A One-Pot Approach to Novel Pyridazine C-Nucleosides

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Abstract: The synthesis of glycosides and modified nucleosides represents a wide research field in organic chemistry. The classical methodology is based on coupling reactions between a glycosyl donor and an acceptor. An alternative strategy for new C-nucleosides is used in this approach, which consists of modifying a pre-existent furyl aglycone. This approach is applied to obtain novel pyridazine C-nucleosides starting with 2- and 3-(ribofuranosyl)furans. It is based on singlet oxygen [4+2] cycloaddition followed by reduction and hydrazine cyclization under neutral conditions. The mild three-step one-pot procedure leads stereoselectively to novel pyridazine C-nucleosides of pharmacological interest. The use of acetyl as protecting groups provides an elegant direct route to a deprotected new pyridazine C-nucleoside.

Keywords: glycosyl furans; singlet oxygen; [4+2] cycloaddition; C-nucleosides; photooxygenation; pyridazines; reduction

1. Introduction

The synthesis of nucleoside analogues has a prominent role in the field of organic chemistry and biology [1]. Among modified nucleosides, C-nucleosides represent a special moiety of this compound class due to their higher stability towards enzymatic and chemical hydrolysis than that of natural N-nucleosides, as well as owing to the interesting biological and pharmacological properties of some of their derivatives [1,2]. The first natural C-nucleoside isolated was pseudouridine [3], followed by showdomycin [4], and oxazino-mycin [5]—all characterized by important pharmacological activities, from antitumor to antibacterial. C-nucleosides comprise a sugar moiety and a non-natural heterocyclic base connected by a carbon–carbon bond. The stability of this bond and the broad structural variation in the heterocyclic base account for the high interest in this compound class [6–9]. The main synthetic approach for C-glycosides is based on coupling reactions between a glycosyl donor and an acceptor in the presence of a promoter [10]. Alternatively, structural elaborations on a pre-existing aglycone are performed to afford the final C-glycoside [10]. In this context, the use of the furan as starting aglycone is of particular interest due to the easy preparation and high versatility of this heterocycle [11]. We elaborated a green procedure based on the use of a furan aglycone as a building block and the [4+2] cycloaddition of singlet oxygen [12] by dye-sensitized photooxygenation as a strategy for providing the final desired structures. Indeed, singlet oxygen addition to furan systems offers various elegant routes to differently functionalized derivatives through structural elaborations of the initial endoperoxides, the 2,3,7-trioxabicyclo[2.2.1]hept-5-enes [13]. Although the furan endoperoxides are thermally unstable, their reactivity can be controlled and opportunely addressed by working at low temperatures. With this strategy, it is possible to synthesize novel glycosyl derivatives, such as glycalcs [14] and spiroketals of monosaccharides, which are structural motifs of many products characterized by important and assorted biological properties [15]. Pyridazine [16], pyrazoline [14], bis-epoxide [17], and spirocyclic C-nucleosides [17] were also obtained. Key intermediates are often unsaturated...
2. Results and Discussion

For this purpose, the suitable furans 2a,b were initially prepared by the β-stereoselective reduction [23] of the corresponding furyl ketoses 1a,b (Scheme 1). The latter were obtained by coupling reactions between 2,3,5-tri-O-benzyl-D-ribo-1,4-lactone as the glycosyl donor, and 2- or 3-furyllithium, according to a previously reported procedure [15].

![Scheme 1. Stereoselective synthesis of 2- and 3-(β-ribofuranosyl)furan 2a,b.](image)

The reduction times were particularly long (overnight), probably owing to the open-chain structures of the furyl derivatives 1a,b in equilibrium with very small amounts of the corresponding cyclic structures, as evidenced by their proton spectra. Although the 1H-NMR spectra of both crude reaction mixtures showed only the presence of products 2a,b, a considerable loss of material occurred during purification by silica gel chromatography, even if performed under N2, as reported in the literature for 2a [24]. Firstly, 2a was photooxygenated at −20 °C in dichloromethane with methylene blue as the sensitizer (Scheme 2). When the reaction was complete (90 min, TLC or 1H-NMR), Et2S (1.2 equiv.) was added to the crude mixture, which was kept at −20 °C to avoid thermal rearrangement of the intermediate endoperoxide [12–17].
One-pot synthesis of the 3-(2′,3′,5′-tri-O-benzyl-β-D-ribofuranosyl)pyridazine (5a).

