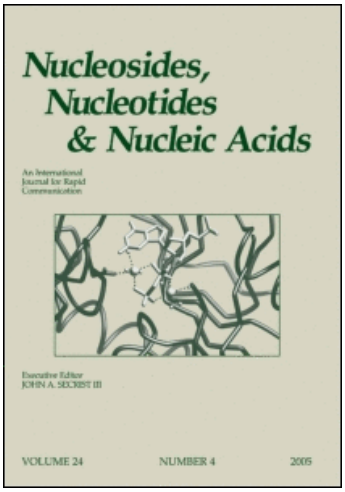

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Synthesis and Antiviral Evaluation of 2'-C-Methyl Analogues of 5-Alkynyl- and 6-Alkylfurano- and Pyrrolo[2,3-*d*]Pyrimidine Ribonucleosides

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SYNTHESIS AND ANTIVIRAL EVALUATION OF 2′-C-METHYL ANALOGUES OF 5-ALKYNYL- AND 6-ALKYLFURANO- AND PYRROLO[2,3-*d*]PYRIMIDINE RIBONUCLEOSIDES

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□ *A series of novel 2′-C-methylribonucleosides, involving 5-iodo and 5-alkynyl uridine analogues as well as related bicyclic furano- and pyrrolo[2,3-d]pyrimidinone compounds, has been synthesized and evaluated for their inhibitory effect on replication of the hepatitis C virus (HCV). The new nucleoside analogues did not show meaningful anti-HCV activity.*

Keywords Nucleoside analogues; 2′-C-methylnucleosides; furano- and pyrrolo[2,3-d]pyrimidine nucleosides

INTRODUCTION

It has been shown that transformation of pyrimidine nucleosides into their bicyclic 6-alkyl-2,3-dihydrofurano[2,3-*d*]-pyrimidin-2(1H)-one or 6-octyl-2,3-dihydropyrrolo[2,3-*d*]-pyrimidin-2(3*H*,7*H*)-one derivatives results in interesting biological properties. The type of biological activity, potency and selectivity, depend on structural factors: (1) structure of the sugar or pseudosugar moiety, and (2) the length of lipophilic alkyl substituent in the 6-position. Thus, the furanopyrimidine compounds are the most potent and selective inhibitors of varicella-zoster virus (VZV) as 2′-deoxynucleosides equiped with C_8 to C_{10} alkyl chains.[1–3] In turn, 2′3′-dideoxynucleosides and their cyclopentyl analogues are not active against VZV but show selective and specific activity against human cytomegalovirus (HCMV).[4]

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In honor and celebration of the 70th birthday of Professor Morris J. Robins.
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Replacement of the 2-deoxyribofuranosyl moiety by the acyclovir-type 3-[(2-hydroxyethoxy)methyl] chain considerably diminishes the antiviral properties of the furano[2,3-*d*]-pyrimidine system.[5] On the other hand, it has been demonstrated that some analogous acyclonucleosides exhibit activity against human immunodeficiency virus (HIV) and herpes simplex virus (HSV) at micromolar concentrations.[6] Further, SAR studies have indicated that furanopyrimidine nucleosides are, in general, more active than related pyrrolopyrimidine compounds.[7] In turn, 3-(β-D-ribofuranosyl)-6-decyl-2,3-dihydrofurano[2,3-*d*]pyrimidin-2-on shows moderate anti-HCV activity in HCV replicon system and efficiently inhibits bovine viral diarrhea virus (BVDA).[8a] More recently, a series of furano- and pyrrolo[2,3-*d*]pyrimidine nucleoside 5′-O-triphosphates have been tested for their substrate properties toward some RNA and DNA polymerases to show that only the 6-hexylfurano compound is recognized by calf thymus terminal deoxynucleotidyl transferase (TDT) and HIV reverse transcriptase (RT).[8]

