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SYNTHESIS OF 5′-*O*-β-D-GLUCOPYRANOSYL AND 5′-*O*-β-D-GALACTOPYRANOSYL DERIVATIVES OF RIBAVIRIN

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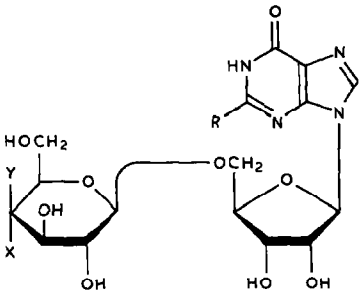
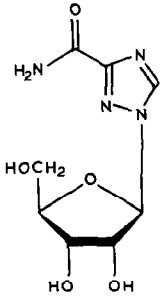
ABSTRACT

The synthesis of 5′-*O*-β-D-glucopyranosyl and 5′-*O*-β-D-galactopyranosyl derivatives (**13** and **15**, respectively) of the antiviral agent ribavirin are described. Direct glycosylation of 2′,3′-*O*-isopropylideneribavirin with either tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4**) or tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**8**) under Koenigs–Knorr conditions (*i.e.*, silver carbonate, silver perchlorate, and Drierite in dichloromethane) followed by *O*-deacetylation of the reaction product gave the corresponding ortho esters. However, treatment of 2′,3′-di-*O*-acetyl-5′-*O*-tritylribavirin (**11**) with **4** under the Bredereck modification of the Koenigs–Knorr reaction (*i.e.*, silver perchlorate and Drierite in nitromethane) and subsequent deacetylation furnished the desired 1-(5-*O*-β-D-glucopyranosyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (**13**). Similarly, reaction of **11** with **8** in the presence of $AgClO_4$, and deprotection of the condensation product, gave 5′-*O*-β-D-galactopyranosylribavirin (**15**). The β-anomeric configuration of the D-glucosyl and D-galactosyl groups of **13** and **15** was assigned by ^{1}H-n.m.r. studies.



1 R = H, X = OH or H
Y = H or OH
2 R = NH_2, X = OH or H
Y = H or OH



Ribavirin
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INTRODUCTION

The isolation of a novel group of disaccharide nucleosides from the fermentation broths of a strain of *Brevibacterium ammoniagenes*[1], as well as of [2] *Bacillus sp.* 102, and their structural elucidation as 5′-*O*-hexosyl-inosine (**1**) and -guanosine (**2**) has prompted considerable interest in the chemical synthesis of 5′-*O*-glycosyl nucleosides[3-10]. The interest in such compounds was further triggered by the isolation of a new antiviral antibiotic, namely, tunicamycin, from a strain of *Streptomyces lysosuperficus*[11] and *Streptomyces chartreusis*[12]. Tunicamycin, a uridine trisaccharide containing D-galactosamine and *N*-acetyl-D-glucosamine, is active against enveloped viruses of plants and animals[13,14].

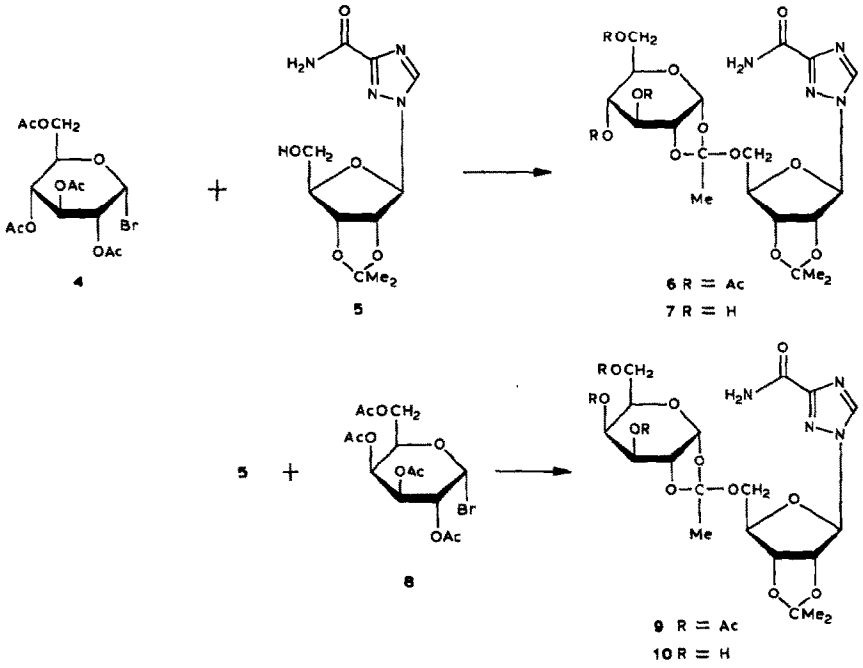
The synthetic antiviral agent ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, **3**), prepared in and reported from our laboratory[15] in 1972, has shown significant, broad-spectrum, antiviral activity against both DNA and RNA viruses *in vitro* and *in vivo*[16,17]. In early 1986, the FDA approved use of ribavirin aerosol for treating severe infections of respiratory syncytial virus (RSV), a disease often fatal to infants and children. It has been shown by single-crystal X-ray studies[18,19] that the carbonyl oxygen atom and the amide nitrogen atom of the carbamoyl group in ribavirin are spatially similar to the O-6 and N-1 atoms of inosine and guanosine.

