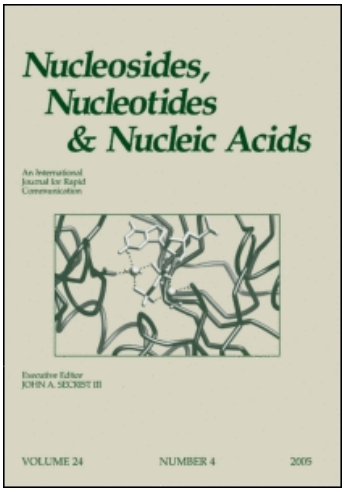

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SYNTHESIS OF 4-ACYL-1H-1,2,3-TRIAZOLIC NUCLEOSIDES

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SYNTHESIS OF 4-ACYL-1H-1,2,3-TRIAZOLIC NUCLEOSIDES

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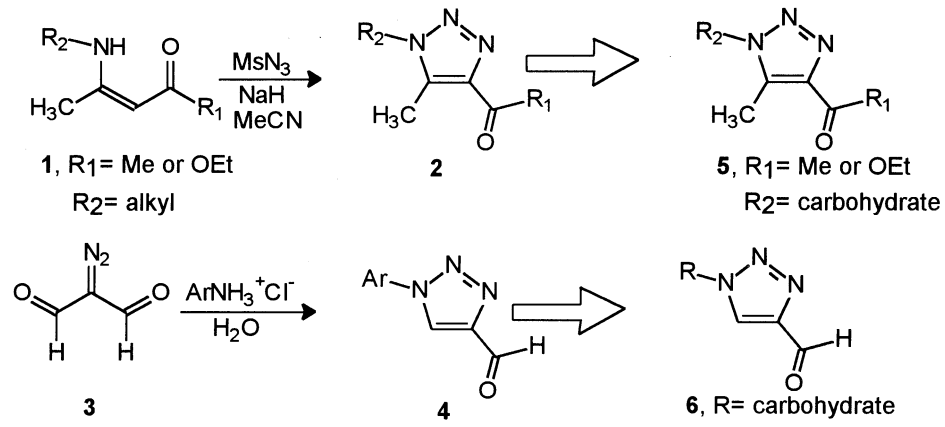
ABSTRACT

Two simple regiospecific methodologies based on triazolic ring construction in the course of synthesis were applied for the synthesis of 1,2,3-triazolic nucleoside analogues. The cycloaddition reactions between diazomalonaldehyde and appropriate glycosylamine derivatives were rather effective, producing the desired nucleosides **11**, **17** and **24**. Diazotization of enamines **21a** and **21b** led to the corresponding triazolic ribonucleoside derivatives **22a** and **22b**, in good yields. Deprotection reaction of **22a**, **22b** and **24** was easily achieved by Lewis acid catalysis, producing the corresponding ribonucleosides **23a**, **23b** and **25**.

The development of triazole-based compounds stimulated by their pronounced biological activities brought about noticeable interest in the synthetic manipulations of triazoles[1].

Recently we reported a versatile and regioselective route for the synthesis of 1,2,3-triazole derivatives presenting different substituents at positions 4 and 5. In all cases, only the isomer characterized by the presence of alkyl or aryl moieties at position 5 and of acetyl or carboxylate groups at position 4 was obtained. (Scheme 1: $\mathbf{1} \rightarrow \mathbf{2}$)[2].

*Corresponding author.



Scheme 1. Methods for preparing triazoles by diazotization of enamines and by cycloaddition between diazocompounds and amines.

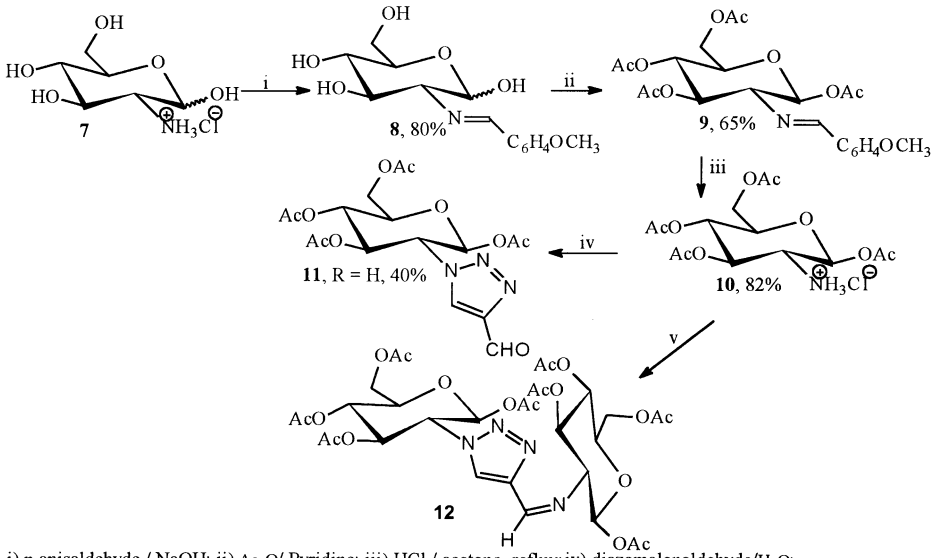
Another regioselective route based on the cycloaddition of amines to α-diazocarbonyl compounds to produce substituted 1,2,3-triazoles was previously described by Arnold (Scheme 1: **3** → **4**)[3].

Proceeding with our research work[4a] on α-diazocarbonyl compounds[4b–4f] and nucleoside derivatives[4g–4k] and grounded in the precedents above, we herein report an extension of these two efficient methods to the nucleoside field. Advances in this area have indicated that changes in the carbohydrate or the nitrogenated base moiety may be compatible with potent therapeutical compounds[5].