Figure 1. NOESY correlation in 5a.

The novel conditions were applied to furan 2b and, in good total yield, led to the new 4-(ribofuranosyl)pyridazine 5b (Scheme 4). The β-configuration was also confirmed for 5b by the 2D-NOESY experiment.
The relevance of the protecting groups in the glycoside chemistry, as well as the possibility of using easily removable groups, motivated us to extend the one-pot route to a sugarfuran protected with acetyl. Hence, we carried out a coupling reaction with the 2,3,5-tetra-1-\(\text{O}\)-acetyl-\(\beta\)-D-ribofuranose as the glycosyl donor and methyl furan-2-carboxylate as the acceptor—both commercially available—in the presence of SnCl\(_4\) as the promoter, according to a reported procedure [17].

This synthetic approach was described to lead mainly to \(\beta\)-anomers due to the participation of the neighboring acetyl group at the C-2 of the sugar ring during the departure of the leaving group at C-1 [25,26].

Surprisingly, the reaction afforded only the ribofuranosyl furan 2c, whose \(\alpha\)-configuration was assigned by the 2D-NOESY experiment (Scheme 5). Indeed, a NOE effect between the H-1' and the H-3' of the sugar ring in C\(_6\)D\(_6\) was evidenced (Figure 2). In this anisotropic solvent, the H-3' and H-4' signals do not overlap as it occurs when the \(^1\)H-NMR spectrum is recorded in CDCl\(_3\) (aromatic-solvent-induced shift (ASIS) effects) [27]. The previously incorrect \(\beta\)-configuration for 2c was assigned on the basis of the constant value of the coupling, in comparison with those of the two anomers of showdomycin, and the synthetic procedure used [17].

![Scheme 4. One-pot synthesis of the 4-(2',3',5'-tri-O-benzyl-\(\beta\)-D-ribofuranosyl)pyridazine (5b).](image)

![Scheme 5. Synthesis of the ribofuranosyl furan \(\alpha\)-2c.](image)

![Figure 2. NOESY correlation in 2c.](image)

Attempts to synthesize the \(\beta\)-anomer of 2c by carrying out the coupling reaction in acetonitrile and/or by using different promoters (BF\(_3\) or TMSOTf) failed, and only the \(\alpha\)-1c was obtained, as evidenced spectroscopically and chromatographically.

A possible rationalization of this unexpected result is that the coupling proceeds here through anchimeric assistance by the acetyl group at the C-5'. A similar stereochemical trend is described in the iodination of some acetylated oxathiolanes [28]. Otherwise, the use of the only \(\beta\)-anomer of 1,2,3,5-tetra-\(\text{O}\)-acetyl-\(\beta\)-D-ribofuranose as a glycosyl donor together with the observed full stereoselectivity suggest that the reaction to methyl furan-2-carboxylate could occur through a concerted pathway leading to the only \(\alpha\)-anomer of 2c. This hypothesis could be confirmed by the use of the only \(\alpha\)-anomer of 1,2,3,5-tetra-\(\text{O}\)-acetyl-\(\beta\)-D-ribofuranose as a glycosyl donor, which should lead to the \(\beta\)-anomer of 1c. Control experiments showed that the peracetylation reaction in pyridine or catalyzed by the
TMSOTf afforded the peracetylated pyranosic form of the sugar as the main product, as well as the β-anomer of 1,2,3,5-tetra-O-acetyl-D-ribofuranose, which is the only commercially available form.