In view of these observations, the synthesis of ribavirin disaccharides was of particular interest. The synthesis of the desired ribavirin disaccharide derivatives may be envisaged as achievable either by (*a*) direct *N*-glycosylation[20] of the ribavirin base precursor, methyl 1,2,4-triazole-3-carboxylate, with the appropriate disaccharide, or (*b*) by 5′-*O*-glycosylation of ribavirin itself. Although the synthesis of disaccharide nucleosides from a nucleobase and the respective disaccharide has long been realized[21-24], the possibility of this approach is limited by the nonavailability of the parent disaccharide and the undesirability of separating the potential positional isomers on the triazole ring. Therefore, we explored the latter approach, (*b*) in order to prepare the desired ribavirin disaccharide derivatives.

RESULTS

Although the synthetic approach *via* glycosylation of the requisite 2′,3′-*O*-isopropylidenenucleoside with an acylglycosyl halide under the Koenigs–Knorr conditions has been reported[7], use of this method for 2′,3′-*O*-isopropylideneribavirin[25] (**5**) met with serious problems. Thus, reaction of **5** with tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4**) in the presence of Ag_2CO_3 and $AgClO_4$ in anhydrous dichloromethane gave a complex reaction-mixture. Flash chromatography on a column of silica gel of the reaction mixture provided a nucleoside product that was identified as the ortho ester derivative (**6**) of ribavirin. The assignment of this structure was based on the elemental analysis and the fact that the ^{1}H-n.m.r. spectrum of **6** contained an additional methyl resonance, centered at δ 1.45, that was assigned to the methyl group of the ortho ester function. The formation of such ortho esters has been

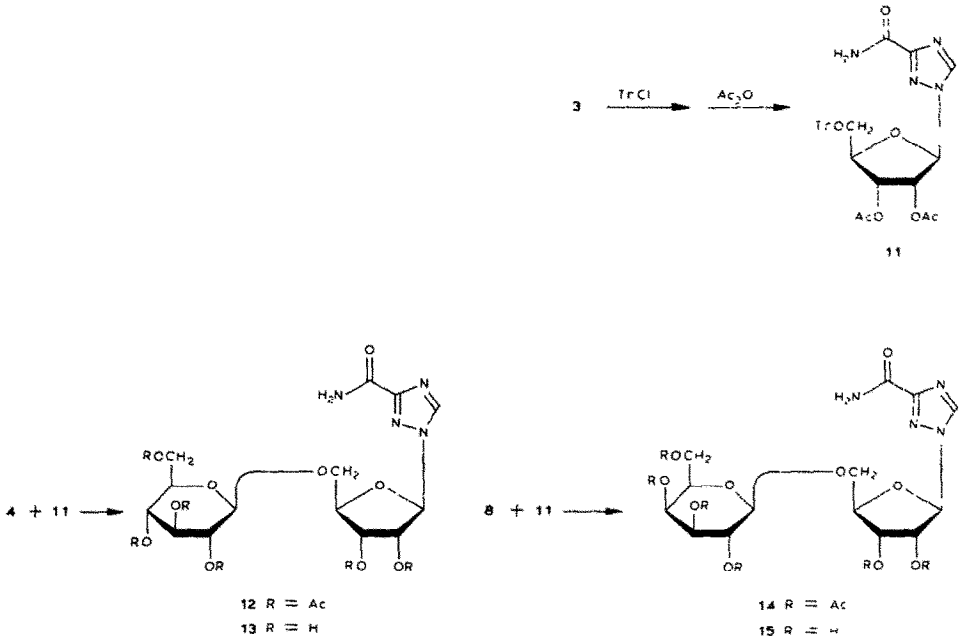
documented in the literature[5]. Deacetylation of **6** with ethanolic ammonia at 0° gave 1-[5-*O*-(1,2-*O*-ethylidene-α-D-glucopyranosyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]-1,2,4-triazole-3-carboxamide (**7**), the ^{1}H-n.m.r. spectrum of which contained the ortho ester methyl resonance at δ 1.45. Attempted *O*-deisopropylidenation of **7** with hot 80% acetic acid gave an intractable reaction-mixture from which ribavirin (**3**) was recovered as the major product after extensive chromatography on a column of silica gel.