RESULTS AND DISCUSSION

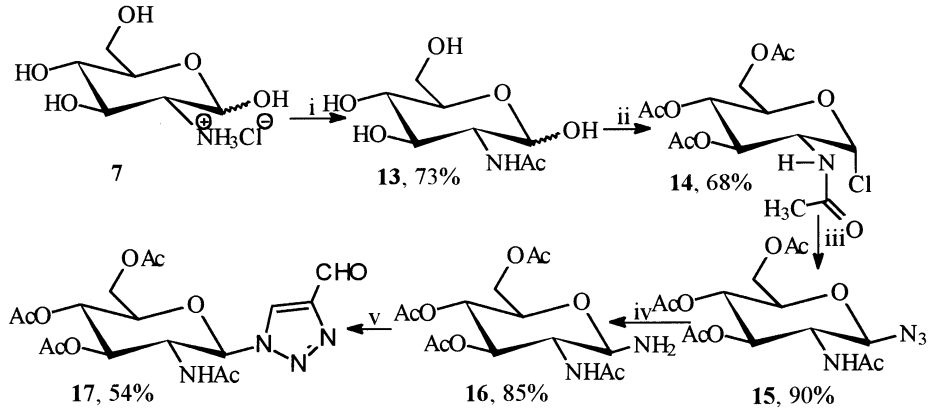
Initially, triazolic gluconucleoside **11** was synthesized by the cycloaddition between diazomalonaldehyde and aminoglucoside **10** (Scheme 2). The treatment of D-glucosamine (7) with p-anisaldehyde in NaOH resulted in 2-(4-methoxybenzylidene)imine-2-desoxy-D-glucopyranose (**8**) as a mixture of two diastereoisomers, α and β, in 80% yield (Scheme 2). The reaction of this mixture with acetic anhydride and pyridine in excess produced imine-tetracetate **9** as the β-isomer. The stereospecificity of this reaction at the anomeric center is due to the bulky group at C-2. Selective acid hydrolysis of **9** led to the desired glucosamine hydrochloride **10** in 82% yield[6]. Cycloaddition reaction between **10** and diazomalonaldehyde in aqueous solution produced the triazolic gluconucleoside **11** in 40% yield. All attempts to improve this yield using an excess of D-glucosamine hydrochloride **10** in methanolic solution led exclusively to bis-triazolic adduct **12**.

In order to synthesize the triazolic gluconucleoside **17** presenting the heterocyclic nucleus at the anomeric position, amine **16** was prepared

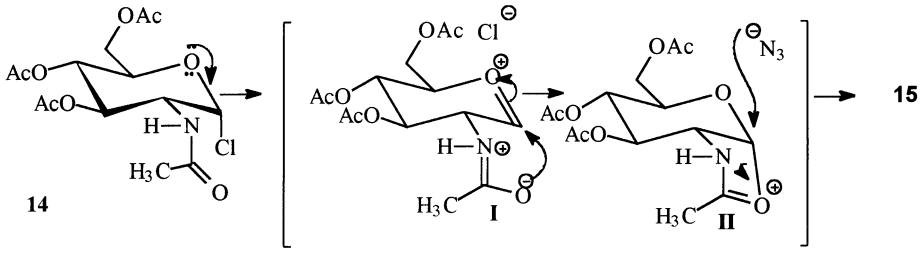


Scheme 2. Synthetic route used for preparing triazolic gluconucleosides **11** and **12**.

(Scheme 3) following the procedure described in the literature[7]. This involved the selective protection of an amine group as the acetamide (**13**), followed by the peracetylation of the hydroxy groups and the replacement of the acetyl group at the anomeric position by a chlorine to form **14**[7]. The nucleophilic



Scheme 3. Synthesis of triazolic gluconucleoside **17**.

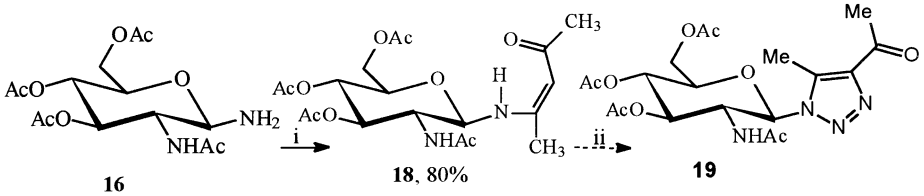


Scheme 4. Anchimeric assistance responsible for the 1,2-*trans* stereochemistry in **15**.

substitution of the chlorine group by the azide anion led to **15** in 90% yield. The 1,2-*trans* stereochemistry of this compound may be explained by a SN_2 attack by the azido anion at the anomeric carbon in the intermediate acyloxonium ion (**II**), which was formed from **I** by an anchimeric assistance of the acetamide group at position 2 (Scheme 4). The catalytic hydrogenation of **15** led to the desired amine **16** in 85% yield. All attempts to form the triazole derivative **17** by the reaction between this amine and diazomalonaldehyde, in water or methanol, failed. However, a slightly modified procedure using acetic acid as co-solvent in methanol successfully gave **17** in 54% yield.