The mild procedure for pyridazine C-nucleoside was later applied to the 2-(2',3',5'-tri-O-acetyl-α-D-ribofuranosyl)furan (2c). Unexpectedly, the sequence of reactions on 2c led in high yield to the deprotected pyridazine C-nucleoside 5c (Scheme 6).

![Scheme 6. One-pot synthesis of the 6-(α-D-ribofuranosyl)pyridazine-3-carbohydrazide (5c).](image)

With the aim of preserving the methyl ester function, as well as the protecting acetyl groups on the sugar ring, the reaction was carried out under the same conditions except for the use of 1.2 equiv. of hydrazine. In this case, the one-pot procedure afforded the protected pyridazine C-nucleoside 5d good yield, showing that the cyclization proceeds more rapidly than the attack to the ester functions (Scheme 7).

![Scheme 7. One-pot synthesis of the 3-(2',3',5'-tri-O-acetyl-α-D-ribofuranosyl)-6-(methoxycarbonyl) pyridazine (5d).](image)

The structure of compound 5d, assigned by NMR data, was confirmed by X-ray crystallographic analysis (Figure 3).

![Figure 3. Molecular structure of 5d showing the α-configuration (Ortep view with ellipsoids drawn at 30% probability level).](image)

Pyridazine 5d was quite stable; however, it slowly aromatized after several days at room temperature, leading to the corresponding furan 6d (Scheme 8). Similar elimination was previously observed in a benzyloxylated pyridazine C-nucleoside [18].
3. Materials and Methods

3.1. General Information

Melting points are uncorrected. The $^1$H- and $^{13}$C-NMR spectra were recorded on a Fourier Transform NMR Varian 500 Unity Inova spectrometer. The carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by $^1$H-$^1$H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences. $^1$H-$^1$H proximities through space within a molecule were determined by NOESY experiments. X-ray analysis was performed on a Bruker-Nonius Kappa CCD (Nonius BV, Delft, The Netherlands) diffractometer (graphite monochromated Mo K$_\alpha$ radiation, $\lambda = 0.71073$ Å, CCD rotation images, thick slices, $\varphi$ and $\omega$ scans to fill asymmetric unit). Analytical TLC was performed on precoated silica gel plates (Macherey-Nagel, Düren, Germany) with 0.2 mm film thickness. Spots were visualized by UV light and by spraying with EtOH/H$_2$SO$_4$ (95:5 on)

Scheme 8. Aromatization of 5d into 6d.

3.2. Synthesis of 2a,b

A solution of 243 mg (0.5 mmol) of 1a [15] in 5.2 mL of acetonitrile, cooled to $-40^\circ$C, was added to 240 µL (3 equiv.) of triethylsilane and 70 µL (1 equiv.) of BF$_3$·Et$_2$O. The solution was stirred at $-40^\circ$C for 4 h, which was allowed to rise to r.t. while the mixture was further stirred overnight. A saturated aqueous solution of K$_2$CO$_3$ was later added (10 mL), and the mixture was kept under stirring for 10 min. The organic layer was extracted with solvents were used.

The synthesis of 2b was performed as reported above for 2a, starting from 1b [15]. The flash silica gel (n-hexane/ether 1:1 v/v) afforded the novel C-nucleoside $\beta$-2b [24] with 35% yield.

$\beta$-2a: oil; $^1$H-NMR; $\delta = 3.61$ (m, 2 H, H-5$'$-A and H-5$'$-B), 4.05 (dd, $J = 4.9$ Hz, 1 H, H-3$'$), 4.18 (dd, $J = 6.5$, 4.9 Hz, 1 H, H-2$'$), 4.30 (m, 1 H, H-4$'$), 4.50–4.66 (m, 6 H, CH$_2$ of Bn), 5.04 (d, $J = 6.5$ Hz, 1 H, H-1$'$), 6.34 (bs, 2 H, H-3 and H-4), 7.23–7.33 (m, 15 H, 3 Ph), 7.34 (bs, 1 H, H-5); $^{13}$C-NMR; $\delta = 70.3$ (t), 72.1 (2× t), 73.4 (t), 76.5 (d), 77.7 (d), 79.9 (d), 81.5 (d), 108.9 (d), 110.3 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.0 (d), 128.3 (d), 137.7 (s), 138.0 (s), 138.2 (s), 142.5 (d), 152.2 (s).

