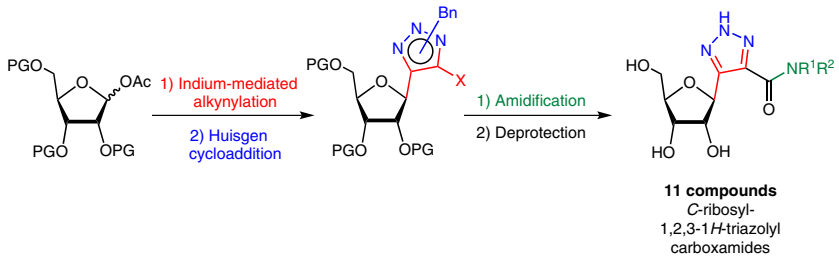
Synthesis C. Solarte et al. Paper

Synthesis of *C*-Ribosyl-1,2,3-triazolyl Carboxamides

Carmen Solarte[a]
Michaël Dos Santos[a]
Simon Gonzalez[a]
Leandro S. M. Miranda[b]
Régis Guillot[c]
Angélique Ferry[a]
Florian Gallier[a]
Jacques Uziel[a]
Nadège Lubin-Germain*[a]

[a] Laboratoire de Chimie Biologique, University of Cergy-Pontoise, 5 mail Gay-Lussac, 95031 Cergy-Pontoise Cedex, France
nadege.lubin-germain@u-cergy.fr
[b] BOSS Laboratory, Federal University of Rio de Janeiro, Av Athos da Silveira Ramos149, 21941909 Ilha do Fundão, Rio de Janeiro, Brazil
[c] ICMMO, University of Paris Sud, 15, rue Georges Clémenceau, 91405 Orsay, France



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Abstract Because of the emergence of new viruses, the need for new antiviral broad-spectrum compounds remains important. In this context, herein the synthesis of *C*-nucleosides, structurally close to ribavirin, a nucleoside presenting various biological activities and used until now particularly for its broad-spectrum antiviral properties, is reported. The compounds were designed in order to increase their stability and the number of hydrogen bond donor or acceptor in comparison to ribavirin, and to investigate the role of the carboxamide group on the biological activity. The efficient synthesis of 11 *C*-nucleosides is based on an indium-mediated alkynylglycosylation as the key step, followed by the construction of the triazole heterocycle. Amidation was performed with primary and secondary amines in yields up to 85%. An analogue nucleoside with a triazole without carboxamide group was also prepared in order to compare its activity. Finally, the carboxamide group was moved to the N-1 triazole position to mimic ribavirin.

Key words *C*-nucleosides, amidation, ribavirin, carboxamides, 1,2,3-triazoles

Ribavirin (RBV) is a non-natural *N*-ribosyl-1,2,4-triazole, synthesized thirty years ago. It exhibits several biological activities such as antitumoral, antiparasitic, and a broad-spectrum antiviral activity.[1] The latter property confers to ribavirin a strategic role in the therapeutic arsenal, especially in the context of emergent infectious diseases such as hemorrhagic infections. Despite its moderate antiviral activity, RBV finds an interest in combination with other direct-acting antiviral (DAA) nucleosides, as it is now the case for the treatment of HCV (hepatitis C virus).[2] However, its use has been significantly limited by its safety profile and side effects, which include hemolytic anemia.

Ribavirin's mechanism of action is problematic since RBV may act through non-specific or pleiotropic mechanism.[3] Five mechanisms are now assumed in the literature. First of all, RBV could act as an antimetabolite against RNA viruses by mimicking natural purine ribonucleosides such as adenosine or guanosine according to the conformation of the nucleosides. Second, RBV could inhibit enzymes such as IMPDH (inosine monophosphate deshydrogenase) or RNA polymerase. IMPDH inhibition leads to a depletion of guanosine whereas RNA polymerase inhibition stops the elongation of nucleic acids. On the other hand, RBV could also act by inhibition of capping enzymes, RBV 5′-triphosphate being structurally similar to the m7 G 'cap' structure.[4] Finally, RBV has been described as an immune modulator or as an error catastrophe agent.

For several reasons, such as reducing the cytotoxicity, avoiding the drug resistance, or the emergence of new viruses, the discovery of new nucleosides has been an objective in medicinal chemistry field. In the last decades, a large number of RBV analogues have been synthesized[5] such as carba-1,2,3-triazoles, 1,2,4-triazole analogues, pyrazoles, and tetrazoles. Besides modifications of the heterocycles mimicking the natural bases, efforts have been made to synthesize *C*-nucleosides[6] presenting a non-hydrolytic carbon–carbon bond at the anomeric position. This C–C link confers more suitable lifetime and better pharmacologic profile. The potential of this family has been recently highlighted by two compounds GS-6620[7] and BCX-4430,[8] which present interesting biological activity against viruses (Figure 1). The first one is a phosphoramidate *C*-adenosine prodrug containing a C2′-Me modification. It has shown a potent and selective HCV inhibitor activity against HCV repli-

cons of genotypes 1 to 6, but presents a limited pharmacological profile. The second one is an imino *C*-adenosine analogue presenting a broad-spectrum antiviral activity, against yellow fever virus, Ebola virus, and filoviruses for instance.

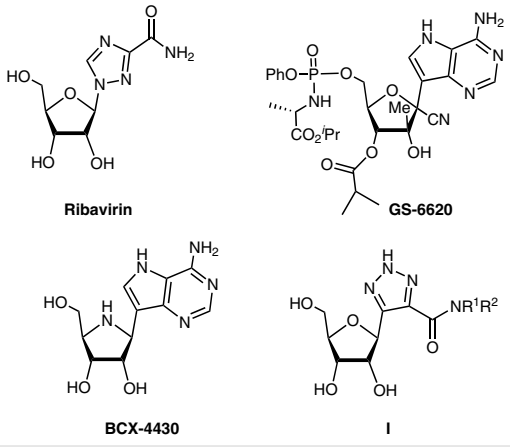
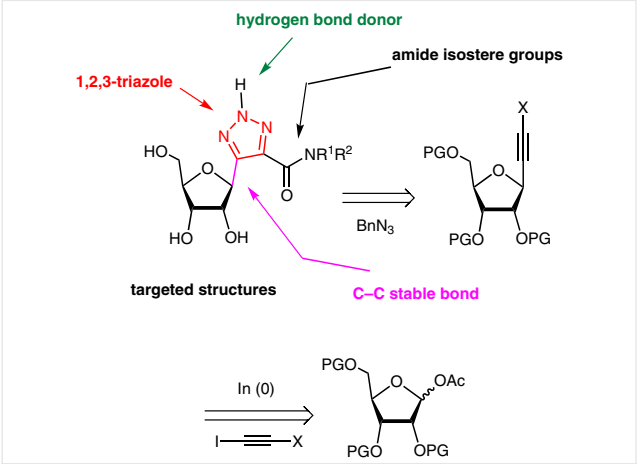


Figure 1 Nucleosides of interest and family targeted

We were interested in developing a *C*-nucleoside family possessing a potential broad-spectrum antiviral activity and structurally close to RBV. In a previous work,[9] we described an access to this family via an indium-mediated alkynyl glycosylation. *C*-Alkynylpyranosides or furanosides were obtained in the presence of indium(0) and iodoalkynes in a good diastereoselective manner. α-Selectivity was observed for pyranosides whereas β-selectivity was noticed for furanosides. The *C*-alkynylribofuranosides could be then engaged in a Huisgen cycloaddition for the triazole construction. This strategy of synthesis leads to 1,2,4-*C*-ribosyltriazole nucleosides, analogues of RBV. We present herein an additional work using the same strategy and leading to several compounds, obtained after chemical modifications of the triazole heterocycle (Scheme 1).

The choice of the targeted nucleosidic structures has been guided by the isosterism of the 1,2,3-triazole compared to the 1,2,4-triazole of RBV and by the stability of the C–C linkage between the triazole and the sugar moiety. Moreover, the targeted nucleosides **I** (Figure 1) present a 2*H*-1,2,3-triazole as potential hydrogen bond donor[10] compared to RBV or recently described 1,2,3-triazole analogues.[11] This N–H bond could enhance interactions with enzymes involved in the viral replication.