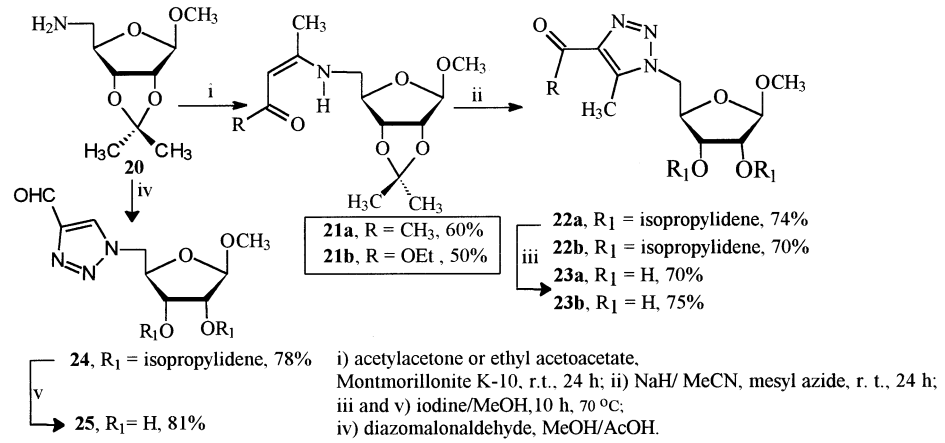
For the purpose of preparing the triazolic gluconucleoside **19**, compound **16** underwent a reaction with acetylacetone in the presence of Montmorillonite (K-10) clay[8] resulting in enamine **18**, in 80% yield. All attempts to carry out the diazotization of **18** using mesyl azide failed to give **19** (Scheme 5). Since this reaction was rather effective with acyclic amines[4] and aminocarbohydrate **20**, a compound where the amine group is not bonded to the anomeric carbon but to C-5 instead, we speculated on the possible elimination of the enamine group before the formation of the triazolic ring.

Ribonucleosides **22a** and **22b** were synthesized by constructing the triazolic nucleus from 5-amino-5-deoxy-1,2-O-isopropylidene-β-D-ribofuranoside (**20**), which was prepared from commercially available D-ribose, in four steps (Scheme 6)[9]. Amine **20** was readily condensed with acetylacetone or ethyl acetoacetate forming **21a** and **21b**, respectively[10]. The diazotization



i) acetylacetone, Montmorillonita K-10/ methanol, 24 h, r.t.;
ii) NaH/acetonitrile, mesyl azide, 24 h, r.t.

Scheme 5. Attempts to obtain **19** by direct diazotization of enamine **18**.



Scheme 6. Synthesis of triazolic ribonucleosides **23a**, **23b** and **25**.

of enamines **21a** or **21b** with the diazo transfer reagent mesyl azide (MsN_3)[2] produced triazolic derivatives **22a** and **22b**, in 74 and 70% yield, respectively. Finally, triazole derivative **24** was prepared from the reaction between **20** and diazomalonaldehyde, in 78% yield. Removal of the isopropylidene group from the carbohydrate moiety of **22a** and **22b** as well as **24** can be easily achieved by mild Lewis acid catalysis producing the corresponding deprotected ribonucleoside derivatives **23a**, **23b** and **25**, respectively, in good yields (Scheme 6).

In conclusion, this work highlights the applicability of two simple regioselective methodologies based on the triazolic ring construction in the course of the synthesis for the synthesis of 1,2,3-triazolic nucleoside analogues. Cycloaddition reactions between diazomalonaldehyde and appropriate glycosylamine derivatives were effective for the preparation of nucleoside derivatives **11** (Scheme 2), **17** (Scheme 3) and **24** (Scheme 6). Diazotization of enamines **21a** and **21b** led to protected triazolic ribonucleosides **22a** and **22b** in good yields (Scheme 6). On the other hand, the diazotization of enamine **18** (Scheme 5) failed to produce gluconucleoside **19**, a compound which presents the triazolic nucleus bonded to the anomeric carbon. Removal of the isopropylidene group from the carbohydrate moiety of **22a**, **22b** and **24** was easily achieved by Lewis acid catalysis producing the corresponding ribonucleoside derivatives **23a**, **23b** and **25** (Scheme 6).

Since many substances containing triazolic nucleus have wide biological activities[11], the development of synthetic methods that grant access to triazolic nucleoside analogues is decidedly important. Further studies including the use of different starting glycosylamine derivatives must be carried out to verify the possibility of using both methods for preparing promising triazolic nucleosides.

EXPERIMENTAL

General Procedures

Melting points were observed on a Fischer-John melting-point apparatus and are uncorrected. Ultraviolet spectra were recorded on a Schimadzu spectrophotometer; λ in nm and ε in $mole^{-1}\,cm^{-1}$. ^1H and ^{13}C NMR spectra were recorded with a Varian Unity Plus 300 spectrometer operating at 300 and 75 MHz respectively, with tetramethylsilane as the internal standard. Low resolution electron-impact mass spectra (12 eV) were obtained using a Hewlett Packard 5985 instrument and high resolution fast atom bombardment mass spectra (HRMS-FAB) were recorded in a 3-NBA (3-nitrobenzyl alcohol) matrix in the positive ion mode on a VG ZAB-E mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Optical rotations were measured on a Perkin Elmer 24 B Polarimeter. Column chromatography was performed using silica gel 60 (Merck 70–230 mesh). Merck silica gel F254 (0.2 mm) was used for TLC plates, detection being carried out by spraying with aqueous ammonium sulfate solution (25%, w/w), followed by heating. Solvents were dried over appropriate agents and were immediately distilled before use[12]. Freshly purified samples were used to measure physical constants and spectral data.