The synthesis of 2b was performed as reported above for 2a, starting from 1b [15]. The flash silica gel (n-hexane/ether 1:1 v/v) afforded the novel C-nucleoside $\beta$-2b [24] with 35% yield.

$\beta$-2b: mp 49–51 °C; $^1$H-NMR; $\delta = 3.56$ (dd, $J = 10.4$, 4.4 Hz, 1 H, H-5$'$-A), 3.59 (dd, $J = 10.4$, 4.4 Hz, 1 H, H-5$'$-B), 3.84 (dd, $J = 6.6$, 4.9 Hz, 1 H, H-2$'$), 3.99 (dd, $J = 4.9$, 3.8 Hz, 1 H, H-3$'$), 4.28 (m, 1 H, H-4$'$), 4.48–4.62 (m, 6 H, CH$_2$ of Bn), 4.97 (d, $J = 6.6$ Hz, 1 H, H-1$'$), 6.31 (bs, 1 H, H-4), 7.22–7.33 (m, 15 H, 3 Ph), 7.35 (bs, 1 H, H-5), 7.40 (s, 1 H, H-2); $^{13}$C-NMR; $\delta = 70.4$ (t), 71.9 (t), 72.2 (t), 73.4 (t), 75.7 (d), 77.5 (d), 81.6 (d), 82.2 (d), 108.5 (d), 124.4 (s), 127.6 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.3 (d), 137.7 (s), 137.9 (s), 138.1 (s), 140.2 (d), 143.2 (d). HRMS (ESI-TOF) calcd. for C$_{30}$H$_{30}$O$_5$ [M + H]$^+$ 471.2171, found 471.2168. Anal. Calcd. for C$_{30}$H$_{30}$O$_5$: C, 76.57; H, 6.43. Found: C, 76.45; H, 6.52.
3.3. Synthesis of Pyridazines: General Procedure

A 0.02 M solution of 2 (0.25 mmol) in dry CH₂Cl₂ was irradiated at −20 °C with a halogen lamp (650 W) in the presence of methylene blue (MB, 1 × 10⁻³ mmol), while dry oxygen was bubbled through the solution. The progress of each reaction was checked by periodically monitoring (TLC, or ¹H-NMR) the disappearance of 2. When the reaction was complete (ca. 90 min), 1.2 equiv. of Et₂S were added to the crude solution, which was kept at −20 °C for 2 h. Thus, the solvent and the unreacted Et₂S were removed under reduced pressure, and 1 mL of a hydrazine solution in THF (2 M) was added (1.2 equiv. for 5d). The resulting mixture was kept under stirring at r.t. for 1 h. Subsequently, the solvent and the excess hydrazine were removed under reduced pressure to afford the crude product 5.

Silica gel chromatography (n-hexane/ether) afforded the pure pyridazine derivatives 5.