Second, it was shown that the carboxamide group plays a key role in the RBV activity and it is present in many drugs.[12] Indeed, the carbonyl group (H-bond acceptor), or the N–H bond (H-bond donor) are capable to establish hydrogen bonds. We were interested in investigating the importance of this carboxamide group by replacing it by isosteric groups or just by eliminating it.

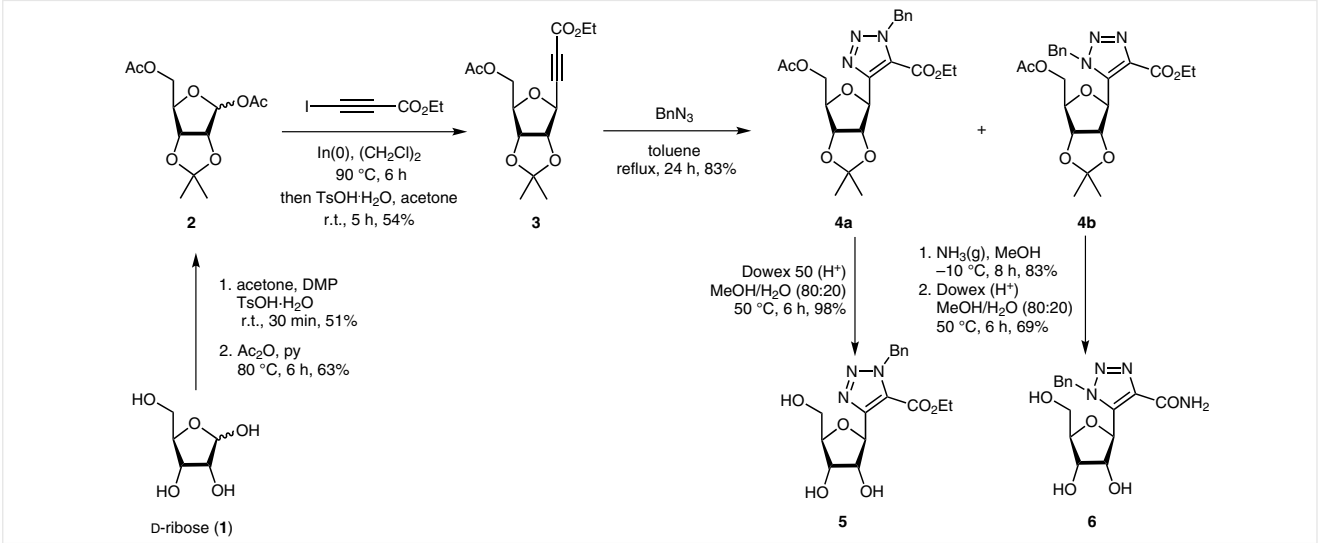


Scheme 1 Retrosynthetic scheme

In our synthetic approach (Scheme 2), compound **3** was obtained in a gram-scale manner from ethyl iodopropiolate and the protected acetyl riboside **2** by alkynyl *C*-glycosylation in the presence of indium(0). The reaction was carried out at reflux in a sealed tube (54% yield) under vigorous stirring. The β-*C*-ribosyl propiolate **3** was then engaged in a Huisgen cycloaddition with benzyl azide leading to a 35:65 mixture of the two regioisomers **4a**,**b**; the structure of each of them was attributed by NMR spectroscopy.[13] Triazoles **4a** and **4b** could be easily separated by flash chromatography but the next steps can be also continued on the mixture. However, a difference of reactivity between **4a** and **4b** was observed, **4b** being more reactive. Compound **5** was obtained from triazole **4a** after deprotection of the acetonide and the acetyl group (99% yield). Compound **6** was synthesized after an amidation reaction (83% yield) followed by the deprotection of the acetonide and the acetyl protecting group (69% yield).

We anticipated that the benzyl group on the triazole heterocycle could lead to steric hindrance. Thus, the synthesis of compounds presenting a deprotected triazole with different amides was planned to evaluate the role of carboxamide group in the biological activity. Different compounds **8** were obtained by amidation of **4b** in the presence of various amines followed by hydrogenolysis in acidic conditions.

Compound **8h** was obtained after amidation of **4b** with gaseous ammonia in methanol (83%), followed by acidic treatment to remove the acetonide, and finally hydrogenolysis of the benzyl group. In previous work,[13] partially regioselective conditions under microemulsion were explored for the cycloaddition, but we underlined that the two regioisomers **4a**,**b** afforded the single tautomer **8h**, identified by X-ray analysis, possessing the H on the central nitrogen atom (Figure 2). The hydrogen atom was located unambiguously (for further details, see the Supporting Information).



Scheme 2 Synthesis of ethyl-3-(β-D-ribofuranosyl)-1-*N*-benzyl-1,2,3-triazole-2-carboxylate (**5**) and 5-(β-D-ribofuranosyl)-1-*N*-benzyl-1,2,3-triazole-4-carboxamide (**6**)

Furthermore, compound **8h** displayed an *anti*-arrangement of the atoms O(1′)–C(1′)–C(1)–N(2) according to the dihedral angle of 0° inferior to 90° (27°).

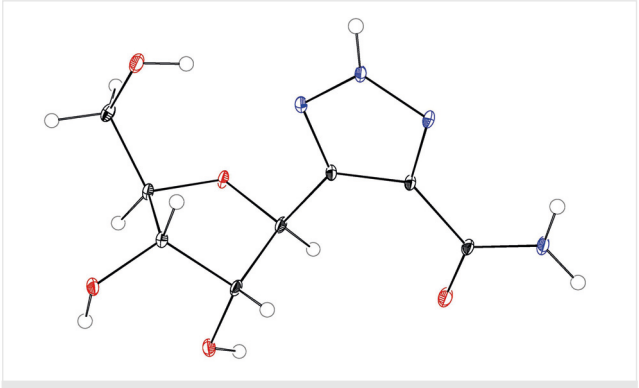
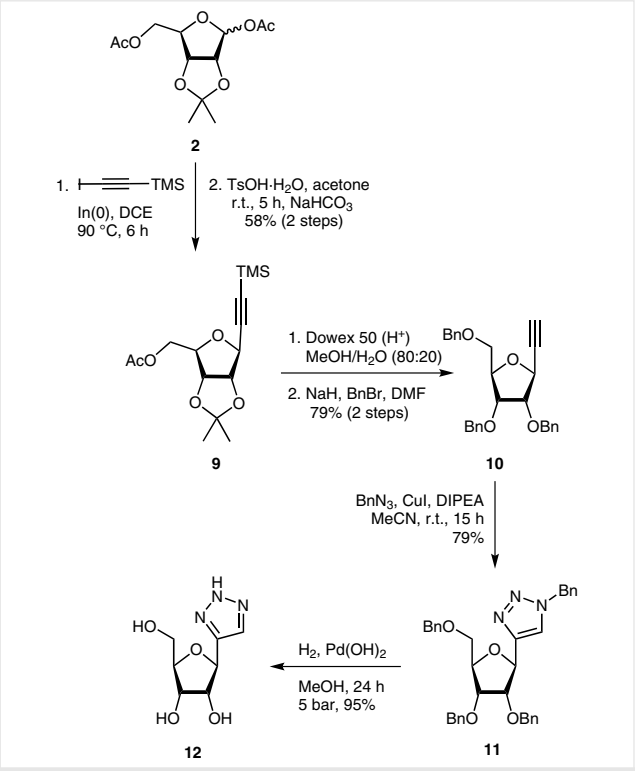


Figure 2 Crystal structure of 5-(β-D-ribofuranosyl)-2*H*-1,2,3-triazole-4-carboxamide (**8h**)

Various primary amines were tested and led to the corresponding carboxamides **7** with yields up to 85% (Table 1). Functionalized amines such as glycine, norephedrine, and tris(hydroxymethyl)amine were also successfully used as well as pyrrolidine, a secondary amine. Unfortunately, deprotection of compounds **7b** and **7i** failed in the hydrogenolysis conditions used previously. The use of other conditions led either to the recovery of starting material or to its degradation.

