alpha]_D^{20}$ –29.84 (*c* 1.00, dioxane); mp 200–202 °C; R_f = 0.82 (EtOAc).

IR (Nujol): 1724 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 3.72 (s, 3 H, 5′-OCH$_3$), 4.30–4.42 (m, 3 H, 5′-H$_2$ and 4′-H), 5.00 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 3.6 Hz, 1 H, 3′-H), 5.33 (dd, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 6.61 (d, $J_{1',2'}$ = 1.5 Hz, 1 H, 1′-H), 8.78 (s, 1 H, NH, D_2O exch.).

^{13}C NMR ($CDCl_3$): δ = 25.38 and 27.26 [C(*C*H$_3$)$_2$], 55.02 (OCH$_3$), 67.66 (C$_{5'}$), 81.66 (C$_{3'}$), 84.05 (C$_{2'}$), 85.78 (C$_{4'}$), 91.19 (C$_{1'}$), 114.57 [*C*(CH$_3$)$_2$], 138.64 (C$_{7a}$), 149.39 (C$_{3a}$), 154.17 (C$_5$), 155.57 (C$_7$).

UV (EtOH): λ_{max} (log ε) = 253 (3.54), 312 nm (3.99).

Anal. Calcd for $C_{13}H_{16}N_4O_6S$: C, 43.82; H, 4.53; N, 15.72. Found: C, 43.91; H, 4.45; N, 15.58.

5′-*O*-Methyl-2′,3′-*O*-isopropylideneuridine (11a)
Yield: 0.17 g (57%); $[\alpha]_D^{20}$ –18.60 (*c* 1.00, dioxane); mp 64–66 °C (Lit.[20] foamy glass); R_f = 0.49 (EtOAc).

IR (Nujol): 1694, 1752 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 3.80 (s, 3 H, 5′-OCH$_3$), 4.33–4.43 (m, 3 H, 4′-H and 5′-H$_2$), 4.84 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 3.3 Hz, 1 H, 3′-H), 4.96 (dd, $J_{1',2'}$ = 2.1 Hz, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 5.72 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 5-H), 5.73 (d, $J_{1',2'}$ = 2.1 Hz, 1 H, 1′-H), 7.30 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 6-H), 8.81 (s, 1 H, NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = 257 nm (3.26) (Lit.[20] 262 nm, MeOH).

5-Bromo-5′-*O*-methyl-2′,3′-*O*-isopropylideneuridine (11b)
Yield: 0.23 g (61%); $[\alpha]_D^{20}$ –22.90 (*c* 1.00, dioxane); mp 88–90 °C (Lit.[21] foamy glass); R_f = 0.71 (EtOAc).

IR (Nujol): 1692, 1754 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 3.82 (s, 3 H, 5′-OCH_3), 4.35 (dd, $J_{4',5'a}$ = 5.4 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H_a), 4.43 (dd, $J_{4',5'b}$ = 3.0 Hz, J_{gem} = 12.3 Hz, 1 H, 5′-H_b), 4.45 (ddd, $J_{3',4'}$ = 3.3 Hz, $J_{4',5'a}$ = 5.4 Hz, $J_{4',5'b}$ = 3.0 Hz, 1 H, 4′-H), 4.83 (dd, $J_{2',3'}$ = 6.3 Hz, $J_{3',4'}$ = 3.3 Hz, 1 H, 3′-H), 4.92 (dd, $J_{1',2'}$ = 2.4 Hz, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 5.83 (d, $J_{1',2'}$ = 2.4 Hz, 1 H, 1′-H), 7.72 (s, 1 H, 6-H), 9.31 (s, 1 H, NH, D_2O exch.).

^{13}C NMR ($CDCl_3$): δ = 25.41 and 27.26 (2 × CH_3), 55.46 (OCH_3), 67.36 ($C_{5'}$), 80.89 ($C_{3'}$), 84.75 ($C_{2'}$), 90.03 ($C_{4'}$), 93.89 ($C_{1'}$), 97.42 (C_5), 114.97 [$C(CH_3)_2$], 140.89 (C_6), 149.60 (C_2), 159.11 (C_4).