3-(2′,3′,5′-tri-O-Benzyl-β-D-ribofuranosyl)pyridazine (5a), (68% yield, from 2a); oil; ¹H-NMR (CDCl₃); δ = 3.66 (dd, J = 10.4, 3.3 Hz, 1 H, H-5′), 3.88 (dd, J = 10.4, 2.5 Hz, 1 H, H-5′), 3.97 (dd, J = 7.7, 4.9 Hz, 1 H, H-3′), 4.31 (dd, J =4.9, 2.7 Hz, 1 H, H-2′), 4.36 (d, J = 12.0 Hz, 1 H, CH of Bn), 4.44 (m, 1 H, H-4′), 4.50 (d, J = 11.5 Hz, 1 H, CH of Bn), 4.56 (d, J = 12.0 Hz, 1 H, CH of Bn), 4.57 (d, J = 11.5 Hz, 1 H, CH of Bn), 4.74 (d, J = 12.0 Hz, 1 H, CH of Bn), 4.86 (d, J = 12.0 Hz, 1 H, CH of Bn), 5.48 (d, J = 2.7 Hz, 1 H, H-1′) 7.20 (dd, J = 8.8, 4.9 Hz, 1 H, H-5), 7.22–7.40 (m, 15 H, 3×Ph), 7.80 (dd, J = 8.8, 1.6 Hz, 1 H, H-4), 9.03 (dd, J = 4.9, 1.6 Hz, 1 H, H-6); ¹³C-NMR; δ = 69.1 (t), 71.7 (t), 72.1 (t), 73.4 (t), 76.3 (d), 80.9 (d), 81.5 (d), 83.3 (d), 124.9 (d), 126.6 (d), 127.7 (d), 127.8 (d), 128.2 (d), 137.7 (s), 138.0 (s), 150.4 (d), 162.8 (s). HRMS (ESI-TOF) calcd. for C₃₀H₃₁N₂O₅ [M + H]⁺ 483.2284, found 483.2280. Anal. Calcd. for C₃₀H₃₀N₂O₅: C, 74.67; H, 6.27; N 5.81. Found: C, 74.56; H, 6.35; N 5.72.

4-(2′,3′,5′-tri-O-Benzyl-β-D-ribofuranosyl)pyridazine (5b), (72% yield, from 2b); oil; ¹H-NMR (CDCl₃); δ = 3.57 (dd, J = 10.4, 3.3 Hz, 1 H, H-5′), 3.65 (dd, J = 10.4, 3.8 Hz, 1 H, H-5′), 3.77 (dd, J = 7.7, 4.9 Hz, 1 H, H-2′), 4.02 (dd, J = 4.9, 2.7 Hz, 1 H, H-3′), 4.38 (m, 2H, H-4′ and CH of Bn), 4.51 (d, J = 12.0 Hz, 1 H, CH of Bn), 4.56 (d, J = 12.0 Hz, 1 H, CH of Bn), 4.57(d, J = 12.0 Hz, 1 H, CH of Bn), 4.60 (s, 2 H, CH₂ of Bn), 4.98 (d, J = 7.7 Hz, 1 H, H-1′), 7.17–7.35 (m, 15 H, 3×Ph), 7.47 (bd, J = 5.5 Hz 1 H, H-5), 9.00 (d, J = 5.5 Hz, 1 H, H-6), 9.16 (bs, 1 H, H-3); ¹³C-NMR; δ = 70.1 (t), 72.0 (t), 72.7 (t), 73.6 (t), 77.1 (d), 78.6 (d), 82.7 (d), 83.4 (d), 123.3 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.1 (d), 136.9 (s), 137.4 (s), 137.6 (s), 140.3 (s), 149.7 (d), 151.0 (d). HRMS (ESI-TOF) calcd. for C₃₀H₃₁N₂O₅ [M + H]⁺ 483.2284, found 483.2281. Anal. Calcd. for C₃₀H₃₀N₂O₅: C, 74.67; H, 6.27; N 5.81. Found: C, 74.53; H, 6.37; N 5.69.

6-(α-D-Ribofuranosyl)pyridazine-3-carboxyhydrazide (5c), (80% yield, from 2c); m.p. 215–217 °C; ¹H-NMR (DMSO); δ = 3.49 (m, 1 H, H-5′), 3.66 (m, 1 H, H-5′), 3.98 (m, 1 H, H-4′), 4.19 (m, 2 H, H-3′ and H-5′), 4.77 (t, J = 4.8 Hz, 1 H, OH), 4.95 (d, J = 4.4 Hz, 1 H, OH), 5.00 (d, J = 6.6 Hz, 1 H, OH), 5.33 (d, J = 3.4 Hz, 1 H, H-1′), 7.80 (d, J = 8.6 Hz, 1 H, H-5), 8.11 (d, J = 8.6 Hz, 1 H, H-4); ¹³C-NMR (DMSO); δ = 61.9 (t), 72.9 (d), 73.9 (d), 82.3 (d), 83.5 (d), 125.3 (d), 128.1 (d), 152.6 (s), 162.0 (s), 164.2 (s) Hz. HRMS (ESI-TOF) calcd. for C₁₅H₁₄N₂O₅ [M + H]⁺ 271.1042, found 271.1040. Anal. Calcd. for C₁₅H₁₄N₂O₅: C, 44.44; H, 5.22; N 20.73. Found: C, 44.33; H, 5.30; N 20.69.

