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SHORT COMMUNICATIONS

First Analog of Pyrimidine Nucleosides with Two D-Ribofuranose Residues

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Abstract—The reaction of 1,3-bis(pent-4-yn-1-yl)-6-methyluracil with 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl azide gave 1,3-bis{3-[1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]propyl}-6-methyluracil which was deprotected by treatment with a solution of sodium methoxide in methanol to obtain 1,3-bis{3-[1-(β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]propyl]-6-methyluracil as a first analog of pyrimidine nucleosides containing two D-ribofuranose fragments.

Keywords: nucleosides, nucleoside analogs, uracil, [3+2]-cycloaddition, click chemistry, 1,2,3-triazoles.

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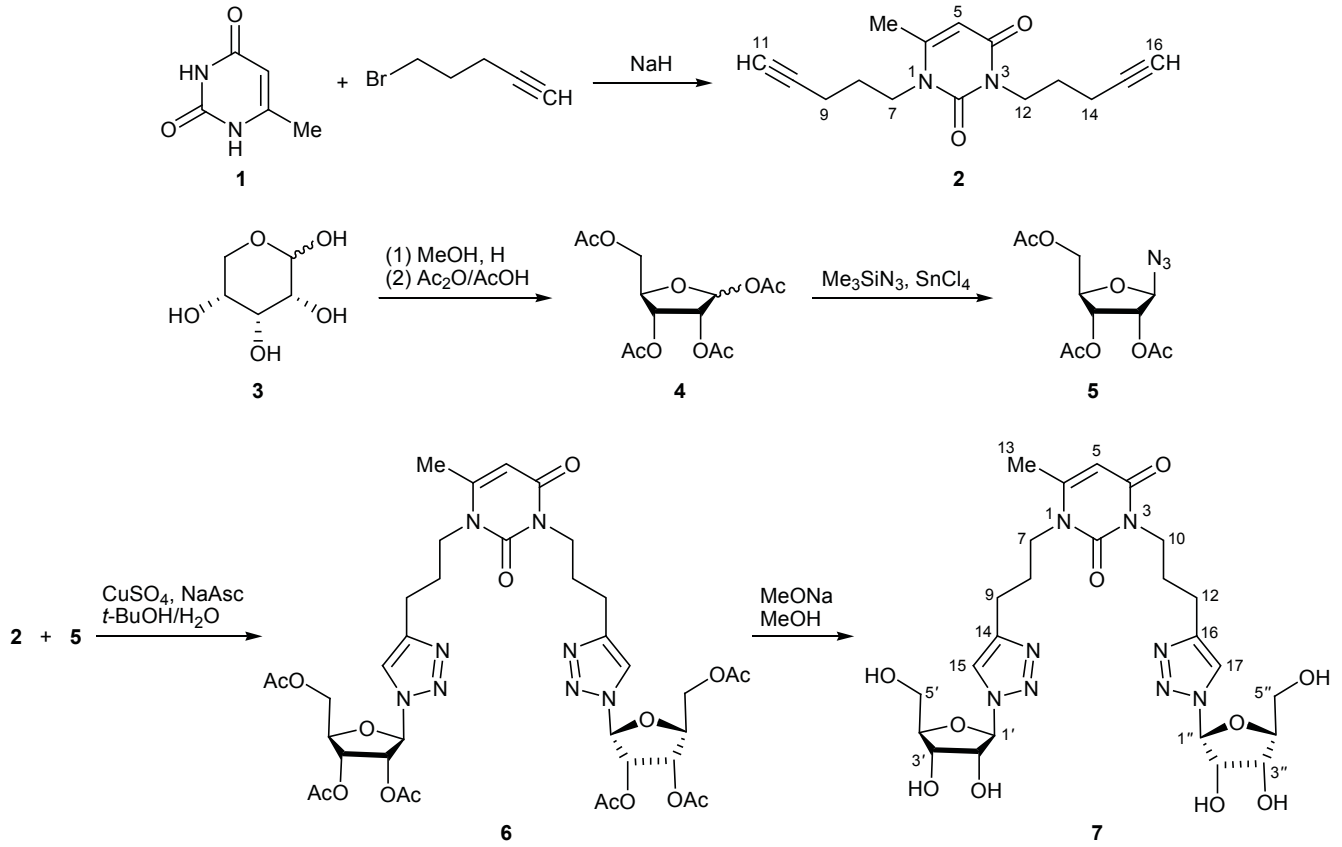
During the past decade, extensive studies have been performed in the field of synthesis of so-called pyrimidine nucleoside analogs [1–6] in which the D-ribose or deoxy-D-ribose residue (hereinafter, D-ribofuranose is meant) is replaced by a five-membered carbocycle [1] or heterocycle [2], one or more heterorings are fused to the nucleobase [3], or the latter is replaced by a nitrogen heterocycle such as 1,2,4-triazole [4]. Most of the synthesized compounds were found to exhibit diverse biological activities [1–3, 5, 6].