UV (EtOH): λ_{max} (log ε) = 274 nm (4.10).

Formation of Deprotected Thiadiazolopyrimidine and Uridine Nucleosides 7a–f, 9, 12a and 12b; General Procedure
A solution of **6a–f**, **8**, **11a** or **11b** (1.0 mmol) in a mixture of MeOH (25 mL) and 0.5 M HCl (10 mL) was heated at 50–60 °C for 3–5 h. After cooling to r.t., the solution was neutralized with Et_3N and evaporated in vacuo. Finally, the solution was co-evaporated with EtOH to complete dryness and the dry residue was treated with absolute EtOH. The insoluble material was filtered off, the filtrate was evaporated in vacuo and the residue was purified by column chromatography (EtOAc–*n*-hexane) to give the corresponding products **7a–f**, **9**, **12a**, and **12b** as colorless powdery crystals.

6-Methyl-4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (7a)
Yield: 0.24 g (75%); $[\alpha]_D^{20}$ –20.09 (*c* 1.00, dioxane); mp 91–93 °C; R_f = 0.32 (EtOAc).

IR (Nujol): 1678, 1725 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.30 (s, 3 H, NCH_3), 3.48 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 6.3 Hz, J_{gem} = 11.7 Hz), $J_{4',5'a}$ = 6.3 Hz, $J_{5'a,OH}$ = 5.7 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a], 3.66 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 4.2 Hz, J_{gem} = 11.7 Hz), $J_{4',5'b}$ = 4.8 Hz, $J_{5'b,OH}$ = 5.4 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b], 3.79 (q, *J* = 6.0 Hz, 1 H, 4′-H), 4.19 [q (t after addition of D_2O, *J* = 5.7 Hz), *J* = 6.0 Hz, 1 H, 3′-H], 4.59 (dd, $J_{5'a,OH}$ = 5.7 Hz, $J_{5'b,OH}$ = 5.4 Hz, 1 H, 5′-OH, D_2O exch.), 4.66 [q (t after addition of D_2O, *J* = 5.1 Hz), *J* = 5.4 Hz, 1 H, 2′-H], 5.05 (d, $J_{3',OH}$ = 6.0 Hz, 1 H, 3′-OH, D_2O exch.), 5.17 (d, $J_{2',OH}$ = 5.4 Hz, 1 H, 2′-OH, D_2O exch.), 6.19 (d, $J_{1',2'}$ = 4.5 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 253 (3.75), 314 nm (4.06).

Anal. Calcd for $C_{10}H_{12}N_4O_6S$: C, 37.97; H, 3.82; N, 17.71. Found: C, 38.02; H, 3.77; N, 17.49.

6-Ethyl-4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (7b)
Yield: 0.26 g (79%); $[\alpha]_D^{20}$ –17.73 (*c* 1.00, H_2O); mp 85–87 °C; R_f = 0.33 (EtOAc).