Similar glycosylation of **5** with tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**8**) under the Koenigs–Knorr conditions (*i.e.*, silver carbonate, silver perchlorate, and Drierite in dichloromethane) also gave an ortho ester derivative, 1-[5-*O*-(3,4,6-tri-*O*-acetyl-1,2-*O*-ethylidene-α-D-galactopyranosyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]-1,2,4-triazole-3-carboxamide (**9**), which was isolated in 54% yield. *O*-Deacetylation of **9** gave 1-[5-*O*-(1,2-*O*-ethylidene-α-D-galactopyranosyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]-1,2,4-triazole-3-carboxamide (**10**), the ^{1}H-n.m.r. spectrum of which contained the methyl resonance of the ortho ester function at δ 1.41.

In an effort to develop a synthetic procedure that would lead to the desired 5'-*O*-β-D-glucopyranosyl and 5'-*O*-β-D-galactopyranosyl derivatives of ribavirin, use of the Bredereck modification[26–28] of the Koenigs–Knorr reaction was considered. This modified procedure has been found useful for the 5'-*O*-glycosylation of pyrimidine 2'-deoxy-ribonucleosides[9,28]. Treatment at ambient temperature of 1-(2,3-di-*O*-acetyl-5-*O*-trityl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (**11**)

with **4** in the presence of $AgClO_4$ in an aprotic polar solvent, such as anhydrous nitromethane, gave a rather low yield of 1-[2,3-di-*O*-acetyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-ribofuranosyl]-1,2,4-triazole-3-carboxamide (**12**). Deacetylation of **12** with ethanolic ammonia gave 5′-*O*-β-D-glucopyranosylribavirin (**13**). Similarly, when **11** was treated with **8** in the presence of $AgClO_4$ in anhydrous nitromethane, 1-[2,3-di-*O*-acetyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-ribofuranosyl]-1,2,4-triazole-3-carboxamide (**14**) was formed; on deacetylation with ethanolic ammonia, it furnished 5′-*O*-β-D-galactopyranosylribavirin (**15**).



That compounds **13** and **15** were indeed 5′-*O*-glycosyl derivatives of ribavirin, and not the carbamoyl-substituted derivatives, was established by observing the carbamoyl resonance (2 broad singlets centered at δ 7.6 and 7.8) in the ^{1}H-n.m.r. spectrum [$(CD_3)_2SO$]. The β-anomeric configuration of the D-glucosyl and D-galactosyl groups of compounds **13** and **15**, respectively, was evident from the large coupling constant ($J_{1'',2''}$ 7.8 Hz)[8,29].

EXPERIMENTAL

General methods. — Melting points were determined in a Thomas–Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Florham Park, New Jersey. T.l.c. was conducted on plates of silica gel 60 F-254 (EM Reagents). Silica gel (E. Merck; 230–400 mesh) was used for flash column chromatography. All solvents used were reagent grade.

Detection of nucleoside components in t.l.c. was by u.v. light, and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30°. I.r. spectra were recorded with a Beckman Acculab 2 spectrophotometer. ^{1}H-n.m.r. spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to Me_4Si as an internal standard. The presence of H_2O as indicated by elemental analysis was verified by ^{1}H-n.m.r. spectroscopy.