By the Huisgen–Meldal–Sharpless reaction of 1,3-bis(5-azidopentyl)-6-methyluracil with terminal alkynes we previously synthesized 6-methyluracil derivatives with 1,2,3-triazole terminal groups in the alkyl chains attached to nitrogen atoms of the pyrimidine ring [7]. These compounds can be regarded as nucleoside analogs; after modification of the 1,2,3-triazole moiety, they showed a high antimicrobial activity [8] and the ability to undergo aggregation in supramolecular systems [9]. Herein, we utilized the opposite approach to the synthesis of nucleoside analogs, according to which a pyrimidine derivative with terminal alkynyl substituents, namely 1,3-di(pent-4-yn-1-yl)-6-methyluracil (**2**), reacted with an azide partner, 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl azide (**5**). The Meldal–Sharpless reaction of **2** and **5** afforded bis-1,2,3-triazole derivative **6** which was treated with sodium methoxide in methanol to remove acetyl protecting groups. We thus obtained the first pyrimidine nucleoside analog **7** containing two D-ribofuranose fragments (Scheme 1). Compound **2** was synthesized by alkylation of 6-methyluracil (**1**) with 5-bromopent-1-yne in the presence of sodium hydride, and azide **5** was prepared according to the known procedure [10] in three steps starting from D-ribose. The anomeric proton of **5** resonated in the ^{1}H NMR spectrum as a doublet at δ 5.35 ppm with a vicinal coupling constant of 2 Hz, which indicated that azide **5** was pure β-anomer [10]. Correspondingly, compounds **6** and **7** were also pure β-anomers. Study of biological activity of nucleoside analog **7** is now in progress.

6-Methyl-1,3-di(pent-4-yn-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2). Sodium hydride, 2.20 g (0.092 mol), was added to a solution of 5 g (0.04 mol) of 6-methyluracil (**1**) in 200 mL of anhydrous DMF, and the mixture was stirred at 70°C for 8 h. The mixture was cooled to room temperature, 33.10 g (0.32 mol) of 5-bromopent-1-yne was added, and the mixture was stirred at 120°C for 24 h. The solvent was evaporated, the residue was treated with 150 mL of chloroform, the precipitate was filtered off, and the filtrate was concentrated to a volume of 20 mL and passed through a column charged with silica gel (60 mesh). The column was eluted in succession with

Scheme 1.