IR (Nujol): 1680, 1724 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.18 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2), 3.48 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 6.3 Hz, J_{gem} = 11.7 Hz), $J_{4',5'a}$ = 6.0 Hz, $J_{5'a,OH}$ = 5.4 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a], 3.67 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 3.9 Hz, J_{gem} = 11.7 Hz), $J_{4',5'b}$ = 4.5 Hz, $J_{5'b,OH}$ = 5.1 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b], 3.80 (ddd, $J_{3',4'}$ = 6.0 Hz, $J_{4',5'a}$ = 6.0 Hz, $J_{4',5'b}$ = 4.5 Hz, 1 H, 4′-H), 3.96 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2), 4.19 [q (dd after addition of D_2O, $J_{2',3'}$ = 5.7 Hz, $J_{3',4'}$ = 6.0 Hz), *J* = 5.7 Hz, 1 H, 3′-H], 4.56 (dd, $J_{5'a,OH}$ = 5.4 Hz, $J_{5'b,OH}$ = 5.1 Hz, 1 H, 5′-OH, D_2O exch.), 4.66 [q (dd after addition of D_2O, $J_{1',2'}$ = 4.5 Hz, $J_{2',3'}$ = 5.7 Hz), *J* = 5.1 Hz, 1 H, 2′-H], 5.02 (d, $J_{3',OH}$ = 6.0 Hz, 1 H, 3′-OH, D_2O exch.), 5.15 (d, $J_{2',OH}$ = 5.1 Hz, 1 H, 2′-OH, D_2O exch.), 6.19 (d, $J_{1',2'}$ = 4.5 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 256 (3.50), 313 nm (3.90).

Anal. Calcd for $C_{11}H_{14}N_4O_6S·2/5H_2O$: C, 39.14; H, 4.42; N, 16.60. Found: C, 39.43; H, 4.49; N, 16.78.

6-*n*-Propyl-4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (7c)
Yield: 0.28 g (82%); $[\alpha]_D^{20}$ –13.18 (*c* 1.00, H_2O); mp 46–48 °C; R_f = 0.31 (EtOAc).

IR (Nujol): 1680, 1725 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, $CH_3CH_2CH_2$), 1.60 (sext, *J* = 7.2 Hz, 2 H, $CH_3CH_2CH_2$), 3.48 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 6.0 Hz, J_{gem} = 11.7 Hz), $J_{4',5'a}$ = 6.3 Hz, $J_{5'a,OH}$ = 5.7 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a], 3.66 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 4.2 Hz, J_{gem} = 11.7 Hz), $J_{4',5'b}$ = 4.8 Hz, $J_{5'b,OH}$ = 5.4 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b], 3.79 (ddd, $J_{3',4'}$ = 6.0 Hz, $J_{4',5'a}$ = 6.3 Hz, $J_{4',5'b}$ = 4.8 Hz, 1 H, 4′-H), 3.86 (t, *J* = 7.2 Hz, 2 H, $CH_3CH_2CH_2N$), 4.20 [q (dd after addition of D_2O, $J_{2',3'}$ = 5.4 Hz, $J_{3',4'}$ = 6.0 Hz), *J* = 6.0 Hz, 1 H, 3′-H], 4.61 (dd, $J_{5'a,OH}$ = 5.7 Hz, $J_{5'b,OH}$ = 5.4 Hz, 1 H, 5′-OH, D_2O exch.), 4.66 [q (dd after addition of D_2O, $J_{1',2'}$ = 4.2 Hz, $J_{2',3'}$ = 5.4 Hz), *J* = 5.4 Hz, 1 H, 2′-H], 5.04 (d, $J_{3',OH}$ = 6.3 Hz, 1 H, 3′-OH, D_2O exch.), 5.17 (d, $J_{2',OH}$ = 5.4 Hz, 1 H, 2′-OH, D_2O exch.), 6.18 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 255 (3.57), 314 nm (4.10).

Anal. Calcd for $C_{12}H_{16}N_4O_6S·2/5H_2$: C, 41.00; H, 4.82; N, 15.94. Found: C, 41.31; H, 4.91; N, 15.85.

6-Benzyl-4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (7d)
Yield: 0.31 g (80%); $[\alpha]_D^{20}$ –20.20 (*c* 1.00, dioxane); mp 83–85 °C; R_f = 0.35 (EtOAc).