*1-[5-*O*-(3,4,6-Tri-*O*-acetyl-1,2-*O*-ethylidene-α-*D*-glucopyranosyl)-2,3-*O*-isopropylidene-β-*D*-ribofuranosyl]-1,2,4-triazole-3-carboxamide* (**6**). — A mixture of 2′,3′-*O*-isopropylideneribavirin[25] (**5**; 1.14 g, 4 mmol), Ag_2CO_3 (2.24 g, 8.3 mmol), and Drierite (4 g) in anhydrous CH_2Cl_2 (100 mL) was stirred for 1 h at ambient temperature under a nitrogen atmosphere. After cooling to 0°, $AgClO_4$ (0.25 g, 1.24 mmol) and tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4**; Sigma Chemical Co.; 1.97 g, 4.1 mmol) were added with stirring. After 20 h, CH_2Cl_2 (140 mL) was added to the mixture, and, after filtering through Celite, the filtrate was washed with water (3 × 25 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified in a flash silica gel column (3 × 60 cm) packed in $CHCl_3$. Elution with $CHCl_3$–MeOH (98:2, 95:5, and 9:1, v/v) gave 0.75 g (30%) of the title compound as a gum; ν_{max}^{KBr} 3600–3200 (NH_2), 1740 (C=O of ester), and 1680 cm^{-1} (C=O of amide); ^{1}H-n.m.r. data [$(CD_3)_2SO$]: δ 8.78 (s, 1 H, *H*-5), 7.88 and 7.68 (2 s, 2 H, CONH_2, exchanged with D_2O), 6.27 (s, 1 H, *H*-1′), 5.72 (d, 1 H, *J* 5.0 Hz, *H*-1″), 2.01–2.06 (3 s, 9 H, 3 COCH_3), and 1.31–1.53 (3 s, 9 H, 3 CH_3, isopropylidene + orthoester group).

Anal. Calc. for $C_{25}H_{34}N_4O_{14}$ (614.56): C, 48.86; H, 5.58; N, 9.12. Found: C, 48.59; H, 5.66; N, 8.84.

*1-[5-*O*-(1,2-*O*-Ethylidene-α-*D*-glucopyranosyl)-2,3-*O*-isopropylidene-β-*D*-ribofuranosyl]-1,2,4-triazole-3-carboxamide* (**7**). — A solution of **6** (1.23 g, 2 mmol) in ethanolic ammonia (50 mL, saturated at 0°) was stirred overnight at 0°, and then evaporated to dryness. The residue was dissolved in MeOH, and adsorbed onto silica gel (10 g). The excess of solvent was evaporated and the concentrate was placed on top of a flash silica gel column (1.5 × 20 cm) packed in $CHCl_3$. The column was eluted with $CHCl_3$–MeOH (8:2, 7:3, v/v). The appropriate fractions were pooled, and evaporated to yield 0.40 g (41%) of **7**; ^{1}H-n.m.r. data [$(CD_3)_2SO$]: δ 8.77 (s, 1 H, *H*-5), 7.90 and 7.67 (2 s, 2 H, CONH_2), 6.24 (s, 1 H, *H*-1′), 5.59 (d, 1 H, *J* 4.5 Hz, *H*-1), 5.27 and 5.09 (2 d, 2 H, *J* 4.0 Hz, O*H*-3″,4″), 5.18 (d, 1 H, *J* 4.5 Hz, *H*-3″), 4.89 (m, 1 H, *H*-4″), 4.64 (t, 1 H, O*H*-5″), 4.32 (dd, 1 H, *H*-3′), 4.12 (m, 1 H, *H*-2′), 3.58 (m, 3 H, *H*-4′, + CH_2-5′), 3.44 (m, 3 H, *H*-2″ + CH_2-5″), 1.49 and 1.32 (2 s, 6 H, isopropylidene), and 1.45 (s, 3 H, orthoester).

Anal. Calc. for $C_{19}H_{28}N_4O_{11}\cdot 0.5\ H_2O$ (497.45): C, 45.87; H, 5.86; N, 11.26. Found: C, 45.88; H, 5.97; N, 10.95.

*1-[5-*O*-(3,4,6-Tri-*O*-acetyl-1,2-*O*-ethylidene-α-*D*-galactopyranosyl)-2,3-*O*-isopropylidene-β-*D*-ribofuranosyl]-1,2,4-triazole-3-carboxamide* (**9**). — A mixture of **5** (2.27 g, 8 mmol), Ag_2CO_3 (4.48 g, 16.6 mmol), and Drierite (8 g) in anhydrous CH_2Cl_2 (200 mL) was stirred for 1 h at room temperature under a nitrogen atmos-

phere. After cooling to 0°, $AgClO_4$ (0.5 g, 2.48 mmol) and tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**8**; Sigma Chemical Co.; 3.93 g, 8.16 mmol) were added, and the mixture was stirred for 20 h. The mixture was worked-up as described for **6**, to give 2.65 g (54%) of **9** as a foam; ν_{max}^{KBr} 3500–3200 (NH_2), 1730 (C = O of ester), and 1680 cm^{-1} (C = O of amide); ^{1}H-n.m.r. data [$(CD_3)_2SO$]: δ 8.77 (s, 1 H, *H*-5), 7.87 and 7.64 (2 s, 2 H, CONH_2, exchanged with D_2O), 6.24 (s, 1 H, *H*-1′), 5.74 (d, 1 H, *J* 4.9 Hz, *H*-1″), 2.0–2.12 (3 s, 9 H, 3 COCH_3), and 1.32–1.49 (3 s, 9 H, 3 CH_3, isopropylidene + orthoester group).