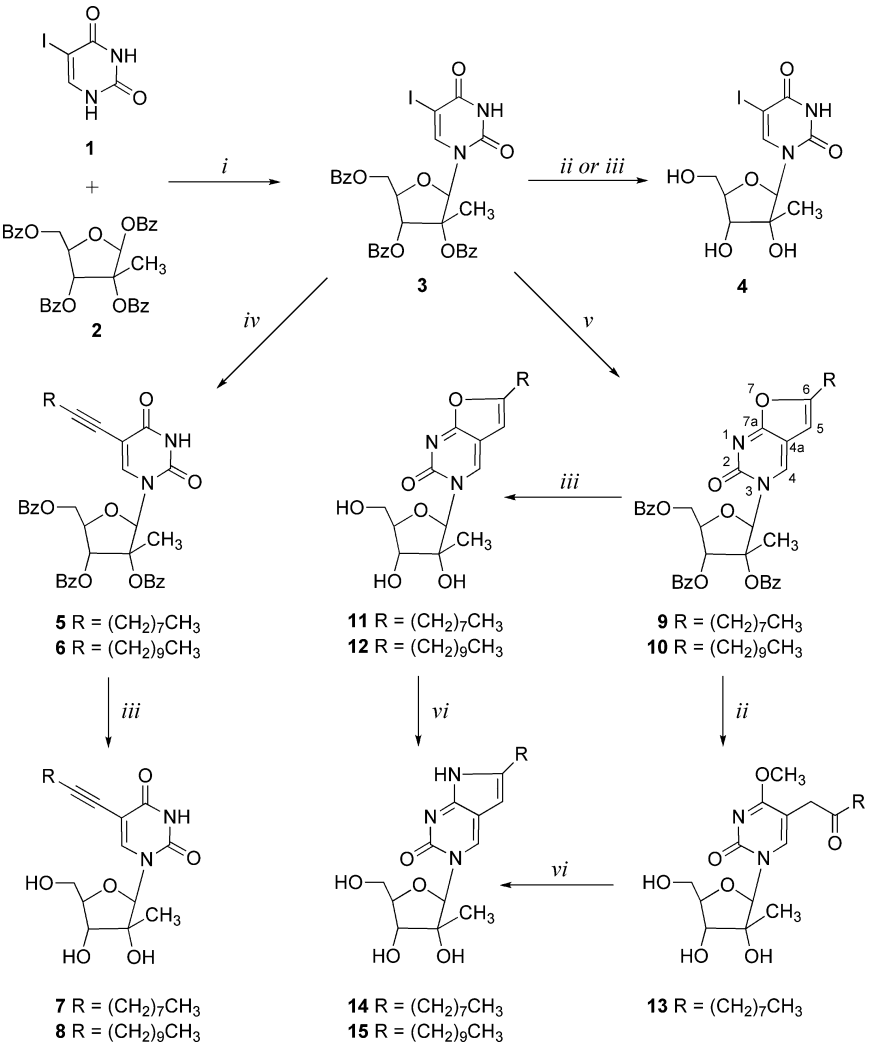
From a synthetic viewpoint, furano[2,3-*d*]pyrimidine nucleosides can be efficiently prepared from the respective 5-iodouracil derivatives and alkynes under Sonogashira cross-coupling conditions. Depending on the temperature and the Pd-catalyst used, the reaction may proceed directly to fluorescent furano[2,3-*d*]pyrimidine products,[9] or to intermediate 5-(alkyn-1-yl)uracil nucleosides.[10] The latter compounds may then undergo an intramolecular cyclization to bicyclic furanopyrimidine nucleosides in a palladium-copper catalyzed reaction.[1–8,10] The 5-(alkyn-1-yl)uracil nucleoside analogues demonstrate in vitro inhibitory activity against HSV-1, HSV-2, and vaccinia virus (VV).[11] The related acyclonucleosides with 1-[(2-hydroxyethoxy)methyl] pseudosugar portion exhibit moderate anti-HIV activity,[6] while the corresponding arabinofuranosyl, 2′-deoxy-2′-fluororibofuranosyl, and 2′,3′-dideoxyfuranosyl derivatives were found to be active against *Mycobacteria*.[12,13]