3-(2′,3′,5′-tri-O-Acetyl-α-D-ribofuranosyl)-6-(methoxycarbonyl)pyridazine (5d), (75% yield, from 1c); m.p. 124–126 °C; ¹H-NMR (CDCl₃); δ = 1.81 (s, 3 H, CH₃CO), 2.02 (s, 3 H, CH₃CO), 2.14 (s, 3 H, CH₃CO), 4.09 (s, 3 H, OCH₃), 4.23 (dd, J = 11.7, 3.9 Hz, 1 H, H-5′), 4.49 (m, 2 H, H-5′ and H-4′), 5.56 (dd, J = 7.4, 4.0 Hz, 1 H, H-3′), 5.78 (d, J = 4.0 Hz, 1 H, H-1′), 5.94 (dd, J = 4.0 Hz, 1 H, H-2′), 7.89 (d, J = 7.4 Hz, 1 H, H-5), 8.22 (d, J = 7.4 Hz, 1 H, H-4); ¹³C-NMR (CDCl₃); δ = 17.0 (q), 20.4 (q), 20.8 (q), 53.4 (q), 63.3 (t), 72.2 (d), 73.4 (d), 78.4 (d), 80.4 (d), 125.8 (d), 127.5 (d), 150.9 (s), 162.0 (s), 164.6 (s), 168.8 (s), 169.5 (s), 170.6 (s). HRMS (ESI-TOF) calcd. for C₁₇H₂₁N₂O₅ [M + H]⁺ 397.1247, found 397.1244. Anal. Calcd. for C₁₇H₂₀N₂O₅: C, 51.52; H, 5.09; N, 7.07. Found: C, 52.33; H, 5.20; N 7.18.
3.4. Aromatization of 5d

Crystals of 5d (25 mg) were kept without solvent at r.t. for one week. A $^1$H-NMR spectrum was then recorded, which showed the presence of the furan 6d and traces of acetic acid. TLC chromatography (n-hexane/ether 6:4 v/v) afforded the furan 6d as solid in 85% yield.

m.p. 169–170 °C; $^1$H-NMR (CDCl$_3$); $\delta$ = 2.12 (s, 3 H, CH$_3$CO), 4.08 (s, 3 H, OCH$_3$), 5.16 (s, 1 H, H-5), 6.64 (d, $J$ = 3.5 Hz, 1 H, H-4'), 7.49 (d, $J$ = 3.5 Hz, 1 H, H-3'), 7.95 (d, $J$ = 8.7 Hz, 1 H, H-5), 1.91 (d, $J$ = 8.7 Hz, 1 H, H-4); $^{13}$C-NMR (CDCl$_3$); $\delta$ = 20.8 (q), 53.2 (q), 57.9 (t), 113.6 (d), 113.7 (d), 121.6 (d), 127.9 (d), 149.4 (s), 150.7 (s), 152.7 (s), 153.1 (s), 164.5 (s), 170.4 (s). HRMS (ESI-TOF) calcd. for C$_{13}$H$_{12}$N$_2$O$_5$ [M + H]$^+$ 277.0824, found 277.0822. Anal. Calcd. for C$_{13}$H$_{12}$N$_2$O$_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.38; H, 4.45; N 10.09.