2-Amino-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glycopyranose Hydrochloride (10)

A solution of **9**[6] (1 g, 2.15 mmol) in acetone (16 mL) was heated in a water bath and then an aqueous solution of HCl (0.5 N, 0.43 mL) was added producing a gel. After adding diethyl ether (5 mL) the mixture was kept in the refrigerator until complete crystallization. The solid was collected by filtration, washed with diethyl ether and dried in desiccator under P_2O_5. Hydrochloride **10** was obtained in 82% yield (676 mg). m.p 199 °C (decomp.); $[\alpha]_D^{25}$ + 39.7 (c 1.00, MeOH); ^1H NMR (300.00 MHz, $CDCl_3$) δ 2.08; 2.11; 2.14; 2.29 (12H, s, 4 $COC\underline{H}_3$), 3.66 (1H, dd, J = 10.2 and 9.0 Hz, H2′), 5.04 (1H, dd, J = 9.3 and 9.3 Hz, H4′), 5.48 (1H, dd, J = 10.3 and 9.0 Hz, H3′), 4.08–4.17 (2H, m, H6′ and H6′), 4.30 (1H, dd, J = 12.3 and 4.5 Hz, H6′′), 5.12 (2H, broad singlet, NH_2) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 20.5; 20.6; 20.9; 21.1 (4 $CO\underline{C}H_3$), 52.3 (C2′), 61.4 (C6′), 67.9 (C4′), 70.4 (C3′), 71.4 (C5′), 90.2 (C1′), 168.8; 169.5; 169.9; 170.5 (4 C=O) ppm.

2-(4-Formyl-1,2,3-triazo-1-yl)-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (11)

A solution of diazomalonaldehyde (91 mg, 0.93 mmol) and hydrochloride 10 (452 mg, 1.18 mmol) in water (7 mL) was stirred at room

temperature for 24 hours. The white solid formed was collected by filtration, washed with water and dried under vacuum leading to triazole **11** as a white solid in 40% yield (158 mg). m.p. 141–142 °C; $[\alpha]_D^{25}$ +38.9 (c 0.46, MeOH); UV λ_{max} (MeOH) 218 (ε 3,847); IR (film) ν_{max} (cm^{-1}): 1702–1780 (C=O); ^1H NMR (300.00 MHz, $CDCl_3$) δ 1.88, 1.99, 2.06 and 2.11 (12H, s, 4 $COC\underline{H}_3$), 4.09 (1H, ddd, J = 10.1; 4.3 and 2.1 Hz, H5′), 4.18 (1H, dd, J = 12.3 and 2.1 Hz, H6′), 4.41 (1H, dd, J = 12.6 and 4.5 Hz, H6′), 4.72 (1H, dd, J = 10.5 and 8.7 Hz, H2′), 5.24 (1H, dd, J = 9.9 and 9.3 Hz, H4′), 5.82 (1H, dd, J = 10.8 and 9.3 Hz, H3′), 6.24 (1H, d, J = 8.7 Hz, H1′); 8.14 (1H, s, H5), 10.14 (1H, s, $\underline{H}C$=O) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 20.0; 20.3; 20.4 and 20.5 (4 $CO\underline{C}H_3$), 61.1 (C5′), 63.1 (C2′), 67.8 (C4′), 71.8 (C3′), 72.9 (C5′), 91.3 (C1′), 125.8 (C5), 147.4 (C4), 167.8; 168.9; 169.4 and 170.4 (4 C=O), 184.7 ($H\underline{C}$=O) ppm; LRMS-FAB (m/z) (relative intensity): 428 (33), 154 (95), 136 (87); HRMS-FAB: calcd for $C_{17}H_{22}N_3O_{10}$ $(M+H)^+$ 428.1305; found 428.1297.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-chloro-2-deoxy-α-D-glucopyranose (14)

A solution of **13** (1.5 g, 6.80 mmol) in 5 mL of acetyl chloride was stirred at room temperature under nitrogen atmosphere for 48 hours. Chloroform (12 mL), ice (12 g) and water (10 mL) were added to this solution. The organic phase was separated and washed with an aqueous solution of sodium bicarbonate (15 mL). After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, using hexane-ethyl acetate (9 : 1) as the eluant, and the resulting solid was crystallized out of diethyl ether. Nucleoside **14** was isolated as a white solid in 68% yield (1.59 mg). m.p. 119 °C; 1H NMR (300.00 MHz, $CDCl_3$) 2.00, 2.06 and 2.11 (12H, s, 4 $COC\underline{H}_3$), 4.14 (1H, dd, J = 13.6 and 3.0 Hz, H6′), 4.25–4.33 (2H, m, H5′ and H6′), 4.55 (1H, ddd, J = 10.6; 8.7 and 3.6 Hz, H2′), 5.22 (1H, dd, J = 9.6 and 9.6 Hz, H4′), 5.35 (1H, dd, J = 10.6 and 9.3 Hz, H3′), 6.07 (1H, d, J = 8.4, N$\underline{H}$Ac), 6.20 (1H, d, J = 3.9 Hz, H1′) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 20.3; 20.5 and 20.8 (4 $CO\underline{C}H_3$), 53.2 (C2′), 61.0 (C6′), 66.8 (C4′), 69.9 (C3′), 70.7 (C5′), 93.5 (C1′), 168.9; 170.0; 170.4 and 171.2 (4 C=O) ppm.

1-Azido-2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranose (15)

After being stirred, a solution of **14** (0.5 g, 1.66 mmol) and sodium azide (0.15 g, 2.31 mmol) in dry DMF (3 mL) was heated under nitrogen atmosphere at 75–80 °C for 4 hours. The mixture was poured into cold water and then extracted with ethyl acetate (4 × 15 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced

pressure. The residue was purified by column chromatography on silica gel using a gradient from pure hexane to hexane-ethyl acetate (1 : 1) producing **15** as a white solid in 90% yield. m.p. 166–167 °C; ^{1}H NMR (300.00 MHz, $CDCl_3$) 1.99, 2.04, 2.05 and 2.11 (12H, s, 4 COC<u>H</u>$_3$), 3.92 (1H, m, H2′), 3.80 (1H, ddd, J = 9.9, 4.8 and 2.4 Hz, H5′), 4.17 (1H, dd, J = 12.5 and 2.4 Hz, H6′), 4.28 (1H, dd, J = 12.5 and 4.8 Hz, H6″), 4.77 (1H, d, J = 9.3 Hz, H1′), 5.11 (1H, dd, J = 9.3 and 9.3 Hz, H4′), 5.74 (1H, d, J = 8.7 Hz, N<u>H</u>Ac) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 20.4; 20.5 and 20.6 and 23.1 (4 COC<u>H</u>$_3$), 53.9 (C2′), 61.7 (C6′), 68.0 (C4′), 72.0 (C3′), 72.0 (C3′), 73.7 (C5′), 82.2 (C1′), 169.2; 170.7, 170.5 and 170.6 (4 C=O) ppm.