IR (Nujol): 1680, 1725 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.47 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 6.3 Hz, J_{gem} = 11.7 Hz), $J_{4',5'a}$ = 6.3 Hz, $J_{5'a,OH}$ = 5.4 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a], 3.66 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 4.2 Hz, J_{gem} = 11.7 Hz), $J_{4',5'b}$ = 4.2 Hz, $J_{5'b,OH}$ = 4.5 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b], 3.78 (ddd, $J_{3',4'}$ = 6.0 Hz, $J_{4',5'a}$ = 6.3 Hz, $J_{4',5'b}$ = 4.2 Hz, 1 H, 4′-H), 4.19 [ddd (t after addition of D_2O, *J* = 5.7 Hz), $J_{2',3'}$ = 5.7 Hz, $J_{3',4'}$ = 6.0 Hz, $J_{3',OH}$ = 6.0 Hz, 1 H, 3′-H], 4.58 (dd, $J_{5'a,OH}$ = 5.4 Hz, $J_{5'b,OH}$ = 4.5 Hz, 1 H, 5′-OH, D_2O exch.), 4.66 [t (t after addition of D_2O, *J* = 5.7 Hz), *J* = 4.8 Hz, 1 H, 2′-H], 5.05 (d, $J_{3',OH}$ = 6.0 Hz, 1 H, 3′-OH, D_2O exch.), 5.10 (s, 2 H, CH_2-Ph), 5.15(d, $J_{2',OH}$ = 5.4 Hz, 1 H, 2′-OH, D_2O exch.), 6.19 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, 1′-H), 7.25–7.38 (m, 5 H, PhH).

UV (EtOH): λ_{max} (log ε) = 255 (3.65), 314 nm (4.01).

Anal. Calcd for $C_{16}H_{16}N_4O_6S$: C, 48.97; H, 4.11; N, 14.28. Found: C, 49.11; H, 4.06; N, 14.26.

Ethyl 2-{4-β-D-Ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dion-6-yl}acetate (7e)
Yield: 0.30 g (77%); $[\alpha]_D^{20}$ –17.53 (*c* 1.00, H_2O); mp 112–114 °C; R_f = 0.30 (EtOAc).

IR (Nujol): 1680, 1728 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.23 (t, *J* = 6.9 Hz, 3 H, CH_3CH_2O), 3.48 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 6.3 Hz, J_{gem} = 11.7 Hz), $J_{4',5'a}$ = 6.3 Hz, $J_{5'a,OH}$ = 6.0 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a], 3.65 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 5.1 Hz, J_{gem} = 11.7 Hz), $J_{4',5'b}$ = 5.1 Hz, $J_{5'b,OH}$ = 4.5 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b], 3.81 (ddd, $J_{3',4'}$ = 5.7 Hz, $J_{4',5'a}$ = 6.3 Hz, $J_{4',5'b}$ = 5.1 Hz, 1 H, 4′-H), 4.14–

4.21 (m, 1 H, 3′-H), 4.17 (q, J = 6.9 Hz, 2 H, CH_3CH_2O), 4.62 (dd, $J_{5'a,OH}$ = 6.0 Hz, $J_{5'b,OH}$ = 4.5 Hz, 1 H, 5′-OH, D_2O exch.), 4.66–4.75 (m, 1 H, 2′-H), 4.68 (s, 1 H, NCH_a), 4.69 (s, 1 H, NCH_b), 5.06 (d, $J_{3',OH}$ = 6.0 Hz, 1 H, 3′-OH, D_2O exch.), 5.24 (d, $J_{2',OH}$ = 5.7 Hz, 1 H, 2′-OH, D_2O exch.), 6.18 (d, $J_{1',2'}$ = 4.5 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 247 (3.75), 314 nm (4.09).

Anal. Calcd for $C_{13}H_{16}N_4O_8S$: C, 40.21; H, 4.15; N, 14.43. Found: C, 40.02; H, 4.36; N, 14.50.

Ethyl 4-{4-β-D-Ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dion-6-yl}butanoate (7f)

Yield: 0.31 g (74%); $[\alpha]_D^{20}$ –20.36 (*c* 1.00, H_2O); mp 47–49 °C; R_f = 0.29 (EtOAc).