3.5. X-ray Crystallography of 5d

X-ray analysis was performed on single crystals of 5d obtained as colorless blocks by slow evaporation of a DCM/hexane solution at room temperature. One selected crystal was mounted at ambient temperature on a Bruker-Nonius KappaCCD diffractometer (graphite monochromated Mo K$_\alpha$ radiation, $\lambda$ = 0.71073 Å, CCD rotation images, thick slices, $\varphi$ and $\omega$ scans to fill asymmetric unit). Semiempirical absorption corrections (SADABS [29]) were applied. The structure was solved by direct methods (SIR97 program [30]) and anisotropically refined by the full matrix least-squares method on $F^2$ against all independently measured reflections using SHELXL-2018/3 To SHELXL (version 2018/3) [31] and WinGX software (version 2014.1) [32]. All of the hydrogen atoms were introduced in calculated positions and refined according to a riding model with C–H distances in the range of 0.93–0.98 Å and with $U_{iso}$ (H) equal to 1.2 $U_{eq}$ or 1.5 $U_{eq}$ (C$_{methyl}$) of the carrier atom. Compound 5d crystallizes in P 2$_1$ 2$_1$ 2$_1$ space group with two independent molecules in the asymmetric unit (see Figure S31 of Supporting Information). The two molecules are very similar to each other; in molecule A, one acetyl group is split into two positions with refined occupancy factors of 0.61 and 0.39. Some restraints were introduced in the last stage of refinement to regularize the geometry. In the absence of strong anomalous scatterer atoms, the Flack parameter is meaningless, so it was not possible to assign the absolute configuration by anomalous dispersion effects with diffraction measurements on the crystal. The absolute configuration has been assigned by reference to unchanging chiral centers in the synthetic procedure. A rather high residual electronic density (0.472 eÅ$^{-3}$) is explained by residual thermal disorder of some acetyl groups at ambient temperature. Unfortunately, it was not possible to re-collect data at low temperatures. Crystal data and structure refinement details are reported in Table S1 of SI. Figures were generated using program Ortep-3 [32]. CCDC-1493362.

4. Conclusions

In summary, we highlight that novel pyridazine C-nucleosides can be easily obtained starting with protected ribofuranosyl furans. Appropriate mild conditions to preserve the Z-configuration of the intermediate 1,4-dicarbonyl compound, necessary for the final step that involves the reaction with hydrazine. It is noteworthy that the use of 2a and 2b provides the corresponding 3- and 4-(ribofuranosyl)pyridazines 5a and 5b, respectively, which would be hard to synthesize through direct coupling reactions with complete regioselectivity. Moreover, the use of an acetylated sugar provides a direct route to deprotected pyridazine-C-nucleosides. The three-step one-pot procedure is completely stereoselective and gives the product 5 the same anomeric configuration as the starting sugar furans.

The ease of methodology, together with the good yields of pyridazine-C-nucleosides 5, foresee novel applications in the field of C-nucleosides synthesis since pyridazines are useful intermediates for constructing heterocycle derivatives [33]. These systems are considered by GlaxoSmithKline as one of the “most developable” heteroaromatic rings [34] and are proposed as privileged structures for drug design [35,36]. Moreover, a broad array of
significant biological activities has been evidenced in several compounds with pyridazine rings [37–39].

**Supplementary Materials:** The following are available online. 1H- and 13C-NMR, COSY and NOESY spectra for all new compounds. X-ray crystallographic data for 5d. Supplementary data associated with this article can be found in the online version, at CCDC-1493962, which contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Author Contributions:** Conceptualization F.C.; methodology F.C. and S.V.; NMR mono- and bimolecular spectra F.C. and M.D.; X-ray crystallographic data A.T.; data curation F.C., M.R.I. and M.D.; resources M.R.I.; draft preparation F.C. and M.R.I. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data are contained within the article or the supplementary data file.

**Acknowledgments:** NMR experiments and X-ray crystallography were run at the Dipartimento di Scienze Chimiche, Università di Napoli Federico II.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Sample Availability:** Samples of the compounds are not available from the authors.

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