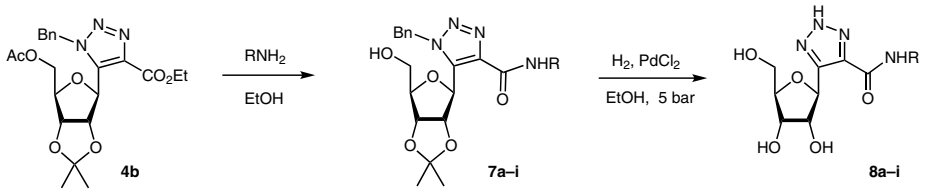
In order to investigate the role of the carboxamide group, compound **12** was synthesized, following the same reactions sequence, but using iodotrimethylsilylacetylene for the *C*-alkynylglycosylation (Scheme 3). In this case, the cycloaddition regioselectivity was controlled by a copper(I) catalysis leading to **11**, which was then fully deprotected by hydrogenolysis. Compound **12** was obtained in 35% overall yield in a four steps synthesis.

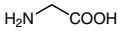
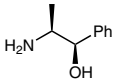
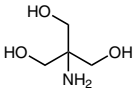


Scheme 3 Synthesis of 4-(β-D-ribofuranosyl)-2*H*-1,2,3-triazole (**12**)

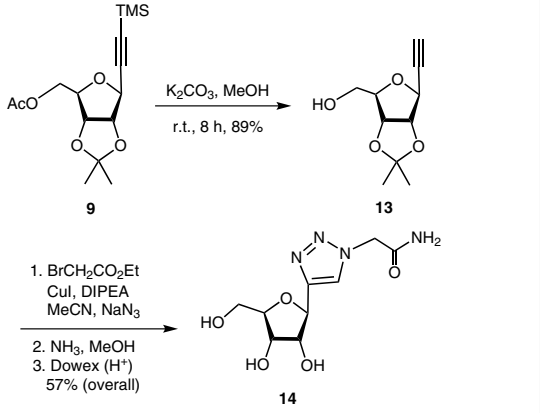
Finally, the functionalized group was shifted onto the N-1 position of triazole heterocycle in order to obtain a closer structure to RBV (Scheme 4). Compound **14** was ob-

Table 1 Synthesis of 5-(1′-β-D-Ribofuranosyl)-2*H*-1,2,3-triazole-4-carboxamides **8a–i**



RNH_2	Compound	Yield (%)	Compound	Yield (%)
$HONH_2$	**7a**	54	**8a**	85
H_2NNH_2	**7b**	60	**8b**	–
$MeCH_2CH_2NH_2$	**7c**	85	**8c**	95
$HOCH_2CH_2CH_2NH_2$	**7d**	84	**8d**	79
	**7e**	77	**8e**	82
	**7f**	77	**8f**	70
	**7g**	75	**8g**	64
NH_3	**7h**	83	**8h**	60
	**7i**	67	**8i**	–

tained starting from intermediate **9**. The latter was deprotected under basic conditions leading to the terminal alkyne **13**, which then underwent a one-pot copper-catalyzed SN-Huisgen cycloaddition step leading, after amidation with gas ammonia and deprotection in acidic conditions, to compound **14**.



Scheme 4 Synthesis of [4-(β-D-ribofuranosyl)-1,2,3-triazol-1-yl]acetamide (**14**)

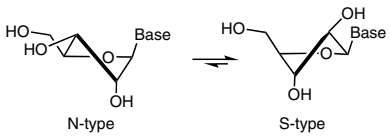
With an aim to ascertain a structural correlation which is our hypothesis, the conformational similarity between RBV, the synthesized *C*-nucleosides, and the purine nucleosides, adenosine and guanosine was examined. The equilibrium between the S- and N-type conformations of the furanose-ring puckering was then considered. For this the following relationship proposed by Altona and co-workers was used:[14]

$$\%S = {}^3J_{1',2'} \times 100/10.1$$

In this way, it is relatively easy to get the population of S-conformation in the nucleosides. As depicted in Table 2, the synthesized *C*-nucleosides **8a–h** present in CD_3OD almost the same coupling constant ${}^3J_{1',2'}$ leading mostly to the N-type conformation, as shown also by the X-ray analysis of compound **8h** in the solid phase (Figure 2). RBV presents also a N-type, contrary to guanosine and adenosine, essentially with a S-type conformation in solution. Compounds **12** and **14** seem relevant for mimicking the two natural nucleosides in a first approach.

In summary, a reliable synthesis of 11 *C*-nucleoside RBV analogues is described. These syntheses generate a series of four related purine-like compounds that can be used directly for studies that probe biological processes involving py-

Table 2 Equilibrium Composition of Compounds **5**, **8a–h**, **12**, and **14**



Compound	$^3J_{1',2'}$ (Hz)	% S
8a–h	4.6 or 4.7	46
12	5.4	54
14	6.2	62
5	5	50
RBV	3.6	36
adenosine	6.5	65
guanosine	5.9	59

rimidine nucleosides. In principle, they can also be converted to the corresponding triphosphates or phosphoramidites for enzyme-mediated or chemical syntheses of modified DNA sequences used in structure and function studies.

All solvents were purified and dried by standard techniques and distilled prior to use. CH_2Cl_2 was distilled over CaH_2 under argon. TLC was carried out on silica gel plates (Macherey-Nagel); spots were detected with UV light and revealed with H_2SO_4 solution. Flash chromatography was performed with silica gel 60, 40–63 µm. Melting points (uncorrected) were determined on a Buchi B-545 apparatus. Optical rotations were determined on an Anton Paar MCP200 instrument and IR spectra were recorded on a Bruker Tensor 27 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Jeol 400 MHz ECX spectrometer. High-resolution mass spectra were obtained with an UPLC-TOF LCT Premier Waters by ESI at the Service de Spectrométrie de Masse of ICSN, Gif-sur-Yvette.

Ethyl 3-(5-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)propiolate (3)

A suspension of In(0) (0.75 g, 6.56 mmol) in anhyd 1,2-dichloroethane (10 mL) under argon was stirred for 20 min at r.t. Ethyl 3-iodopropiolate (1.2 g, 5.47 mmol) and the ribofuranoside **2** (0.75 g, 2.74 mmol) were then added into the reaction tube, which was then sealed. The reaction mixture was stirred for 6 h under argon at 90 °C. The mixture was filtered over Celite and evaporated. The crude residue was taken in anhyd acetone (4 mL) and treated with *p*-TsOH·H_2O (16 mg, 3 mol%). After stirring at r.t. for 5 h, the mixture was neutralized with $NaHCO_3$, filtered through Celite, and concentrated under reduced pressure. The crude residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 2:1) to afford the product as a yellow oil; yield: 464 mg (54% from compound **2**); $[\alpha]_D^{25}$ –30.42 (*c* 1.0, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$): δ = 4.90 (dd, *J* = 6.2, 2.5 Hz, 1 H), 4.80 (d, *J* = 2.5 Hz, 1 H), 4.72 (dd, *J* = 6.2, 2.2 Hz, 1 H), 4.34 (dt, *J* = 5.2, 2.2 Hz, 1 H), 4.26 (dd, *J* = 11.8, 5.2 Hz, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 4.18 (dd, *J* = 11.8, 5.4 Hz, 1 H), 2.11 (s, 3 H), 1.51 (s, 3 H), 1.34 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 153.1, 114.4, 86.1, 84.1, 83.7, 82.9, 78.5, 74.9, 64.1, 62.5, 27.0, 25.4, 21.1, 14.2.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{20}O_7$: 312.1209; found: 312.1210.

Ethyl 1-Benzyl-4-(5′-*O*-acetyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-5-carboxylate (4a) and Ethyl 1-Benzyl-5-(5′-*O*-acetyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (4b)

To a solution of ethyl ribosylpropiolate (**3**; 4 g, 12.8 mmol) in toluene (30 mL) was added benzyl azide (6.8 g, 51.3 mmol). The mixture was stirred at reflux for 24 h. After evaporation of the solvent, the crude product was purified by flash column chromatography (cyclohexane/EtOAc 9:1) to give the compound **4a** as a yellow oil and **4b** as a yellow solid.