IR (Nujol): 1680, 1730 (C=O) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.18 (t, J = 7.2 Hz, 3 H, CH_3CH_2O), 1.86 (quin, J = 6.9 Hz, 2 H, $CH_2CH_2CH_2N$), 2.38 (q, J = 7.2 Hz, 2 H, $CH_2CH_2CH_2N$), 3.48 [ddd (dd after addition of D_2O, $J_{4',5'a}$ = 6.3 Hz, J_{gem} = 11.7 Hz), $J_{4',5'a}$ = 6.3 Hz, $J_{5'a,OH}$ = 6.0 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a], 3.67 [ddd (dd after addition of D_2O, $J_{4',5'b}$ = 5.1 Hz, J_{gem} = 11.7 Hz), $J_{4',5'b}$ = 5.1 Hz, $J_{5'b,OH}$ = 5.4 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b], 3.79 (ddd, $J_{3',4'}$ = 6.0 Hz, $J_{4',5'a}$ = 6.3 Hz, $J_{4',5'b}$ = 5.1 Hz, 1 H, 4′-H), 3.95 (t, J = 6.9 Hz, 2 H, $CH_2CH_2CH_2N$), 4.04 (q, J = 7.2 Hz, 2 H, CH_3CH_2O), 4.19 [q (br s after addition of D_2O), J = 6.0 Hz, 1 H, 3′-H], 4.58 (dd, $J_{5'a,OH}$ = 6.0 Hz, $J_{5'b,OH}$ = 5.4 Hz, 1 H, 5′-OH, D_2O exch.), 4.64 [q (br s after addition of D_2O), J = 5.1 Hz, 2′-H], 5.03 (d, $J_{3',OH}$ = 6.3 Hz, 1 H, 3′-OH, D_2O exch.), 5.15 (d, $J_{2',OH}$ = 5.1 Hz, 1 H, 2′-OH, D_2O exch.), 6.18 (d, $J_{1',2'}$ = 4.2 Hz, 1 H, 1′-H).

UV (EtOH): λ_{max} (log ε) = 253 (3.70), 313 nm (4.02).

Anal. Calcd for $C_{15}H_{20}N_4O_8S{\cdot}2/5H_2O$: C, 42.53; H, 4.95; N, 13.23. Found: C, 42.58; H, 5.00; N, 13.62.

5′-*O*-Methyl-4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (9)

Yield: 0.27 g (84%); $[\alpha]_D^{20}$ –21.58 (*c* 1.00, H_2O); mp 94–96 °C; R_f = 0.20 (EtOAc).

IR (Nujol): 1715 (C=O) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.68 (s, 3 H, 5′-OCH_3), 3.96 (ddd, $J_{3',4'}$ = 5.7 Hz, $J_{4',5'a}$ = 7.2 Hz, $J_{4',5'b}$ = 3.3 Hz, 1 H, 4′-H), 4.18 (dd, $J_{4',5'a}$ = 7.2 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a), 4.30 [q (t after addition of D_2O, J = 6.3 Hz), J = 6.3 Hz, 1 H, 3′-H], 4.39 (dd, $J_{4',5'b}$ = 3.3 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b), 4.60 [ddd (dd after addition of D_2O, $J_{1',2'}$ = 3.9 Hz, $J_{2',3'}$ = 6.3 Hz), $J_{1',2'}$ = 3.9 Hz, $J_{2',3'}$ = 5.7 Hz, $J_{2',OH}$ = 5.1 Hz, 1 H, 2′-H], 5.23 (d, $J_{3',OH}$ = 6.3 Hz, 1 H, 3′-OH, D_2O exch.), 5.29 (d, $J_{2',OH}$ = 5.1 Hz, 1 H, 2′-OH, D_2O exch.), 6.14 (d, $J_{1',2'}$ = 3.9 Hz, 1 H, 1′-H), 12.03 (s, 1 H, NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = 243 (3.46), 313 nm (3.98).