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine (16)

A mixture of **15** (1.50 g; 4.04 mmol) in ethyl acetate (50 mL) was hydrogenated at room temperature and 2.5 atm pressure for 2 hours in the presence of 0.63 g of Adam′s platinum oxide catalyst. The catalyst was removed by filtration and washed with ethyl acetate. Activated charcoal was added to the resulting mixture which was filtrated and the solution was evaporated under reduced pressure producing a white solid. This solid was refluxed in ethyl acetate-hexane (2 : 1, 30 mL) and then collected by filtration and washed with diethyl ether leading to **16** in 85% yield (1.19 mg). m.p. 220–221 °C (decomp.); ^{1}H NMR (300.00 MHz, CD_3OD) 2.01, 2.07, 2.09 and 2.13 (12H, s, 4 COC<u>H</u>$_3$), 3.84 (1H, ddd, J = 9.6, 4.8 and 2.4 Hz, H5′), 3.90 (1H, dd, J = 10.2 and 9.6 Hz, H2′), 4.18 (1H, dd, J = 12.0 and 2.4 Hz, H6′), 4.31 (1H, d, J = 9.3 Hz, H1′), 4.33 (1H, dd, J = 12.0 and 4.8 Hz, H6″), 5.05 (1H, dd, J = 9.9 and 9.6 Hz, H4′), 5.25 (1H, dd, J = 10.5 and 9.3 Hz, H3′), 4.97 (3H, broad singlet, N<u>H</u>Ac and NH_2) ppm; ^{13}C NMR (75.0 MHz, CD_3OD) δ 11.2 and 11.3 (CO<u>C</u>H$_3$), 46.7 (C2′), 54.3 (C6′), 61.1 (C4′), 64.4 (C5′), 65.5 (C3′), 76.7 (C1′), 161.9, 162.5, 163.0 and 164.3 (4 C=O) ppm.

1-(2-Acetamide-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-4-formyl-1,2,3-triazole (17)

A solution of diazomalonaldehyde (220 mg, 2.25 mmol) and 16 (152 mg, 0.44 mmol) in 3 mL of methanol and 0.2 mL of acetic acid was stirred at room temperature for 24 hours. Concentration of the solution under reduced pressure produced a residue which was purified by column chromatography on silica gel, using a gradient from pure hexane to hexane-acetone (1 : 1) as the eluant. 17 was obtained as a yellow solid in 54% yield (101 mg). m.p. 228–229 °C; $[\alpha]_D^{25} + 6.3$ (c 0.47, MeOH); UV λ_{max} (MeOH) 217 (ε 3,645); IR (film) ν_{max} (cm^{-1}): 1668–1747 (C=O); ^{1}H NMR (300.00 MHz, $CDCl_3$) 1.80, 2.08, 2.09 and 2.10 (12H, s, 4 COC<u>H</u>$_3$), 4.06 (1H, dd, J = 10.1; 4.8 and 2.1 Hz, H5′), 4.17 (1H, dd, J = 12.6 and 2.1 Hz, H6′), 4.31 (1H, dd, J = 12.6 and

4.8 Hz, H6′), 4.55 (1H, ddd, J = 10.5, 9.9 and 9.9 Hz, H2′), 5.28 (1H, dd, J = 10.2. and 9.3 Hz, H4′), 5.45 (1H, dd, J = 10.5 and 9.3 Hz, H3′), 6.06 (1H, d, J = 9.9 Hz, H1′); 8.50 (1H, s, H5), 10.14 (1H, s, HC=O) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 20.4; 20.5; 20.6 and 20.7 (4 $CO\underline{C}H_3$), 61.5 (C6′), 57.3 (C2′), 67.7 (C4′), 74.9 (C5′), 71.7 (C3′), 86.1 (C1′), 125.6 (C5), 147.3 (C4), 169.2, 170.4, 170.7 and 170.8 (4 C=O), 184.2 (H<u>C</u>=O) ppm; LRMS-FAB (m/z) (relative intensity): 427 (4)168 (41), 154 (69), 136 (65); HRMS-FAB: calcd for $C_{17}H_{23}N_4O9(M+H)^+$427.1465; found 427.1459.

1-[N-2-(4-Oxopenten)]amino-2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranose (18)