light petroleum ether and petroleum ether–ethyl acetate (1.5 : 1 by volume). Yield 6.49 g (63%), mp 61°C. ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm: 1.84–1.87 m (4H, 8-H, 13-H), 1.93 t (1H, 11-H, ^4J = 2.8 Hz), 2.00 t (1H, 16-H, ^4J = 2.7 Hz), 2.21–2.23 m (2H, 9-H), 2.24 s (6-CH_3), 2.25–2.27 m (2H, 14-H), 3.90–3.93 t (2H, 7-H, ^3J = 7.7 Hz), 3.98–4.00 t (2H, 12-H, ^3J = 7.0 Hz), 5.55 s (1H, 5-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.85 (C^8), 16.29 (C^{13}), 20.51 (6-CH_3), 40.46 (C^7), 44.14 (C^{12}), 68.51 (C^{10}), 69.51 (C^{15}), 82.58 (C^{11}), 83.39 (C^{16}), 101.73 (C^5), 151.14 (C^6), 152.00 (C^2), 162.12 (C^4). Mass spectrum, *m*/*z*: 259.1 $[M + H]^+$, 281.1 $[M + Na]^+$, 297.2 $[M + K]^+$. Found, %: C 69.68; H 7.10; N 10.93. $C_{15}H_{18}N_2O_2$. Calculated, %: C 69.74; H 7.02; N 10.84. *M* 258.14.

6-Methyl-1,3-bis{3-[1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]propyl}pyrimidine-2,4(1*H*,3*H*)-dione (6). Azide **5**, 1.6 g (5.4 mmol), was dissolved in a mixture of 15 mL of *tert*-butyl alcohol and 5 mL of water, 1.34 g (5.4 mmol) of $CuSO_4 \cdot 5H_2O$ in 5 mL of water was added, and 1.07 g (5.4 mmol) of sodium ascorbate in 5 mL of water was then added. A solution of 0.7 g (2,7 mmol) of uracil **2** in a mixture of 40 mL of *tert*-butyl alcohol and 40 mL of water was added dropwise, and the mixture was stirred at 50°C for 5 days, concentrated under reduced pressure, diluted with water, and extracted with methylene chloride. The extract was washed with water and dried over $MgSO_4$, and the solvent was distilled off under reduced pressure. Yield 2.0 g (87%), off-white amorphous powder. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 2.05–2.16 m (22H, OAc, 8-H, 11-H), 2.23 s (3H, 13-H), 2.75–2.88 m (4H, 9-H, 12-H), 3.86–4.04 m (4H, 7-H, 10-H), 4.18–4.26 m and 4.37–4.42 m (2H each, 5′-H, 5″-H), 4.44–4.49 m (2H, 4′-H, 4″-H), 5.54 s (1H, 5-H), 5.56–5.64 m (2H, 2′-H, 2″-H), 5.78–5.83 m (2H, 3′-H, 3″-H), 6.12 d (2H, 1′-H, 1″-H, J = 3.7 Hz), 7.62 s (1H, 15-H), 7.68 s (1H, 17-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.79 (C^{13}); 20.51 (2C), 20.58 (2C), 20.81 (2C) (**C**H_3CO); 22.83, 23.19, 26.79, 27.97, 40.68, 44.65 (C^7–C^{12}); 63.16 ($C^{5'}$), 63.18 ($C^{5''}$), 70.95 ($C^{4'}$), 71.02 ($C^{4''}$), 74.38 ($C^{3'}$), 74.41 ($C^{3''}$), 80.86 ($C^{2'}$), 80.93 ($C^{2''}$), 89.94 ($C^{1'}$), 90.06 ($C^{1''}$), 101.77 (C^5), 120.46 (C^{15}), 120.55 (C^{17}), 147.08 (C^{14}), 148.01 (C^{16}), 151.49 (C^6), 152.24 (C^2), 162.31 (C^4); 169.34, 169.38, 169.53, 169.54, 170.44, 170.55 (CH_3**C**O). Mass

spectrum, *m*/*z*: 861.4 $[M + H]^+$, 883.4 $[M + Na]^+$, 899.4 $[M + K]^+$. Found, %: C 51.65; H 5.70; N 13.10. $C_{37}H_{48}N_8O_{16}$. Calculated, %: C 51.62; H 5.62; N 13.02. *M* 860.82.