Anal. Calc. for $C_{25}H_{34}N_4O_{14}$ (614.56): C, 48.86; H, 5.58; N, 9.12. Found: C, 48.61; H, 5.61; N, 9.00.

1-[5-O-(1,2-O-Ethylidene-α-D-galactopyranosyl)-2,3-O-isopropylidene-β-D-ribofuranosyl] - 1,2,4 - triazole - 3 - carboxamide (**10**). — A solution of **9** (0.61 g, 1 mmol) in ethanolic ammonia (30 mL, saturated at 0°) was treated as described for **7**, to give 0.2 g (41%) of **10**; ^{1}H-n.m.r. data [$(CD_3)_2SO$]: δ 8.75 (s, 1 H, *H*-5), 7.87 and 7.64 (2 s, 2 H, CONH_2), 6.21 (s, 1, *H*-1′), 5.59 (d, 1, *J* 3.1 Hz, *H*-1″), 5.23 and 4.80 (2 d, 2 H, *J* 4.0 Hz, O*H*-3″,4″), 5.18 (d, 1 H, *J* 4.5 Hz, *H*-3″), 4.88 (d, 1 H, *J* 4.0 Hz, *H*-4″), 4.66 (t, 1 H, O*H*-5″), 4.35 (m, 1 H, *H*-3′), 4.09 (m, 1 H, *H*-2′), 3.62 (m, 3 H, *H*-4′ + CH_2-5′), 3.48 (m, 3 H, *H*-2″ + CH_2-5″), 1.50 and 1.32 (2 s, 6 H, isopropylidene), and 1.41 (s, 3 H, orthoester).

Anal. Calc. for $C_{19}H_{28}N_4O_{11}$·0.5 H_2O (497.45): C, 45.87; H, 5.86; N, 11.26. Found: C, 45.67; H, 5.77; N, 11.04.

1-(2,3-Di-O-acetyl-5-O-trityl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (**11**). — A solution of ribavirin[15] (**3**; 10 g, 41 mmol) and chlorotriphenylmethane (12.6 g, 45 mmol) in anhydrous pyridine (100 mL) was heated for 3 h at 100°, and cooled to room temperature; acetic anhydride (80 mL, 840 mmol) was added, and, after 20 h, the solution was slowly added to vigorously stirred ice-water (1 L), giving a gummy precipitate. The precipitate was collected, washed with water, and purified on a flash silica gel column (5 × 50 cm), using $CHCl_3$–MeOH (98:2, 95:5, v/v) as eluant, to give 20 g (85%) of **11**; ν_{max}^{KBr} 3500–3300 (NH_2), 1740 (C = O of acetyl), and 1700 cm^{-1} (C = O of amide); ^{1}H-n.m.r. data [$(CD_3)_2SO$]: δ 8.86 (s, 1 H, *H*-5), 7.66 (s, 2 H, CONH_2), 7.28 (m, 15 H, 3 C_6H_5), 6.30 (d, 1 H, *J* 5.2 Hz, *H*-1′), and 2.0–2.08 (2 s, 6 H, 2 COCH_3).

Anal. Calc. for $C_{31}H_{30}N_4O_7$ (570.61): C, 65.25; H, 5.30; N, 9.82. Found: C, 64.99; H, 5.44; N, 9.75.