Anal. Calcd for $C_{10}H_{12}N_4O_6S$: C, 37.97; H, 3.82; N, 17.71. Found: C, 38.05; H, 3.78; N, 17.57.

5′-*O*-Methyluridine (12a)

Yield: 0.22 g (85%); $[\alpha]_D^{20}$ –13.04 (*c* 1.00, H_2O); mp 153–155 °C (Lit.[17,22] 134–135 °C); R_f = 0.09 (EtOAc).

IR (Nujol): 1696, 1742 (C=O) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.72 (s, 3 H, 5′-OCH_3), 3.93 [ddd (t after addition of D_2O, J = 5.1 Hz), $J_{1',2'}$ = 5.1 Hz, $J_{2',3'}$ = 5.4 Hz, $J_{2',OH}$ = 5.4 Hz, 1 H, 2′-H], 3.99 (ddd, $J_{3',4'}$ = 5.1 Hz, $J_{4',5a'}$ = 5.7 Hz, $J_{4',5b'}$ = 3.6 Hz, 1 H, 4′-H), 4.07 [ddd (t after addition of D_2O, J = 5.1 Hz), $J_{2',3'}$ = 5.4 Hz, $J_{3',4'}$ = 5.1 Hz, $J_{3',OH}$ = 5.4 Hz, 1 H, 3′-H], 4.24 (dd, $J_{4',5a'}$ = 5.7 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_a), 4.33 (dd, $J_{4',5b'}$ = 3.6 Hz, J_{gem} = 11.7 Hz, 1 H, 5′-H_b), 5.31 (d, $J_{3',OH}$ = 5.4 Hz, 1 H, 3′-OH, D_2O exch.), 5.48 (d, $J_{2',OH}$ = 5.4 Hz, 1 H, 2′-OH, D_2O exch.), 5.64 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 5-H), 5.75 (d, $J_{1',2'}$ = 5.1 Hz, 1 H, 1′-H), 7.59 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 6-H), 11.36 (s, 1 H, NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = 260 nm (3.96).

5-Bromo-5′-*O*-methyluridine (12b)

Yield: 0.28 g (82%); $[\alpha]_D^{20}$ –15.58 (*c* 1.00, dioxane); mp 190–192 °C; R_f = 0.52 (EtOAc).

R (Nujol): 1680, 1751 (C=O) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.74 (s, 3 H, 5′-OCH_3), 3.94 [q (t after addition of D_2O, J = 5.1 Hz), J = 5.1 Hz, 1 H, 2′-H], 4.01 (ddd, $J_{3',4'}$ = 5.4 Hz, $J_{4',5a'}$ = 4.8 Hz, $J_{4',5b'}$ = 3.3 Hz, 1 H, 4′-H), 4.09 [ddd (t after addition of D_2O, J = 5.1 Hz), $J_{2',3'}$ = 5.1 Hz, $J_{3',4'}$ = 5.4 Hz, $J_{3',OH}$ = 5.4 Hz, 1 H, 3′-H], 4.27 (dd, $J_{4',5a'}$ = 4.8 Hz, J_{gem} = 12.0 Hz, 1 H, 5′-H_a), 4.35 (dd, $J_{4',5b'}$ = 3.3 Hz, J_{gem} = 12.0 Hz, 1 H, 5′-H_b), 5.26 (d, $J_{3',OH}$ = 5.4 Hz, 1 H, 3′-OH, D_2O exch.), 5.46 (d, $J_{2',OH}$ = 5.4 Hz, 1 H, 2′-OH, D_2O exch.), 5.72 (d, $J_{1',2'}$ = 5.1 Hz, 1 H, 1′-H), 7.99 (s, 1 H, 6-H), 11.85 (s, 1 H, NH, D_2O exch.).

UV (EtOH): λ_{max} (log ε) = 277 nm (3.96) [Lit.[21] 279 (pH 1), 277 (pH 10)].

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