A solution of **16** (301 mg, 0.87 mmol) in 2 mL dry methanol was slowly added to a mixture of acetylacetone (683 mg, 6.82 mmol), Montmorillonite K-10 (0.31 g) and 2 mL of dry methanol, under nitrogen atmosphere. After stirring for 24 hours at room temperature, the mixture was filtrated and the resulting solution was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the remaining solid was purified by column chromatography on silica gel, using a gradient from hexane to hexane-acetone (1 : 1) as the eluant. Enamine **18** was obtained in 80% yield (298 mg). m.p. 188−190 °C; $[\alpha]_D^{25}$ +5.2 (c 1.33, MeOH); UV λ_{max} (MeOH) 301 (ε 13.977); IR (film) ν_{max} (cm^{-1}): 3446 (N-H), 1746 (C=O); ^{1}H NMR (300.00 MHz, $CDCl_3$) δ 1.91 ($C\underline{H}_3C4$), 2.02, 2.05 and 2.08 (12H, s, 4 $C\underline{H}_3C$=O), 2.00 ($C\underline{H}_3C$=O, enamine moiety), 3.68−3.76 (1H, m, H2′), 3.78 (1H, ddd, J = 10.1, 5.3 and 2.4 Hz, H5′), 4.10 (1H, dd, J = 12.3 and 2.1 Hz, H6′), 4.21 (1H, dd, J = 12.3 and 5.1 Hz, H6″), 5.04 (1H, dd, J = 9.9 and 9.3 Hz, H4′), 5.13 (1H, s, H3), 5.23 (1H, dd, J = 9.0 and 9.0 Hz, H1′), 5.51 (1H, dd, J = 10.4 and 9.0 Hz, H3′), 6.51 (1H, s, N<u>H</u>Ac), 10.76 (1H, d, J = 8.7 Hz, N-H) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 18.4, 20.4 and 20.5 ($\underline{C}H_3C$=O, sugar moiety), 22.9 ($\underline{C}H_3C_4$), 29.4 ($\underline{C}H_3C$=O, enamine moiety), 54.5 (C2′), 62.0 (C6′), 68.7 (C4′), 72.0 (C3′), 72.6 (C5′), 81.8 (C1′), 98.6 (C3), 161.0 (C4), 169.8, 170.5 and 170.8 (C=O, sugar moeity), 197.0 (C=O, enamine moiety) ppm; LRMS-FAB (m/z) (relative intensity): 429 (100), 168 (38), 154 (53), 136 (48);); HRMS-FAB: calcd for $C_{19}H_{29}N_2O_9(M+H)^+$ 428.1873; found 428.1864.

General procedure for the preparation of methyl 5′-[N-2-(4-oxopenten)]amino-5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranoside (21a) and methyl 3-[N-3-ethyl-acryloyl]-amino-5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranoside (21b)

Compound **20** (500 mg, 2.46 mmol) was added either to a mixture of acetylacetone (0.39 g, 3.90 mmol) or ethyl acetoacetate (0.28 g, 15.0 mmol),

montimorillonite K-10 (0.67 g) and 5 mL of dry dichloromethane at 0 °C. The reaction was kept under stirring for 6 h (acetylacetone) or 24 h (ethyl acetoacetate) at room temperature. The solid material was removed by filtration and the resulting organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure leading to the crude product which was chromatographed on a silica gel column eluted with a gradient from pure hexane to hexane-ethyl acetate (3 : 7).

21a: obtained in 60% yield (214 mg) yield as a pale yellow solid: m.p. 49–50 °C; IR (KBr) $\nu_{max}(cm^{-1})$: 1613, 1573, 3427; ^1H NMR ($CDCl_3$) δ: 1.32 (3H, s, H7′), 1.48 (3H, s, H8′), 1.94 (3H, s, C4), 2.01 (3H, s, C$\underline{H}_3$C=O), 3.41 (3H, s, OC$\underline{H}_3$), 3.33–3.36 (2H, m, H5′ and H5″), 4.26 (1H, dd, J = 7.5 and 7.5 Hz, H4′), 4.60 (1H, d, J = 6.6 Hz, H3′), 4.63 (1H, d, J = 6.0 Hz, H2′), 5.0 or 5.02 (1H, s, H1′), 5.0 or 5.02 (1H, s, H2), 8.76 (1H, broad singlet, N-H); ^{13}C NMR ($CDCl_3$) δ: 18.7 (C4), 24.9 (C7′), 26.3 (C8′), 46.1 (C5′), 55.3 (O$\underline{C}H_3$), 81.8 (C3′), 85.1 (C2′), 85.3 (C4′), 95.9 (C2), 109.5 (C1′), 112.5 (C6′), 162.1 (C3), 195.2 (C=O); LRMS-FAB (m/z) (relative intensity): 286 (100), 254 (43), 154 (47), 112 (59); HRMS-FAB: calcd for $C_{14}H_{24}N_1O_5$ $(M+H)^+$286.1654; found 286.1643.

21b: obtained in 50% yield (349 mg) as a yellow oil; IR (film) $\nu_{max}\,(cm^{-1})$: 1613, 1573, 3427; ^1H NMR ($CDCl_3$) δ: 1.32 (3H, s, C7′), 1.48 (3H, s, C8′), 1.94 (3H, s, C4), 2.01 (3H, s, C$\underline{H}_3$C=O), 3.41 (3H, s, OC$\underline{H}_3$), 3.33–3.36 (2H, m, H5′ and H5″), 4.26 (1H, dd, J = 7.5 and 7.5 Hz, H4′), 4.60 (1H, d, J = 6.6 Hz, H3′), 4.63 (1H, d, J = 6.0 Hz, H2′), 5.00 or 5.02 (1H, s, H1′), 5.00 or 5.02 (1H, s, H2), 10.98 (1H, broad singlet, N-H); ^{13}C NMR ($CDCl_3$) δ: 18.7 (C4), 24.9 (C7′), 26.3 (C8′), 46.1 (C5′), 55.3 (O$\underline{C}H_3$), 81.8 (C-3′), 85.1 (C2′), 85.3 (C4′), 95.9 (C2), 109.5 (C1′), 112.5 (C6′), 162.1 (C3), 195.2 (C=O); HRMS-FAB: calcd for $C_{15}H_{25}N_1O_6(M+H)^+$315.1681; found 315.1674.