6-Methyl-1,3-bis{3-[1-(β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]propyl}pyrimidine-2,4(1*H*,3*H*)-dione (7). A freshly prepared 0.1 M solution of sodium methoxide in methanol was added dropwise with stirring to a solution of 1.6 g (2 mmol) of compound **6** in 10 mL of anhydrous methanol until pH 8. The mixture was stirred at room temperature for 2 days, while intermittently adding new portions of methanolic sodium methoxide when pH reached 7. The progress of the reaction was monitored by TLC. The mixture was then neutralized with Amberlyst 15, and the solvent was distilled off under reduced pressure. Yield 0.98 g (87%), white amorphous powder. ^{1}H NMR spectrum (400 MHz, CD_3OD), δ, ppm: 1.97–2.08 m (4H, 8-H, 11-H), 2.26 s (3H, 6-CH_3), 2.75 t (2H, 9-H, J = 7.4 Hz), 2.80 t (2H, 12-H, J = 7.3 Hz), 3.69 d.d (2H, 5′-H, 5″-H, J = 12.2, 3.3 Hz), 3.81 d.d (2H, 5′-H, 5″-H, J = 12.2, 3.2 Hz), 3.92 t (2H, 7-H, J = 7.0 Hz), 3.97 t (2H, 10-H, J = 7.1 Hz), 4.09–4.15 m (2H, 4′-H, 4″-H), 4.31 t (2H, 2′-H, 2″-H, J = 4.6 Hz), 4.47 d.d (2H, 3′-H, 3″-H, J = 9.0, 4.8 Hz), 5.58 s (1H, 5-H), 6.00 t (2H, 1′-H, 1″-H, J = 4.2 Hz), 8.03 s (1H, 15-H), 8.08 s (1H, 17-H). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 19.72 (C^{13}); 23.49, 23.86, 27.90, 28.83, 41.76, 45.69 (C^7–C^{12}); 62.91 ($C^{5'}$), 62.94 ($C^{5''}$), 71.91 ($C^{4'}$, $C^{4''}$), 76.99 ($C^{3'}$, $C^{3''}$), 87.08 ($C^{2'}$, $C^{2''}$), 94.29 ($C^{1'}$, $C^{1''}$), 101.75 (C^5), 121.93 (C^{15}), 122.09 (C^{17}), 148.08 (C^{14}), 148.51 (C^{16}), 153.37 (C^6), 154.85 (C^2), 164.57 (C^4). Mass spectrum, *m*/*z*: 609.4 $[M + H]^+$, 631.3 $[M + Na]^+$, 647.3 $[M + K]^+$. Found, %: C 49.65; H 5.83; N 18.30. $C_{25}H_{36}N_8O_{10}$. Calculated, %: C 49.34; H 5.96; N 18.41. *M* 608.60.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (Germany) at 400 or 600 MHz (^{1}H) and 100.6 MHz (^{13}C); the chemical shifts were measured relative to the residual proton and carbon signals of the solvent ($CDCl_3$, CD_3OD). The mass spectra (electrospray ionization) were recorded on a Bruker AmazonX mass spectrometer (Germany) equipped with an ion trap [positive ion detection, a.m.u. range 70–3000; capillary voltage 3500 V; drying gas nitrogen, flow rate 10 L/min, temperature 250°C; eluent methanol–water (70:30 by volume), flow rate 0.2 mL/min (Agilent 1260 chromatograph, USA); samples were dissolved in methanol to a concentration of 10^{-6} g/L and introduced through a Rheodyne 7725 injector (USA), sample volume 20 μL]; the data were acquired using TrapControl 7.0 software (Bruker Daltonik, Germany) and processed by DataAnalysis 4.0 SP4 (Bruker Daltonik, Germany). The progress of reactions and the purity of compounds were monitored by thin-layer chromatography on Sorbfil plates (*Imid* Ltd., Krasnodar, Russia); spots were visualized by treatment with a 5% solution of sulfuric acid, followed by heating to 120°C. 6-Methyluracil (**1**) and D-ribose were commercial products (Acros Organics, Belgium).

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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