1-[2,3-Di-O-acetyl-5-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-ribofuranosyl] - 1,2,4 - triazole - 3 - carboxamide (**12**). — A mixture of **11** (1.14 g, 2 mmol), $AgClO_4$ (0.46 g, 0.96 mmol), and Drierite (0.5 g) in anhydrous nitromethane (6 mL) was stirred for 20 min at room temperature. To the cooled (0–5°) mixture was added **4** (0.9 g, 2.2 mmol), and stirring was continued for 30 min at 20°. The precipitated solid was collected by filtration, and washed with nitromethane (2 × 5 mL). The filtrates were combined, washed with aqueous saturated $NaHCO_3$ solution (25 mL), and extracted with $CHCl_3$ (2 × 25 mL). The extracts were combined, washed with water (2 × 10 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was

purified in a flash silica gel column (3 × 30 cm) using $CHCl_3$–MeOH (98:2, 97:3, and then 96:4, v/v) as the eluant, and crystallized from 1:1 (v/v) diethyl ether–hexane, to yield amorphous, solid **12**, 0.18 g (15%); ν_{max}^{KBr} 3500–3350 (NH_2), 1750 (C=O of ester), and 1690 cm^{-1} (C=O of amide); ^{1}H-n.m.r. data [$CDCl_3$]: δ 8.59 (s, 1 H, *H*-5), 7.26 (s, 2 H, CONH_2), 6.10 (d, 1 H, *J* 4.1 Hz, *H*-1′ of ribose), 4.61 (d, 1 H, *J* 8 Hz, *H*-1″ of glucose), and 2.01–2.13 (m, 18 H, 6 COCH_3).

Anal. Calc. for $C_{26}H_{34}N_4O_{16}$ (658.57): C, 47.42; H, 5.20; N, 8.51. Found: C, 47.25; H, 5.45; N, 8.42.

1-(5-O-β-D-Glucopyranosyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (**13**). — A solution of **12** (0.66 g, 1 mmol) in ethanolic ammonia (70 mL) was treated as described for **7**, to give 0.2 g (42%) of **13**; ν_{max}^{KBr} 3500–3300 (OH, NH_2), and 1680 cm^{-1} (C=O of amide); ^{1}H-n.m.r. data [$(CD_3)_2SO$]: δ 8.55 (s, 1 H, *H*-5), 7.80 and 7.58 (2 br s, 2 H, CONH_2), 5.84 (d, 1 H, *J* 2.8 Hz, *H*-1′ of ribose), and 4.24 (d, 1 H, *J* 7.8 Hz, *H*-1″ of glucose).

Anal. Calc. for $C_{14}H_{22}N_4O_{10}\cdot 0.5\ H_2O$ (415.35): C, 40.48; H, 5.58; N, 13.48. Found: C, 40.25; H, 5.64; N, 13.23.

1-[2,3-Di-O-acetyl-5-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-ribofuranosyl]-1,2,4-triazole-3-carboxamide (**14**). — In a similar manner as for **12**, compound **14** was prepared by using **11** (11.4 g, 20 mmol), $AgClO_4$ (4.6 g, 9.6 mmol), Drierite (5 g), and **8** (9 g, 22 mmol) in nitromethane (60 mL), to yield after crystallization from 1:1 (v/v) diethyl ether–hexane 3.0 g (22%) of **14** as an amorphous solid; ν_{max}^{KBr} 3500–3300 (NH_2), 1740 (C=O of ester), and 1690 cm^{-1} (C=O of amide); ^{1}H-n.m.r. data [$CDCl_3$]: δ 8.65 (s, 1 H, *H*-5), 7.26 (s, 2 H, CONH_2), 6.11 (d, 1 H, *J* 4.2 Hz, *H*-1′ of ribose), 4.58 (d, 1 *J* 7.9 Hz, *H*-1″ of galactose), and 2.0–2.2 (m, 18 H, 6 *COCH*$_3$).

Anal. Calc. for $C_{26}H_{34}N_4O_{16}\cdot H_2O$ (676.58): C, 46.16; H, 5.36; N, 8.28. Found: C, 46.25; H, 5.16; N, 8.54.

1-(5-O-β-D-Galactopyranosyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (**15**). — A solution of **14** (0.67 g, 1 mmol) in ethanolic ammonia (70 mL) was treated as described for **7**, to give 0.12 g (30%) of **15**; ν_{max}^{KBr} 3450–3300 (OH, NH_2), and 1670 cm^{-1} (C=O of amide); ^{1}H-n.m.r. data [$(CD_3)_2SO$]: δ 8.85 (s, 1 H, *H*-5), 7.88 and 7.63 (2 br s, 2 H, CONH_2), 5.82 (d, 1 H, *J* 3.2 Hz, *H*-1′ of ribose), and 4.14 (d, 1 H, *J* 7.8 Hz, *H*-1″ of galactose).

Anal. Calc. for $C_{14}H_{22}N_4O_{10}$ (406.34): C, 41.38; H, 5.46; N, 13.79. Found: C, 41.18; H, 5.59; N, 13.57.

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