In continuation of our study on the chemistry and biology of base-modified 2′-C-β-methylnucleosides,[14,15] we synthesized a new series of 5-(alkyn-1-yl)uracil, furano[2,3-*d*]pyrimidine and pyrrolo[2,3-*d*]pyrimidine nucleosides, in order to evaluate the compounds for their antiviral properties. The 2′-C-branched nucleoside analogues are promising synthetic targets due to their potent antiviral activity against RNA viruses, including the hepatitis C virus (HCV). One of the most active compounds of this type is 2′-C-β-methylcytidine, a potent and selective inhibitor of the replication of *Flaviviridae* in cell culture.[16–18] A number of its new derivatives modified within the sugar portion has been obtained, including 2′-deoxy-[19,20] and 3′-deoxyribosides,[21] 2′-C-β-methyl-1-(β-D-xylofuranoside,[21] 2′-fluoro[22] and 3′-fluoro[21] derivatives, the 3′-O-valyl ester,[18] and the 3′-methoxynucleoside.[21] Modifications of the pyrimidine moiety have received relatively minor attention.[14] Herein, we report the synthesis and

antiviral evaluation of a novel series of 2′-C-β-methylribosides of 5-(alkyn-1-yl)uracil, furano[2,3-*d*]pyrimidine and pyrrolo[2,3-*d*]pyrimidine.

RESULTS AND DISCUSSION

The starting nucleoside synthon, tri-O-benzoyl-5-iodo-2′-C-β-methyluridine (**3**) was obtained in the direct coupling reaction of 5-iodouracil (**1**) and 1,2,3,5-tetra-O-benzoyl-2-C-methyl-β-D-ribofuranose (**2**) under Vorbrüggen conditions (Scheme 1). Because 5-iodopyrimidine



SCHEME 1 *Reagents and conditions:* (i) BSA, CH_2Cl_2, room temperature, 20 minutes, then $SnCl_4$, room temperature, 24 hours; (ii) 0.1 M MeONa, room temperature, 24 hours; (iii) NH_3/MeOH, room temperature, 24 hours; (iv) 1-alkyne, $Pd(Ph_3P)_4$, CuI, Et_3N, DMF, Ar, room temperature, 19 hours; (v) 1-alkyne, 10% Pd/C, CuI, Et_3N, MeCN, Ar, 80°C, 5 hours; (vi) NH_3/MeOH, 50°C, 48 hours.

nucleosides had never been synthesized in the 2′-C-branched series, we decided to include the compound in the antiviral screening. Therefore, the tri-O-benzoyl derivative **3** was deprotected with sodium methoxide in methanol (method A) or with methanolic ammonia (method B) to get 5-iodo-2′-C-β-methyluridine (**4**).

To prepare 5-alkynyl and furano[2,3-*d*]pyrimidine products, compound **3** was treated with 1-alkynes under the Sonogashira coupling conditions. Depending on reaction temperature and the nature of palladium catalyst used, we were able to obtain either 5-alkynyluridine analogues (**5**, **6**), or the bicyclic furano nucleosides (**9**, **10**). Thus, reaction of **3** with 1-decyne or 1-dodecyne in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(Ph_3P)_4$] performed at room temperature gave the respective 5-decyn-1-yl (**5**) and 5-dodecyn-1-yl (**6**) nucleosides as main products. The tri-O-benzoyl derivtives **5** and **6** were then treated with methanolic ammonia to give nucleosides **7** and **8**.

In turn, the coupling reaction of **3** and 1-alkynes at higher temperature (80°C) and catalyzed by 10% Pd/C resulted in the formation of fluorescent, bicyclic 6-decyl and 6-dodecyl furanopyrimidine nucleosides (compounds **9** and **10**, respectively), which were deprotected to **11** and **12** by using methanolic ammonia. Interestingly, the use of sodium methoxide in methanol instead of NH_3/MeOH in an attempted debenzoylation of **9** resulted in an almost equimolar mixture of **11** and a new pyrimidine nucleoside, 4-O-methyl-5-(2-oxodecyl)-2′-C-β-methyluridine (**13**). The formation of **13** can be due to a nucleophilic attack of the methoxide anion at C7a of the furano[2,3-*d*]pyrimidine system and the subsequent ring opening. The ring-opening reaction is reversible. For instance, treatment of **13** with saturated solution of NH_3/MeOH at 50°C for 48 hours gave the pyrrolo[2,3-*d*]pyrimidine derivative (**14**) as a single product. For a preparative scale, however, 6-octyl- and 6-decyl-pyrrolo[2,3-*d*]pyrimidine nucleosides (**14**, **15**) were prepared directly from the respective furano compounds (**11**, **12**).