4a

Yield: 1.79 g (31% from compound **3**); $[\alpha]_D^{25}$ –36.78 (*c* 1.0, $CHCl_3$).

IR (ATR): 2984, 1725, 1497, 1370, 1211, 1097, 859 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (m, 5 H), 5.82 (d, *J* = 14.2 Hz, 1 H), 5.78 (d, *J* = 14.2 Hz, 1 H), 5.46 (d, *J* = 3.3 Hz, 1 H), 5.22 (dd, *J* = 6.4, 3.2 Hz, 1 H), 4,77 (dd, *J* = 6.4, 3.2 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 4.21 (m, 1 H), 4.05 (d, *J* = 5.2 Hz, 2 H), 1.97 (s, 3 H), 1.51 (s, 3 H), 1.30 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6, 158.2, 148.4, 134.7, 128.8, 128.5, 128.0, 125.7, 114.2, 83.9, 83.4, 82.6, 78.1, 76.4, 64.2, 62.1, 53.9, 27.2, 25.4, 20.8, 13.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{27}N_3O_7$: 445.1849; found: 455.1828.

4b

Yield: 2.99 g (52% from compound **3**); mp 75–77 °C; $[\alpha]_D^{25}$ –1.63 (*c* 1.0, $CHCl_3$).

IR (ATR): 2989, 1739, 1728, 1439, 1379, 1237, 1188, 1096, 858 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 5 H), 5.71 (d, *J* = 16.0 Hz, 1 H), 5.63 (d, *J* = 16.0 Hz, 1 H), 5.50 (d, *J* = 5.0 Hz, 1 H), 4.43 (dd, *J* = 6.9, 5.0 Hz, 1 H), 4.37 (m, 1 H), 4.35 (m, 2 H), 4.24 (m, 2 H), 1.13 (s, 3 H), 4.05 (d, *J* = 5.0 Hz, 1 H), 1.99 (s, 3 H), 1.46 (s, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=166.2, 156.7, 133.4, 133.3, 130.5, 129.1, 128.7, 128.0, 127.0, 111.8, 84.3, 82.7, 81.3, 76.7, 59.2, 57.2, 48.8, 26.6, 22.9, 20.9, 16.5, 10.0.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{27}N_3O_7$: 445.1849; found: 455.1864.

Ethyl 1-Benzyl-4-β-D-ribofuranosyl-1,2,3-triazole-5-carboxylate (5)

To a solution of compound **4a** (0.115 g, 0.258 mmol) in MeOH/H_2O (4:1, 10 mL) was added Dowex 50W (H^+) (1.30 g). The mixture was stirred at 50 °C for 6 h, then filtered and washed with MeOH. After solvent evaporation, **5** was obtained as a yellow oil; yield: 92 mg (98% from **4a**); $[\alpha]_D^{25}$ +5.22 (*c* 1.0, MeOH).

IR (ATR): 3269, 2928, 2499, 1722, 1455, 1256, 1102, 1029, 852, 730 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.2 (m, 5 H), 5.85 (s, 2 H), 5.34 (d, *J* = 5.0 Hz, 1 H), 4.32–4.37 (m, 3 H), 4.24 (dd, *J* = 5.5, 5.1 Hz, 1 H), 3.99 (ddd, *J* = 5.1, 4.1, 2.8 Hz, 1 H), 3.82 (dd, *J* = 11.9, 2.8 Hz, 1 H), 3.67 (dd, *J* = 11.9, 4.1 Hz, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 159.5, 150.2, 136.6, 129.7, 129.2, 128.6, 127.1, 86.1, 78.2, 77.0, 72.4, 63.4, 63.3, 54.9, 14.2.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{21}N_3O_6$: 363.1430; found: 363.1425.

1-Benzyl-5-β-D-ribofuranosyl-1,2,3-triazole-4-carboxamide (6)

A solution of compound **4b** (0.100 g, 0.224 mmol) in MeOH (5 mL) was cooled to –10 °C and treated with gaseous ammonia. The solution was maintained at –10 °C for 8 h and then warmed to r.t. overnight. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (PE/EtOAc 1:1) to give the intermediate amide as a white powder; yield: 80 mg (83% from **4b**); mp 178–180 °C; $[\alpha]_D^{25}$ –22.39 (*c* 1, $CHCl_3$).

IR (ATR): 3409, 3278, 2921, 1730, 1663, 1602, 1466, 1054, 870 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ=7.12–7.29 (m, 5 H), 5.62 (d, *J* = 15.5 Hz, 1 H), 5.60 (d, *J* = 15.5 Hz, 1 H), 4.97 (m, 3 H), 4.24 (d, *J* = 11.2 Hz, 1 H), 4.18 (s, 1 H), 3.86 (d, *J* = 12.4 Hz, 1 H), 3.72 (dd, *J* = 12.4, 11.2 Hz, 1 H), 1.40 (s, 3 H), 1.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 134.6, 132.4, 129.6, 124.8, 124.7, 122.4, 124.2, 110.4, 81.0, 79.9, 77.0, 72.1, 71.9, 57.9, 48.3, 23.0, 20.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}N_4O_5$: 374.1590; found: 374.1585.

To a solution of the amide obtained as above (0.067 g, 0.179 mmol) in MeOH/H_2O (4:1, 5 mL) was added Dowex 50W (H^+) (0.5 g). The reaction mixture was stirred at 50 °C for 6 h, then filtered and washed with MeOH. After solvent evaporation, **6** was obtained as a powder; yield: 41 mg (69% from the intermediate amide); mp 208–210 °C; $[\alpha]_D^{25}$ +3.95 (*c* 1, MeOH).

IR (ATR): 3389, 2937, 1652, 1497, 1286, 1111, 872 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.2 (m, 5 H), 5.8 (d, *J* = 15.6 Hz, 1 H), 5.75 (d, *J* = 15.6 Hz, 1 H), 5.36 (d, *J* = 7.8 Hz, 1 H), 4.03 (dd, *J* = 7.8, 6.4 Hz, 1 H), 3.93 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.83 (d, *J* = 2.7 Hz, 1 H), 3.64 (dd, *J* = 12.4, 3.2 Hz, 1 H), 3.60 (dd, *J* = 12.4, 2.7 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 135.5, 132.1, 131.0, 128.5, 127.8, 126.9, 86.9, 75.2, 74.5, 70.9, 61.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}N_4O_5$: 334.1277; found: 334.1256.

1-Benzyl-*N*-hydroxy-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (7a)

To a solution of **4b** (220 mg, 0.5 mmol) in EtOH (1 mL) was added dropwise at r.t. a solution of hydroxylamine hydrochloride (100 mg, 1.44 mmol) and NaOH (120 mg, 3 mmol) in H_2O (0.75 mL). After stirring for 4 h, the solution was acidified to pH 6. The solvent was removed in vacuo and the residue was dissolved in MeOH. After filtration and solvent evaporation, the crude was purified by flash column chromatography (EtOAc/cyclohexane 7:3 to 1:0) leading to **7a** as a yellow oil; yield: 101 mg (54% from **4b**); $[\alpha]_D^{25}$ –17.68 (*c* 0.58, $CHCl_3$).

IR (ATR): 3229, 2930, 1665, 1455, 1376, 1254, 1212, 1075, 853, 723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 3 H), 7.24–7.14 (m, 2 H), 5.68 (d, *J* = 16.0 Hz, 1 H), 5.62 (d, *J* = 16.0 Hz, 1 H), 5.06–4.91 (m, 3 H), 4.24–4.13 (m, 1 H) 3.87 (d, *J* = 12.3 Hz, 1 H), 3.75 (d, *J* = 12.4 Hz, 1 H), 1.46 (s, 3 H), 1.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 137.6, 136.7, 134.0, 129.2, 128.7, 127.1, 115.2, 85.4, 84.5, 81.4, 76.6, 62.1, 52.9, 27.4, 25.3.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{23}N_4O_6$: 391.1618; found: 391.1613.