General procedure for the preparation of methyl 5-deoxy-5-*C*-(4-acetyl-5-methyl-1,2,3-triazol-1-yl)-2,3-*O*-isopropylidene-(-*D*-ribofuranoside (22a) and methyl 5-deoxy-5-*C*-(4-ethoxycarbonyl-5-methyl-1,2,3-triazol-1-yl)-2,3-*O*-isopropylidene-*β*-D-ribofuranoside (22b)

A solution of *β*-amino-*α*,*β*-unsaturated ketone **21a** (227 mg, 1.12 mmol) or ester **21b** (400 mg, 1.27 mmol) in 3 mL of acetonitrile was added to a mixture of sodium hydride (2.83–6.67 mmol, oil free) in 1 mL of anhydrous acetonitrile, under nitrogen, at room temperature. The mixture was stirred for 0.5 h, followed by dropwise addition of a solution of methanesulfonyl azide (3.31–6.61 mmol) in 1 mL of acetonitrile. After an additional stirring for 24 h the reaction was quenched with an aqueous solution of sodium hydroxide (10%, w/w). The separated organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced

pressure. The residue was extracted with methylene chloride (3×10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure. Crude nucleosides **22a** and **22b** were purified by column chromatography on silica gel, using hexane-ethyl acetate (8 : 2) as the eluant.

22a: the reaction using 0.068 g (2.83 mmol) of sodium hydride and 400 mg (3.31 mmol) of methanesulfonyl azide led to 183 mg of **22a** (74%) as a colorless oil; IR (film): 1683; ^{1}H NMR ($CDCl_3$) δ: 1.30 (3H, s, C7′), 1.46 (3H, s, C8′), 2.62 (3H, s, C$\underline{H}_3$C = O), 2.69 (3H, s, CH_3C_2), 3.41 (3H, s, OC$\underline{H}_3$), 4.36 (1H, dd, J = 16.8 and 9.3 Hz, H5′), 4.46–4.54 (2H, m, H4′ and H5″), 4.69 (1H, dd, J = 5.7 Hz, H2′), 4.87 (1H, d, J = 6.0 Hz, H3′), 5.01 (1H, s, H1′); ^{13}C NMR ($CDCl_3$) δ: 9.0 ($\underline{C}H_3C_2$), 24.7 (C7′), 26.2 (C8′), 27.5 ($\underline{C}H_3$C=O), 50.0 (C5′), 55.6 (O$\underline{C}H_3$), 81.4 (C3′), 84.2 (C4′), 84.8 (C2′), 110.0 (C1′), 112.7 (C6′), 136.8 (C5), 143.5 (C4), 194.1 (C=O); LRMS-FAB (m/z) (relative intensity): 312 (50), 154 (100), 136 (70); HRMS-FAB: calcd for $C_{14}H_{22}N_3O_5$:$(M + H)^+$ 312.1559; found 312.1556.

22b: the reaction using 160 mg (6.67 mmol) of sodium hydride and 800 mg (6.61 mmol) of methanesulfonyl azide led to 303 mg (70%) of **3b** as a yellow oil; IR (film) ν_{max} (cm^{-1}): 1716 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, s, C7′), 1.45 (3H, s, C8′), 1.43 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.63 (3H, s, C$\underline{H}_3C_2$), 3.40 (3H, s, OC$\underline{H}_3$), 4.42–4.51 (1H, m, H4′), 4.36 (1H, dd, J = 11.7 and 4.2 Hz, H5′), 4.42–4.51 (3H, m, $OC\underline{H}_2CH_3$ and H4′), 4.55 (1H, dd, J = 11.7 and 8.1 Hz, H5″), 4.68 (1H, d, J = 5.7 Hz, H2′), 4.86 (1H, d, J = 6.0 Hz, H3′), 5.0 (1H, s, H1′); ^{13}C NMR ($CDCl_3$) 8.9 ($\underline{C}H_3C_2$), 24.6 (C7′), 26.1 (C8′), 50.2 (C5′), 55.5 (O$\underline{C}H_3$), 81.3 (C3′), 60.8 (O$\underline{C}H_2CH_3$), 84.5 (C-4′), 84.8 (C-2′), 110.1 (C1′), 112.6 (C6′), 136.5 (C5), 138.2 (C4), 161.5 (C=O); LRMS-FAB (m/z) (relative intensity): 342 (100), 154 (16); HRMS-FAB: calcd for $C_{15}H_{24}N_3O_6$: $(M + H)^+$ 342.1665; found: 342.1664.

Methyl 5-Deoxy-5-C-(4-formyl-1,2,3-triazol-1-yl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (24)

A solution of methyl 5-amino-5-deoxy-1,2-**O**-isopropylidene-β-D-ribofuranoside[9] (**20**, 200 mg, 0.99 mmol) in methanol (5 mL) was slowly added to a freshly prepared[3a] solution of diazomalonaldehyde (129 mg, 1.17 mmol) in 0.1 mL acid acetic and 4 mL of methanol-water (2 : 1) solution. The mixture was stirred at room temperature for 24 hours and then concentrated under reduced pressure. The oil produced was chromatographed on a silica gel column, using chloroform-ethyl acetate (9 : 1) as the eluant, giving a pale yellow solid in 78% yield (217 mg): m.p. 210–212 °C (decomp.); IR (KBr) ν_{max} (cm^{-1}): 1700; ^{1}H NMR ($CDCl_3$) δ: 1.30 (3H, s, H8′), 1.47 (3H, s, H7′), 3.39 (3H, s, OCH_3), 4.50 (1H, dd, J = 12.5 and 7.8 Hz, H5′), 4.59 (1H, ddd, J = 7.8, 4.7 and 0.9 Hz, H4′), 4.68 (1H, d, J = 6.0 Hz, H2′), 4.67

(1H, dd, J = 12.3 and 4.8, H5″), 4.77 (1H, dd, J = 6.0 and 0.9 Hz, H3′), 5.03 (1H, s, H1′), 10.16 (CHO); ^{13}C NMR ($CDCl_3$) δ: 24.7 (C-7′), 26.2 (C-8′), 55.6 (OCH_3), 53.4 (C- 5′), 81.5 (C-3′), 84.7 or 84.9 (C-2′), 84.7 or 84.9 (C-4′), 110.1 (C-1′), 113.0 (C-6′), 125.6 (C-5), 147.7 (C-4), 184.8 (C=O); LRMS-FAB (m/z) (relative intensity): 284 (100), 252 (39), 154 (62); HRMS-FAB: calcd for: $C_{12}H_{18}N_3O_5$ $(M+H)^+$ 284.1246; found: 284.1253.