The newly synthesized compounds: 5-iodo- (**4**) and 5-alkynyluridine analoges (**5**, **6**), 6-alkyl furanopyrimidine nucleosides (**11**, **12**), their 6-alkyl pyrrolopyrimidine congeners (**14**, **15**), and ring-opened analogue (**13**) were examined using HCV subgenomic replicon system in Huh-5–2-cells. The compounds **4** and **13** were inactive as antiviral agents. The other nucleosides demonstrated low anti-HCV activity (EC_{50} in the range of 31–85 μM).

EXPERIMENTAL

General Procedures

1,2,3,5-Tetra-O-benzoyl-2-C-β-methyl-β-D-ribofuranose (**2**) was obtained.[16] Melting points were determined on a Laboratory Devices Mel-Temp II micromelting points apparatus (Laboratory Devices, Holliston, MA, USA)

and are uncorrected. UV spectra were measured on a Beckman DU-65 spectrophotometer (Beckman, South Pasadena, CA, USA). The ^{1}H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Varian Unity 300 FT NMR 300 MHz spectrometer (Varian, Palo Alto, CA, USA) in DMSO-d_6 with tetramethylsilane as an internal standard: chemical shifts are reported in δ-values (ppm), and coupling constants are given in Hz. High resolution mass spectra (HRMS) were taken on an AMD-604 spectrometer (AMD Intectra GmbH, Harpstedt, Germany) using the LSIMS technique (Cs^+, 9 keV; in NBA). Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F_{254} plates (E. Merck, Darmstadt, Germany) using the following solvent systems (measured by volume): A, chloroform-methanol (95:5); B, ethyl acetate-hexane (2:1); C, ethyl acetate-toluene (2:1). For preparative short-column chromatography Merck TLC gel H 60 was used.

5-Iodo-2′,3′,5′-tri-O-benzoyl-2′-C-β-methyl-D-uridine (3)

BSA (0.6 mL, 2.4 mmol) was added to an anhydrous suspension of 5-iodouracil (**1**; 238 mg, 1.0 mmol) in methylene chloride (15 mL). After 20 minutes of stirring at room temperature, when a clear solution was obtained, a portion of well-dried 1,2,3,5-tetra-O-benzoyl-2-C-β-methyl-β-D-ribofuranose (**2**; 580 mg, 1.0 mmol) and $SnCl_4$ (0.4 mL, *ca.* 3.4 mmol) were added, then stirred at room temperature for 24 hours. The reaction mixture was treated with a cold solution of $NaHCO_3$, the layers were separated, and aqueous layer was washed with methylene chloride (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to an oil. The product was purified on a silica gel short column in hexane-ethyl acetate (2:1) to get **3** as a homogenous by TLC white oily solid. Yield 502 mg (72%). ^{1}H NMR 11.96 (bs, 1H, NH), 8.16 (s, 1H, H6), 7.99–7.34 (m, 15H, Ph), 6.47 (s, 1H, H1′), 5.75 (d, 1H, H3′), 4.76–4.70 (m, 3H, H4′, H5′), 1.67 (s, 3H, 2′CH_3). ^{13}C NMR 165.6, 164.6, 164.5 (3 × PhC=O), 160.4 (C4), 150.0 (C2), 145.5 (C6), 133.9, 133.6, 129.4, 129.3, 129.1, 128.8, 128.7, 128.6, 128.5 (Ph), 89.4 (C1′), 84.6 (C4′), 78.9 (C2′), 75.4 (C3′), 70.1 (C5), 63.8 (C5′), 18.1 (2′CH_3). HRMS calcd for $[C_{31}H_{25}N_2O_9I + H]^+$ *m/z* 697.0683, found 697.0650. Anal. ($C_{31}H_{25}N_2O_9I$) C, H, N.

5-Iodo-2′-C-β-methyl-D-uridine (4)

Method A. Compound **3** (69.6 mg, 0.1 mmol) was stirred in 0.1 M MeONa (4 mL) at room temperature for 24 hours. The solution was then neutralized with AcOH and evaporated to a solid residue; the crude product **4** was purified on a silica gel short column in $CHCl_3$-MeOH (4:1), then crystallized from toluene-ethanol, m.p. 205°C (dec.). Yield 28 mg (73%). Anal. C,H,N.