Amidation Reactions; General Procedure

To a solution of **4b** in EtOH was added the appropriate amine (3–4 equiv). After completion of the reaction, the solution was concentrated and the crude was purified by flash column chromatography.

1-Benzyl-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carbohydrazide (7b)

Starting from **4b** (300 mg, 0.67 mmol) and hydrazine monohydrate (100 µL, 2 mmol) in EtOH (4 mL), **7b** was obtained as a sticky solid after purification by flash column chromatography (EtOAc/cyclohexane 7:3 to 1:0); yield: 168 mg (60% from **4b**); $[\alpha]_D^{25}$ –52.01 (*c* 0.9, $CHCl_3$).

IR (ATR): 3320, 2985, 2936, 1733, 1664, 1075 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.14 (m, 5 H), 5.68 (d, *J* = 15.6 Hz, 1 H), 5.61(d, *J* = 15.6 Hz, 1 H), 5.04 (dd, *J* = 6.3, 2.9 Hz, 1 H), 4.95 (m, 1 H), 4.90 (m, 1 H), 4.18 (m, 1 H), 3.87 (dd, *J* = 12.5, 1.6 Hz, 1 H), 3.74 (m, 1 H), 1.46 (s, 3 H), 1.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.11, 138.33, 136.65, 134.08, 129.24, 128.77, 127, 115.06, 85.59, 84.60, 81.51, 62.44, 52.84, 27.55, 25.30.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}N_5O_5$: 390.1777; found: 390.1790.

1-Benzyl-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-*N*-propyl-1,2,3-triazole-4-carboxamide (7c)

Starting from **4b** (150 mg, 0.33 mmol) and propylamine (110 µL, 79 mg, 1.34 mmol) in EtOH (2 mL), **7c** was obtained as an oil after purification by flash column chromatography (EtOAc/cyclohexane 7:3 to 6:4); yield: 120 mg (85% from **4b**); $[\alpha]_D^{25}$ –11.1 (*c* 1.1, $CHCl_3$).

IR (ATR): 3341, 2934, 1652, 1075 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.14 (m, 5 H), 5.68 (d, *J* = 15.6 Hz, 1 H), 5.62 (d, *J* = 15.6 Hz, 1 H), 5.08 (m, 2 H), 4.97 (m, 1 H), 4.57 (s, 1 H), 4.20 (m, 1 H), 3.88 (m, 1 H), 3.74 (m, 1 H), 3.38 (m, 2 H), 1.61 (m, 2 H), 1.45 (s, 3 H), 1.28 (s, 3 H), 0.96 (t, *J* = 8.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 139.9, 136.2, 134.2, 129.2, 128.6, 126.9, 114.8, 85.6, 84.4, 81.5, 76.6, 62.5, 52.7, 41.1, 27.5, 25.3, 22.8, 11.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{29}N_4O_5$: 417.2137; found: 417.2138.

1-Benzyl-*N*-(3-hydroxypropyl)-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (7d)

Starting from **4b** (300 mg, 0.67 mmol) and 3-aminopropanol (205 µL, 2.7 mmol) in EtOH (4 mL), **7d** was obtained as a solid after purification by flash column chromatography (EtOAc/cyclohexane 1:1 to 1:0); yield: 242 mg (84% from **4b**); mp 117 °C; $[\alpha]_D^{25}$ –36.4 (*c* 1.6, $CHCl_3$).

IR (ATR): 3312, 2920, 1649, 1077 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.17 (m, 5 H), 5.70 (d, *J* = 15.6 Hz, 1 H), 5.64 (d, *J* = 15.6 Hz, 1 H), 5.03 (m, 3 H), 4.50 (s, 1 H), 4.19 (s, 3 H), 3.89 (d, *J* = 12.1 Hz, 1 H), 3.74 (d, *J* = 12.1 Hz, 1 H), 3.69 (m, 2 H), 3.57 (m, 2 H), 1.79 (t, *J* = 5.7 Hz, 2 H), 1.47 (s, 3 H), 1.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 139.7, 136.3, 134.2, 129.1, 128.6, 127.00, 114.9, 85.50, 84.4, 81.4, 76.5, 62.4, 59.6, 52.7, 36.3, 32.1, 27.5, 25.3.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{29}N_4O_6$: 433.2087; found: 433.2087.

[1-Benzyl-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazol-4-yl](pyrrolidin-1-yl)methanone (7e)

Starting from **4b** (150 mg, 0.33 mmol) and pyrrolidine (140 µL, 2.27 mmol) in MeOH (2 mL), **7e** was obtained as a solid after purification by flash column chromatography (EtOAc/cyclohexane 6:4 to 1:1); yield: 111 mg (77% from **4b**); mp 47–55 °C; $[\alpha]_D^{25}$ –7.9 (*c* 1, MeOH).

IR (ATR): 3374, 2967, 1614, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.14 (m, 5 H), 5.74 (d, *J* = 15.7 Hz, 1 H), 5.57 (d, *J* = 15.7 Hz, 1 H), 5.07 (dd, *J* = 6.4, 2.4 Hz, 1 H), 4.98 (dd, *J* = 6.4, 6.2 Hz, 1 H), 4.91 (d, *J* = 6.2 Hz, 1 H), 4.63 (br s, 1 H), 4.18 (ddd, *J* = 2.4, 1.8, 1.6 Hz, 1 H), 4.04–3.93 (m, 1 H), 3.81 (dd, *J* = 12.7, 1.6 Hz, 1 H), 3.69 (dd, *J* = 12.7, 1.8 Hz, 1 H), 3.67–3.53 (m, 3 H), 2.00–1.80 (m, 4 H), 1.52 (s, 3 H), 1.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 141.1, 136.4, 134.3, 129.2, 128.7, 127.2, 114.8, 85.6, 84.8, 81.8, 78.0, 62.7, 52.6, 49.1, 46.8, 27.7, 26.3, 25.4, 24.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}N_4O_5$: 429.2138; found: 429.2146.

N-[1-Benzyl-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carbonyl]glycine (7f)

Starting from **4b** (150 mg, 0.33 mmol) and potassium glycinate (190 mg, 1.68 mmol) in MeOH (2 mL), **7f** was obtained as a solid after purification by flash column chromatography (CH_2Cl_2/MeOH 19.1 + 1% AcOH); yield: 112 mg (77% from **4b**); mp 80–88 °C; $[\alpha]_D^{25}$ –21.3 (*c* 1, MeOH).

IR (ATR): 3312, 2967, 1736, 1665, 1055 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H), 5.85 (d, *J* = 16.4 Hz, 1 H), 5.81 (d, *J* = 16.4 Hz, 1 H), 5.54 (d, *J* = 5.6 Hz, 1 H), 4.74 (dd, *J* = 6.9, 4.1 Hz, 1 H), 4.69 (dd, *J* = 6.9, 5.6 Hz, 1 H), 4.09 (s, 2 H), 4.03 (ddd, *J* = 4.1, 4.0, 3.3 Hz, 1 H), 3.80 (dd, *J* = 12.1, 3.3 Hz, 1 H), 3.72 (dd, *J* = 12.1, 4.0 Hz, 1 H), 1.49 (s, 3 H), 1.20 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 163.0, 140.8, 137.7, 137.0, 130.1, 129.5, 128.4, 116.6, 87.0, 85.8, 82.7, 77.5, 62.6, 53.8, 41.8, 27.8, 25.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}N_4O_7$: 433.1723; found: 433.1727.

1-Benzyl-*N*-[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (7g)

Starting from **4b** (50 mg, 0.112 mmol) and (–)-norephedrine (75 mg, 0.5 mmol) in MeOH (0.7 mL), **7g** was obtained as a white solid after purification by flash column chromatography (EtOAc/cyclohexane 3:7 to 4.6); yield: 46 mg (75% from **4b**); $[\alpha]_D^{25}$ –28.6 (*c* 1.3, $CHCl_3$).