General procedure for deprotection reaction with iodine in methanol

A solution of **22a** (87 mg, 0.28 mmol), **22b** (85 mg, 0.25 mmol) or **24** (82 mg, 0.29 mmol), iodine (30 mg) and methanol (3 mL) was stirred at 65–70 °C for 10 hours. The excess of iodine was eliminated by adding aqueous sodium thiosulfate solution (0.5 N). After filtration, the solvent was evaporated under reduced pressure yielding a solid material, which was chromatographed on a silica gel column using a gradient from pure hexane to hexane-ethyl acetate (1 : 4).

Methyl 5-C-(4-Acetyl-5-methyl-1,2,3-triazole-1-yl)-5-deoxy-β-D-ribofuranoside (23a)

Obtained in 70% yield (53 mg), m.p. 159–160 °C; IR (film) ν_{max} (cm^{-1}): 3235–3502 (OH, br), 1674 (C=O); ^{1}H NMR (300.00 MHz, $CDCl_3$) δ 2.68 (3H, s, CH_3C_2), 2.67 (3H, s, CH_3C=O), 3.23 (3H, s, OCH_3), 3.78 (1H, dd, J = 4.5 and 4.5 Hz, H2′), 4.08 (1H, td, J = 6.9 e 4.5 Hz, H3′), 4.23 (1H, td, J = 7.2 e 3.6 Hz, H4′), 4.53 (1H, dd, J = 14.4 and 6.6 Hz, H5′), 4.52 (1H, = 4.2 Hz, C2-OH); ^{13}C NMR(75.0 MHz, $CDCl_3$)δ 9.0(CH_3C2), 27.5 (CH_3 C=O),49.8(C5′), 54.9 (OCH_3, 71.8(C3′), 73.9(C2′), 80.2(C4′), 108.7(C1′), 135.4 (C4), 139.6(C5), 161.3(C=O) ppm; LRMS-FAB (m/z) (relative intensity): 272 (75), 154 (100), 136 (67); HRMS-FAB: calcd for: $C_{11}H_{18}N_3O_5$ $(M+H)^+$ 272.1246; found: 272.1210.

Methyl 5-C-(4-Carbethoxy-5-methyl-1,2,3-triazol-1-yl)-5-deoxy-β-D-ribofuranoside (23b)

Obtained in 75% yield (56 mg); m.p. 97–98 °C; IR (filme) ν_{max} (cm^{-1}): 3324–3482 (br, OH), 1724 (C=O); ^{1}H NMR (300.00 MHz, $CDCl_3$ δ 1.42 (3H, t, J = 7.2 Hz, OCH_2CH_3), 2.68 (3H, s, CH_3C2), 3.25 (3H, s, OCH_3), 4.42 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.77 (1H, dd, J = 4.2 and 4.2 Hz, H2′), 4.03–4.09 (1H, m, H3′), 4.22 (1H, td, J = 6.6 e 4.2 Hz, H4′), 4.53 (1H, dd, J = 14.7 and 6.6 Hz, H5′), 4.73 (1H, dd, J = 14.7 and 3.6 Hz, H5″), 4.71 (1H, s, H1′), 5.29 (1H, d, J = 7.2 Hz, C3-OH), 5.32 (1H, d, J = 4.2 Hz, C2-OH) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 9.1 (CH_3C2), 50.1 (C5′), 55.5

($O\underline{C}H_3$), 60.3 ($O\underline{C}H_2CH_3$), 71.7 (C3′), 73.9 (C2′), 80.2 (C4′), 108.7 (C1′), 136.5 (C5), 138.2 (C4), 161.5 (C=O) ppm; LRMS-FAB (m/z) (relative intensity): 302 (100); 154 (33); 136 (34); HRMS-FAB: calcd for: $C_{12}H_{20}N_3O_6$ $(M + H)^+$ 302.1352; found: 302.1318.

Methyl 5-Deoxy-5-C-(4-formyl-5-methyl-1,2,3-triazol-1-yl)-β-D-ribofuranoside (25)

Obtained in 81% yield (57 mg). IR (film) ν_{max} (cm^{-1}): 3200−3500 (br, OH); 1696 (C=O); ^1H NMR (300.00 MHz, $CDCl_3$) δ 3.28 (3H, s, $OC\underline{H}_3$), 3.81 (1H, d, J = 4.5 Hz, H2′), 4.01 (1H, dd, J = 6.9 and 5.1 Hz, H3′), 4.27 (1H, d, J = 6.9 and 3.9 Hz, H4′), 4.73 (1H, s, H1′), 4.63 (1H, dd, J = 14.1 and 6.9 Hz, H5′), 4.85 (1H, dd, J = 14.1 and 3.6 Hz, H5″), 5.30 (2H, broad singlet, O<u>H</u>), 8.94 (1H, s, H5), 10.14 ($\underline{H}C=O$) ppm; ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 54.8 ($O\underline{C}H_3$), 52.8 (C5′), 71.8 (C3′), 74.2 (C2′), 80.8 (C4′), 108.6 (C1′), 129.2 (C5), 146.9 (C4), 185.2 ($H\underline{C}=O$) ppm.

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