Method B. **3** (69.5 mg, 0.1 mmol) was deprotected in saturated methanolic ammonia (20 mL), room temperature, 24 hours. After

evaporation of the solvent the product was purified like in method A. Yield 34 mg (90%). ^{1}H NMR 11.70 (bs, 1H, NH), 8.75 (s, 1H, H6), 5.73 (s, 1H, H1′), 5.42 (t, J = 3.3, 1H, 5′OH), 5.18 (d, J = 6.3, 1H, 3′OH), 5.15 (s, 1H, 2′OH), 3.82 (m, 2H, H4′, H5′a), 3.70 (d, 1H, H3′), 3.60 (dd, 1H, H5′b), 1.01 (s, 3H, 2′CH_3). ^{13}C NMR 160.5 (C4), 150.5 (C2), 144.8 (C6), 91.1 (C1′), 82.2 (C4′), 78.4 (C2′), 70.8 (C3′), 69.0 (C5),57.9 (C5′), 19.6 (2′CH_3). HRMS calcd for $[C_{10}H_{13}N_2O_6I + H]^+$ m/z 384.9897, found 384.9861. Anal. ($C_{10}H_{13}N_2O_6I$) C, H, N.

5-Decyn-1-yl-2′,3′,5′-tri-O-benzoyl-2′-C-β-methyl-D-uridine (5)

An anhydrous mixture of **3** (696 mg, 1.0 mmol), 1-decyne (0.54 mL, 3.0 mmol), $Pd(Ph_3P)_4$ (115 mg, 0.1 mmol), CuI (38 mg, 0.2 mmol) and triethylamine (0.28 mL, 2.0 mmol) in DMF (10 mL) was stirred under argon atmosphere, room temperature for 19 hours. After evaporation of volatiles in vacuo, the residue was chromatographed on silica gel column using hexane-ethyl acetale (7:3) as an eluent to yield **5** (530 mg, 75%) as a colorless oil. This material, homogenous by TLC, was used for next steps without further purification. ^{1}H NMR 11.86 (bs, 1H, NH), 8.01–7.36 (m, 15H, Ph), 7.95 (s, 1H, H6), 6.49 (s, 1H, H1′), 5.75 (d, 1H, H3′), 4.77–4.74 (m, 3H, H4′, H5′), 2.38 (t, J = 6.3, 2H, αCH_2), 1.50 (m, 2H, βCH_2), 1.69 (s, 3H, 2′CH_3), 1.38–1.25 (m, 10H, 5 × CH_2), 0.86 (t, J = 7.2, 3H, CH_3). ^{13}C NMR 165.6, 164.6, 164.5 (3 × PhC=O), 161.7 (C4), 149.3 (C2), 143.1 (C6), 133.9, 133.6, 129.4, 129.3, 129.2, 128.8, 128.7, 128.6, 128.5 (Ph), 99.5 (C5), 93.9 (C≡C), 89.4 (C1′), 84.5 (C4′), 79.0 (C2′), 75.4 (C3′), 72.4 (C≡C), 63.9 (C5′), 31.2 (αCH_2), 28.6, 28.5, 28.3, 28.1, 22.1, 18.8 (6 x CH_2), 18.1 (2′CH_3), 14.0 (CH_3).

5-Decyn-1-yl-2′-C-β-methyl-D-uridine (7)