IR (ATR): 3397, 2979, 2937, 2880, 1654, 1508, 1454, 1253, 1214, 1154, 1080, 1002, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.70 (m, 1 H), 7.38–7.16 (m, 10 H), 5.67 (d, *J* = 15.8 Hz, 1 H), 5.62 (d, *J* = 15.8 Hz, 1 H), 5.08–5.03 (m, 2 H), 4.98–4.96 (m, 2 H), 4.46–4.41 (m, 1 H), 4.20–4.19 (m, 1 H), 3.88 (dd, *J* = 12.5, 1.6 Hz, 1 H), 3.73 (dd, *J* = 12.5, 2.0 Hz, 1 H), 1.45 (s, 3 H), 1.28 (s, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 140.8, 139.8, 136.5, 134.2, 129.2, 128.7, 128.4, 127.7, 127.0, 126.2, 114.9, 85.6, 84.5, 81.6, 76.7, 75.8, 62.6, 52.8, 50.8, 27.6, 25.4, 13.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{33}N_4O_6$: 509.2400; found: 509.2403.

1-Benzyl-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (7h)

To a solution of **4b** (100 mg, 0.224 mmol) in MeOH (5 mL) was bubbled gaseous ammonia for 2 h at 0 °C. The solution was then stirred at r.t. for 12 h. The solvent was then removed in vacuo and the residue was purified by flash column chromatography (EtOAc/cyclohexane 1.1 to 1.0) leading to a white solid **7h**; yield: 100 mg (83% from **4b**); mp 178–180 °C; $[\alpha]_D^{25}$ –22.39 (*c* 1.0, $CHCl_3$).

The physicochemical properties were in accordance with published data.

IR (ATR): 3409, 3278, 2921, 1730, 1663, 1602, 1466, 1245, 870 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.12 (m, 5 H), 5.62 (d, *J* = 15.5 Hz, 1 H), 5.60 (d, *J* = 15.5 Hz, 1 H), 4.97 (m, 3 H), 4.24 (d, *J* = 11.2 Hz, 1 H), 4.18 (s, 1 H), 3.86 (d, *J* = 12.4 Hz, 1 H), 3.72 (dd, *J* = 12.4, 11.2 Hz, 1 H), 1.40 (s, 3 H), 1.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 134.6, 132.4, 129.6, 124.8, 124.7, 124.2, 122.4,110.4, 81.0, 79.9, 77.0, 72.1, 71.9, 57.9, 48.3, 23.0, 20.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}N_4O_5$: 374.1590; found: 374.1585.

1-Benzyl-*N*-[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (7i)

Starting from **4b** (50 mg, 0.112 mmol) and tris(hydroxymethyl)amine (60 mg, 0.5 mmol) in MeOH (0.7 mL), **7i** was obtained as a colorless oil after purification by flash column chromatography (CH_2Cl_2/MeOH 98:2); yield: 38 mg (67% from **4b**); $[\alpha]_D^{25}$ –17.3 (*c* 0.48, MeOH).

IR (ATR): 3362, 2984, 2936, 2887, 1649, 1584, 1516, 1498, 1456, 1441, 1384, 1319, 1253, 1214, 1156, 1078, 1050, 859, 726, 695 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.41–7.34 (m, 3 H), 7.24 (d, *J* = 6.6 Hz, 2 H), 5.86 (s, 2 H), 5.66 (d, *J* = 5.8 Hz, 1 H), 4.75 (dd, *J* = 6.8, 4.2 Hz, 1 H), 4.67– 4.64 (m, 1 H), 4.07 (dd, *J* = 7.5, 3.8 Hz, 1 H), 3.85–3.81 (m, 7 H), 3.75 (dd, *J* = 12.0, 4.1 Hz, 1 H), 1.53 (s, 3 H), 1.23 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 162.9, 141.0, 137.5, 136.9, 130.0, 129.4, 128.2, 116.4, 86.6, 85.5, 82.6, 77.1, 63.5, 62.6, 62.3, 53.8, 27.6, 25.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{31}N_4O_8$: 479.2142; found: 479.2129.

Deprotection of the Benzyl Group in 7a–h; General Procedure

To a solution of carboxamide **7** in EtOH (15 mL/mmol) was added $PdCl_2$ (40 mg/mmol). The mixture was stirred at r.t. under 5 bar H_2 pressure for 48 h. After filtration of the catalyst over Celite and solvent evaporation, the crude product was purified by flash column chromatography.

N-Hydroxy-5-β-D-ribofuranosyl-2*H*-1,2,3-triazole-4-carboxamide (8a)

Starting from **7a** (88 mg, 0.2 mmol) and $PdCl_2$ (8 mg) in EtOH (4 mL), **8a** was obtained as a white solid after purification by flash column chromatography (EtOAc/cyclohexane 8:2 to EtOAc/MeOH 1:1); yield: 51 mg (85% from **7a**); mp 206–207 °C; $[\alpha]_D^{25}$ +24.64 (*c* 0.97, CH_3OH).

IR (ATR): 3210, 2924, 1650, 1450, 1219, 1077, 1020, 893 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.35 (d, *J* = 4.7 Hz, 1 H), 4.20–4.11 (m, 2 H), 4.00 (d, *J* = 3.4 Hz, 1 H) 3.84 (dd, *J* = 12.1, 2.9 Hz, 1 H), 3.70 (dd, *J* =12.1, 3.9 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 161.0, 144.0, 137.2, 86.1, 77.9, 77.4, 72.1, 62.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_8H_{13}N_4O_6$: 261.0835; found: 261.0827.

N-Propyl-5-β-D-ribofuranosyl-2*H*-1,2,3-triazole-4-carboxamide (8c)

Starting from **7c** (102 mg, 0.2 mmol) and $PdCl_2$ (8 mg) in EtOH (4 mL), **8c** was obtained as a white solid after purification by flash column chromatography (EtOAc/MeOH 1:0 to 9:1); yield: 70 mg (95% from **7c**); mp 280 °C; $[\alpha]_D^{25}$ +6.3 (*c* 1, MeOH).

IR (ATR): 3307, 2930, 1637, 1046 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.37 (d, *J* = 4.6 Hz, 1 H), 4.14 (m, 2 H), 4.01 (m, 1 H), 3.85 (dd, *J* = 12.1, 3.0 Hz, 1 H), 3.71 (dd, *J* = 12.1, 3.8 Hz, 1 H), 3.30 (m, 2 H), 1.61 (sext, *J* = 7.4 Hz, 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 161.63, 139.77, 84.83, 76.89, 76.41, 70.77, 61.37, 40.63, 22.47, 10.39.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{19}N_4O_5$: 287.1355; found: 287.1366

N-(3-Hydroxypropyl)-5-β-D-ribofuranosyl-2*H*-1,2,3-triazole-4-carboxamide (8d)

Starting from **7d** (194 mg, 0.4 mmol) and $PdCl_2$ (18 mg) in EtOH (7 mL), **8c** was obtained as a white solid after purification by flash column chromatography (EtOAc/MeOH 8:2); yield: 106 mg (79% from **7d**); mp 220 °C; $[\alpha]_D^{25}$ +30.6 (*c* 1.1, MeOH).

IR (ATR): 3295, 2927, 1637, 1042 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.37 (d, *J* = 4.6 Hz, 1 H), 4.13 (m, 2 H), 4.00 (m 1 H), 3.85 (dd, *J* = 12.0, 3.0 Hz, 1 H), 3.71 (dd, *J* = 12.0, 3.8 Hz, 1 H), 3.63 (t, *J* = 6.2 Hz, 2 H), 3.46 (t, *J* = 6.8 Hz, 2 H), 1.80 (tt, *J* = 6.8, 6.2 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 161.78, 142.25, 137.56, 84.81, 76.89, 76.14, 70.76, 61.53, 59.24, 36.06, 31.86.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{19}N_4O_6$: 303.1305; found: 303.1306.

(Pyrrolidin-1-yl)(5-β-D-ribofuranosyl-2*H*-1,2,3-triazol-4-yl)methanone (8e)

Starting from **7e** (67 mg, 0.106 mmol) and $PdCl_2$ (5 mg) in EtOH (2 mL), **8e** was obtained as a white foam after purification by flash column chromatography (CH_2Cl_2/MeOH 19:1); yield: 38 mg (82% from **7e**); mp 179–182 °C; $[\alpha]_D^{25}$ +22.4 (*c* 1, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 5.30 (d, *J* = 4.6 Hz, 1 H), 4.17–4.11 (m, 2 H), 4.00 (ddd, *J* = 4.3, 3.8, 3.1 Hz, 1 H), 3.84 (dd, *J* = 12.1, 3.1 Hz, 1 H), 3.88–3.80 (m, 2 H), 3.70 (dd, *J* = 12.1, 3.8 Hz, 1 H), 3.64–3.58 (m, 2 H), 2.00–1.80 (m, 4 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 162.3, 145.3, 140.4, 86.2, 78.5, 77.7, 72.4, 63.2, 50.3, 47.9, 27.3, 25.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}N_4O_5$: 299.1355; found: 299.1361.

N-(5-β-D-Ribofuranosyl-2*H*-1,2,3-triazole-4-carbonyl)glycine (8f)

Starting from **7f** (50 mg, 0.105 mmol) and Pd/C (24 mg) in EtOH (1 mL) a colorless oil (24 mg) was obtained, which was purified by flash column chromatography (CH_2Cl_2/MeOH 8:2 to CH_2Cl_2/MeOH 8:2 + 1% AcOH). After evaporation of the solvent, the residue (19 mg) was dissolved in H_2O (1 mL) and Dowex 50W (H^+) was added and shaken for 3 h. Product **8f** was obtained after filtration and evaporation as a white foam; yield: 17 mg (70% overall); mp 97–99 °C; $[\alpha]_D^{25}$ +20.4 (*c* 1, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 5.39 (d, *J* = 4.7 Hz, 1 H), 4.22–4.13 (m, 2 H), 4.11 (m, 2 H), 4.03 (ddd, *J* = 4.8, 3.7, 2.9 Hz, 1 H), 3.88 (dd, *J* = 12.1, 2.9 Hz, 1 H), 3.74 (dd, *J* = 12.1, 3.7 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 172.0, 163.4, 144.4, 138.5, 86.3, 78.5, 77.5, 72.1, 62.8, 41.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{15}N_4O_7$: 303.0941; found: 303.0936.

N-[(1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl]-5-β-D-ribofuranosyl-2*H*-1,2,3-triazole-4-carboxamide (8g)

Compound **7g** (61 mg, 0.11mmol) was dissolved in EtOH (3 mL). Pd/C (30 mg, 50% wt) was added and the atmosphere was replaced by H_2. The resulting mixture was stirred at r.t. under 8 bar of H_2 for 48 h. The crude was filtered on Celite, concentrated and purified by flash column chromatography (EtOAc/cyclohexane 5:5 then 100:0). The residue obtained was dissolved in MeOH (2 mL) and treated with Dowex 50W (H^+) for 5 h. The resulting mixture was filtered and concentrated to give **8g** as a colorless oil; yield: 29 mg (64% from **7g**); $[\alpha]_D^{25}$ +27.4 (*c* 1.45, MeOH).

IR (ATR): 3326, 2925, 2875, 1641, 1532, 1451, 1092, 1073, 1023, 996, 746, 701 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.44–7.42 (m, 2 H), 7.35–7.31 (m, 2 H), 7.26–7.22 (m, 1 H), 5.35 (d, *J* = 4.7 Hz, 1 H), 4.85 (d, *J* = 4.6 Hz, 1 H), 4.36–4.33 (m, 1 H), 4.15–4.10 (m, 2 H), 4.04–4.01 (m, 1 H), 3.88 (dd, *J* = 12.1, 3.0 Hz, 1 H), 3.73 (dd, *J* = 12.1, 3.8 Hz, 1 H), 1.14 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 162.0, 143.3, 138.7, 132.4, 129.1, 128.4, 127.4, 86.0, 78.2, 77.4, 76.5, 72.0, 62.8, 51.9, 14.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_4O_6$: 379.1618; found: 379.1634.

5-β-D-Ribosyl-2*H*-1,2,3-triazole-4-carboxamide (8h)

Starting from **7h** (1.34 g, 3.22 mmol) and $PdCl_2$ (127 mg) in EtOH (55 mL), **8h** was obtained as a white solid after purification by flash column chromatography (EtOAc/cyclohexane 8:2 to EtOAc/MeOH 1:1); yield: 522 mg (60% from **7h**); mp 204–206 °C; $[\alpha]_D^{25}$ +13.82 (*c* 1.0, MeOH).

IR (ATR): 3327, 2927, 2365, 1670, 1540, 1459, 1225, 1110, 995, 897 cm$^{-1.}$

^{1}H NMR (400 MHz, CD_3OD): δ = 3.72 (dd, *J* = 12.4, 3.7 Hz, 1 H), 3.85 (dd, *J* = 12.4, 2.8 Hz, 1 H), 4.01 (dd, *J* = 3.7, 2.8 Hz, 1 H), 4.14 (s, 2 H), 5.38 (d, *J* = 4.6 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 61.2, 70.1, 75.8, 76.1, 84.7, 137.3, 142.4, 144.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}N_4O_5$: 244.0808; found: 244.0811.

5-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-ribofuranosyltrimethylsilylacetylene (9)

A suspension of In(0) (0.75 g, 6.56 mmol) in anhyd 1,2-dichloroethane (10 mL) under argon was stirred for 20 min at r.t. 1-Iodo-2-trimethylsilylacetylene (1.2 g, 5.47 mmol) and the ribofuranoside **2** (0.75 g, 2.73 mmol) were added to the reaction tube, which was sealed, then evacuated, and backfilled with argon (this process was repeated a total of 3 times). The reaction mixture was stirred for 6 h at 90 °C. The mixture was filtered over Celite and evaporated. The crude residue was taken in anhyd acetone (4 mL) and treated with *p*-TsOH·H_2O (16 mg, 3 mol%). After stirring at r.t. for 5 h, the mixture was neutralized with $NaHCO_3$, filtered through Celite, and concentrated under reduced pressure. The crude residue obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 3:1) to give **9** as a yellow oil; yield: 431 mg (58% from **2**); $[\alpha]_D^{25}$ +22.0 (*c* 1.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.81 (dd, *J* = 6.4, 2.2 Hz, 1 H), 4.66–4.69 (m, 2 H), 4.09–4.34 (m, 3 H), 2.09 (s, 3 H), 1.50 (s, 3 H), 1.33 (s, 3 H), 0.15 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.69, 114.06, 102.74, 92.77, 86.54, 83.71, 82.98, 75.18, 63.94, 26.95, 25.42, 20.97, 20.26.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{25}O_5Si$: 313.1466; found: 313.1471.

2,3,5-Tri-*O*-Benzyl-β-D-ribofuranosylacetylene (10)

To a solution of compound **9** (0.96 g, 3.07 mmol) in a mixture of MeOH/H_2O (4:1, 50 mL) was added Dowex 50W (H^+) (6 g) and concd

HCl (0.5 mL). The mixture was stirred at 50 °C for 30 h. The solution was filtered and washed with MeOH, and MeOH was carefully evaporated. The residue was dissolved in anhyd DMF (40 mL), and benzyl bromide (2.59 mL, 27.36 mmol) and NaH (60%; 1.09 g, 45.60 mmol) were added at 0 °C. The reaction mixture was stirred at r.t. overnight. After cooling, a few drops of MeOH were added, and the mixture was dissolved in Et_2O (50 mL). The mixture was washed with sat. aq NH_4Cl (2 × 20 mL) and H_2O (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude was purified by flash chromatography on silica gel (cyclohexane/EtOAc 9:1) to give **10** as a yellow solid; yield: 1.54 g (79% from **9**); mp 58–60 °C; $[\alpha]_D^{25}$ +0.012 (*c* 1.0, $CHCl_3$).