Compound **5** (353 mg, 0.5 mmol) was stirred in saturated methanolic ammonia (25 mL), room temperature, for 24 hours. After evaporation of the solvent the product was purified by short-column silica gel chromatography in $CHCl_3$-MeOH (6:1) to obtain the deprotected nucleoside 7 as a white solid. Yield 189 mg (96%). An analytical sample was crystallized from ethyl acetate, m.p. 145°C. ^{1}H NMR 11.61 (s, 1H, NH), 8.44 (s, 1H, H6), 5.71 (s, 1H, H1′), 5.34 (t, J = 4.2, 1H, 5′OH), 5.19 (d, J = 6.6, 1H, 3′OH), 5.17 (s, 1H, 2′OH), 3.83–3.57 (m, 4H, H3′, H4′, H5′), 2.32 (t, J = 6.9, 2H, αCH_2), 1.45 (m, 2H, βCH_2), 1.37–1.25 (m, 10H, 5 x CH_2), 0.99 (s, 3H, 2′CH_3), 0.85 (t, J = 6.6, 3H, CH_3). ^{13}C NMR 161.7 (C4), 149.8 (C2), 142.5 (C6), 98.9 (C5), 93.3 (C≡C), 91.2 (C1′), 82.2 (C4′), 78.4 (C2′), 72.8 (C≡C), 71.1 (C3′), 58.2 (C5′), 31.3 (αCH_2), 28.6, 28.5, 28.3, 28.2, 22.1, 18.9 (6 × CH_2), 19.7 (2′CH_3), 14.0 (CH_3). HRMS calcd for $[C_{20}H_{30}N_2O_6 + H]^+$ *m/z* 395.2182, found 395.2191. Anal. ($C_{20}H_{30}N_2O_6$) C, H, N.

5-Dodecyn-1-yl-2′-C-β-methyl-D-uridine (8)

Treatment of **3** (279 mg, 0.4 mmol) with 1-dodecyne (80 mg, 0.10 mL, 0.48 mmol) by the method described above for the synthesis of **5** followed by deblocking of **6** with saturated methanolic ammonia and purification, as in the case of **7** gave the nucleoside **8** (27.3 mg, total yield 32%), m.p. 135–138°C. ^{1}H NMR 11.59 (bs, 1H, NH), 8.44 (s, 1H, H6), 5.75 (s, 1H, H1′), 5.33 (t, $J = 4.2$, 1H, 5′OH), 5.19 (d, $J = 6.3$, 1H, 3′OH), 5.16 (s, 1H, 2′OH), 5.16 3.83–3.33 (m, 4H, H3′, H4′, H5′), 2.32 (t, $J = 6.6$, 2H, αCH_2), 1.46 (m, 2H, βCH_2), 1.37–1.23 (m, 14H, 7 × CH_2), 1.00 (s, 3H, 2′CH_3), 0.83 (t, $J = 6.9$, 3H, CH_3). ^{13}C NMR 161.6 (C4), 149.7 (C2), 142.4 (C6), 98.8 (C5), 93.2 (C≡C), 91.2 (C1′), 82.1 (C4′), 78.3 (C2′), 72.8 (C≡C), 71.0 (C3′), 58.2 (C5′), 31.3 (αCH_2), 29.0 28.9, 28.7, 28.5, 28.3, 28.2, 22.1, 18.8 (8 x CH_2), 19.7 (2′CH_3), 14.0 (CH_3). HRMS calcd for $[C_{22}H_{34}N_2O_6 + H]^+$ *m/z* 423.2520, found 423.2495. Anal. ($C_{22}H_{34}N_2O_6$) C, H, N.

3-(2,3,5-Tri-O-benzoyl-2-C-β-methyl-β-D-ribofuranosyl)-6-octyl-2,3-dihydro-furano[2,3-d]-pyrimidin-2(1H)-one (9)

An anhydrous mixture of **3** (696 mg, 1.0 mmol), 1-decyne (0.22 mL, 1.2 mmol), 10% Pd/C (42 mg) and CuI (10 mg, 0.053 mmol) in triethylamine (25 mL) and acetonitrile (25 mL) was stirred under argon atmosphere at 80°C for 5 hours. After this time TLC showed the single fluorescent spot of product **9**. The reaction mixture was filtered, a precipitate was washed with acetonitrile, and the solvents were removed in vacuo. The product was purified by silica gel chromatography in hexane-ethyl acetate (3:2), to yield 580 mg (82%) of a homogenous by TLC, colorless oil. This material was applied for the next step without further purification. ^{1}H NMR 8.52 (s, 1H, H4), 8.03–7.37 (m, 15H, Ph), 6.79 (s, 1H, H1′), 6.42 (s, 1H, H5), 5.78 (d, 1H, H3′), 4.78 (m, 3H, H4′, H5′), 2.66 (t, $J = 7.2$, 2H, αCH_2), 1.60 (m, 5H, βCH_2, 2′CH_3), 1.27 (m, 10H, 5 × CH_2), 0.85 (t, $J = 7.2$, 3H, CH_3). ^{13}C NMR 171.8 (C7a) 165.6, 164.7, 164.6 (3 × PhC = O), 159.3 (C6), 153.8 (C2), 138.0 (C4), 133.8, 133.7, 133.5, 129.5, 129.3, 129.2, 128.8, 128.7, 128.6, 128.5 (Ph), 107.3 (C4a), 99.7 (C5), 89.6 (C1′), 84.9 (C4′), 79.6 (C2′), 75.6 (C3′), 64.1 (C5′), 31.2 (αCH_2), 28.6, 28.5, 28.3, 27.3, 26.3, 22.0 (6 × CH_2), 18.3 (2′CH_3), 13.9 (CH_3).