IR (ATR): 3285, 3030, 2861, 1496, 1453, 1356, 1207, 1026, 734 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.41 (m, 15 H), 4.74 (d, *J* = 11.9 Hz, 2 H), 4.72 (dd, *J* = 4.5, 1.8 Hz, 1 H), 4.64 (d, *J* = 12.4 Hz, 2 H), 4.55 (dd, *J* = 10.5 Hz, 2 H), 4.26 (dd, *J* = 9.1, 4.6 Hz, 1 H), 4.10 (t, *J* = 5.0 Hz, 1 H), 4.07 (t, *J* = 5.0 Hz, 2 H), 3.66 (dd, *J* = 11.0, 6.4 Hz, 1 H), 3.57 (dd, *J* = 11.0, 4.6 Hz, 1 H), 2.57 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 137.8, 137.6, 127.7–128.5, 81.9, 81.7, 81.5, 78.0, 75.2, 75.0, 72.5, 72.4, 72.3, 70.9, 70.8, 70.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{28}O_4$: 428.1988; found: 428.1990

1-Benzyl-4-(2′,3′,5′-tri-*O*-benzyl-β-D-ribofuranosyl)-1,2,3-triazole (11)

A mixture of alkyne **10** (0.40 g, 0.93 mmol), benzyl azide (0.15 g, 1.12 mmol), CuI (0.35 g, 1.86 mmol), and DIPEA (0.36 g, 2.79 mmol) in MeCN (20 mL) was stirred at r.t. for 20 h. The mixture was evaporated, and the residue was partitioned between EtOAc and H_2O (20 mL). The organic layer was washed with aq NH_4Cl (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (cyclohexane/EtOAc 8:2) to give **11** as a yellow solid; yield: 0.41 g (79% from **10**); mp 122–124 °C; $[\alpha]_D^{25}$ –3.40 (*c* 1.0, $CHCl_3$).

IR (ATR): 3061, 2888, 1479, 1454, 1349, 1048, 910, 751, 671 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.0–7.3 (m, 20 H), 5.36 (d, *J* = 15.1 Hz, 1 H), 5.29 (d, *J* = 3.1 Hz, 1 H), 5.19 (d, *J* = 15.1 Hz, 1 H), 4.75 (d, *J* = 11.9 Hz, 1 H), 4.68 (d, *J* = 11.9 Hz, 1 H), 4.60 (d, *J* = 11.9 Hz, 1 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.44 (d, *J* = 11.9 Hz, 1 H), 4.42 (d, *J* = 11.9 Hz, 1 H), 4.31 (m, 1 H), 4.25 (t, *J* = 4.1 Hz, 1 H), 4.05 (dd, *J* = 6.9, 5.0 Hz, 1 H), 3.75 (dd, *J* = 10.5, 2.8 Hz, 1 H), 3.59 (dd, *J* = 10.5, 3.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 138.2, 137.9, 137.8, 134.7, 129.0, 127.7–128.7, 122.5, 80.8, 80.6, 76.7, 73.3, 72.1, 72.0, 69.4, 54.

HRMS: *m*/*z* $[M+ H]^+$ calcd for $C_{35}H_{35}N_3O_4$: 561.2628; found: 561.2639.

4-β-D-Ribofuranosyl-2*H*-1,2,3-triazole (12)

To a solution of **11** (0.070 g, 0.12 mmol) in MeOH (5 mL) was added $Pd(OH)_2$ (20%) and the reaction mixture was hydrogenolyzed at r.t. for 24 h at 5 bar. The catalyst was filtered over Celite and washed with MeOH. The solvents were then evaporated and **12** was obtained after silica gel column chromatography purification as a white solid; yield: 0.024 g (95% from **11**); mp 118–120 °C; $[\alpha]_D^{25}$ +11.3 (*c* 1.0, MeOH).

IR (ATR): 3335, 2965, 2374, 1675, 995, 897 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.66 (s, 1 H), 4.95 (d, *J* = 5.4 Hz, 1 H), 4.13 (m, 2 H), 3.95 (m, 1 H), 3.77 (dd, *J* = 11.9, 3.2 Hz, 1 H), 3.63 (dd, *J* = 11.9, 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 143.9, 128.0, 84.8, 77.6, 76.2, 71.3, 62.2.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_7H_{11}N_3O_4$: 201.0750; found: 201.0746.

2,3-*O*-isopropylidene-β-D-ribofuranosylacetylene (13)

To a solution of **9** (1.2 g, 3.87 mmol) in MeOH (12 mL) was added K_2CO_3 (0.8 g, 5.81 mmol) and the mixture was stirred at r.t. for 8 h. The mixture was concentrated, the residue was taken in H_2O (5 mL), and acidified with AcOH to pH 5–6. The aqueous phase was extracted with EtOAc (2 × 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Heptane was used to remove the excess of AcOH. The yellow oil obtained was purified by flash column chromatography on silica gel (heptane/EtOAc 9:1 to 7:3) to give **13** as a colorless oil; yield : 680 mg (89% from **9**); $[\alpha]_D^{25}$ –4.0 (*c* 1.2, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.81 (dd, *J* = 6.2, 2.7 Hz, 1 H), 4.74 (dd, *J* = 6.3, 2.2 Hz, 1 H), 4.68 (t, *J* = 2.5 Hz, 1 H), 4.19–4.22 (m, 1 H), 3.75–3.76 (m, 2 H), 2.60 (d, *J* = 2.3 Hz, 1 H), 2.12 (br s, 1 H), 1.33 (s, 3 H), 1.51 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.97, 86.67, 86.61, 82.29, 81.69, 75.58, 74.76, 62.93, 27.02, 25.35.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{14}O_4$: 198.0885; found: 198.0892.

[4-β-D-Ribofuranosyl-1,2,3-triazol-1-yl]acetamide (14)

A solution of ethyl bromoacetate (222 mg, 1.3 mmol) in MeCN and NaN_3 (99.5 mg, 1.5 mmol) was stirred at reflux for 2 h. A solution of sugar **13** (200 mg, 1.0 mmol) in MeCN was then introduced, followed by DIPEA (395 mg, 3.1 mmol) and CuI (389 mg, 2.0 mmol), and stirred for another 2 h. The reaction mixture was filtered through a short bed of Celite. After removal of the solvent, the residue was purified by chromatography on silica gel (cyclohexane/MeOH 95:5) to afford the triazole ester intermediate as a yellow oil; yield: 248 mg (62% from **13**).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 5.13 (s, 2 H), 4.97 (dd, *J* = 6.1, 3.6 Hz, 1 H), 4.93 (dd, *J* = 6.1, 1.6 Hz, 1 H), 4.35 (s, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 3.88 (br d, *J* = 12.4 Hz, 1 H), 3.66 (dd, *J* = 12.4, 3.1 Hz, 1 H), 1.57 (s, 3 H), 1.30 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.07, 114.11, 85.99, 85.57, 82.3, 80.5, 62.36, 62.9, 50.75, 25.17, 27.17, 13.9.

A solution of the above triazole ester (248 mg, 0.8 mmol) in MeOH was cooled to –10 °C and treated with gaseous NH_3. The reaction was maintained at this temperature for 8 h. The reaction mixture was evaporated under reduced pressure, and the crude oil (295 mg) was pure enough to be used in the next step. To the crude in MeOH/H_2O (4:1) was added Dowex 50W (H^+) (1 g). The reaction mixture was stirred at reflux for 6 h, then filtered, and washed with MeOH. The solvent was removed in vacuo to give **14** as a yellow oil; yield: 146 mg (57% from **13**); $[\alpha]_D^{25}$ –63.0 (*c* 0.2, MeOH).

^1H NMR (400 MHz, CD_3OD): δ = 8.1 (s, 1 H), 5.35 (s, 2 H), 4.91 (d, *J* = 6.2 Hz, 1 H), 4.17 (dd, *J* = 6.2, 4.9 Hz, 1 H), 4.11 (t, *J* = 4.9 Hz, 1 H), 3.98 (m, 1 H), 3.75 (dd, *J* = 12.0, 3.4 Hz, 1 H), 3.66 (dd, *J* = 12.0, 4.5 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 167.4, 146.7, 125.1, 85.3, 76.7, 76.1, 71.3, 62.1, 50.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_9H_{14}N_4O$: 258.0964; found: 258.0965.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588409.

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