3-(2,3,5-Tri-O-benzoyl-2-C-β-methyl-β-D-ribofuranosyl)-6-decyl-2,3-dihydro-furano[2,3-d]-pyrimidin-2(1H)-one (10)

Treatment of 5-iodo derivative **3** (280 mg, 0.40 mmol) with 1-dodecyne (80 mg; 0.10 mL, 0.48 mmol) by the method described for synthesis of **9,** gave nucleoside **10** (372 mg, 51%) as a colorless oil. ^{1}H NMR 8.52 (s, 1H, H4), 8.03–7.34 (m, 15H, Ph), 6.80 (s, 1H, H1′), 6.42 (s, 1H, H5), 5.79 (d, 1H, H3′), 4.80 (m, 3H, H4′, H5′), 2.66 (t, $J = 6.6$, 2H, αCH_2), 1.60 (m, 5H, βCH_2, 2′CH_3), 1.26 (m, 14H, 7 x CH_2), 0.81 (t, $J = 6.2$, 3H, CH_3). ^{13}C NMR

171.8 (C7a) 165.5, 164.5, 164.6 (3 × PhC=O), 159.2 (C6), 153.8 (C2), 138.0 (C4), 133.7, 133.5, 133.5, 129.4, 129.3, 128.7, 128.7, 128.6, 128.5 (Ph), 107.3 (C4a), 99.7 (C5), 89.6 (C1′), 84.9 (C4′), 79.2 (C2′), 75.6 (C3′), 64.1 (C5′), 31.2 (αCH_2), 28.9, 28.8, 28.7, 28.6, 28.3, 27.3, 26.2, 22.0 (6 × CH_2), 18.3 (2′CH_3), 13.9 (CH_3).

3-(2-C-β-Methyl-β-D-ribofuranosyl)-6-octyl- 2,3-dihydrofurano[2,3-d]-pyrimidin-2(1H)-one (11)

Compound **9** (353 mg, 0.5 mmol) was stirred in saturated methanolic ammonia (25 mL), room temperature, for 24 hours. After evaporation of the solvent the product was purified by short-column silica gel chromatography in $CHCl_3$-MeOH (9:1) to get nucleoside **11** as an oil. Yield 187 mg (95%). An analytical sample was crystallized from methanol/ethyl acetate, m.p. 155°C. ^{1}H NMR 8.87 (s, 1H, H4), 6.41 (s, 1H, H5), 6.03 (s, 1H, H1′), 5.36 (t, J = 4.8, 1H, 5′OH), 5.24 (s, 1H, 2′OH), 5.14 (d, J = 7.2, 1H, 3′OH), 3.89–3.84 (m, 2H, H3′, H4′), 3.74–3.64 (m, 2H, H5′), 2.64 (t, J = 7.2, 2H, αCH_2), 1.61 (m, 2H, βCH_2), 1.29–1.24 (m, 10H, 5 × CH_2), 0.94 (s, 3H, 2′CH_3), 0.85 (t, J = 6.9, 3H, CH_3). ^{13}C NMR 171.1 (C7a), 158.7 (C6), 154.3 (C2), 136.9 (C4), 106.6 (C4a), 99.6 (C5), 92.8 (C1′), 82.9 (C4′), 78.6 (C2′), 71.2 (C3′), 58.7 (C5′), 31.2 (αCH_2), 28.6, 28.5, 28.4, 27.4, 26.3, 22.1 (6 x CH_2), 19.7 (2′CH_3), 13.9 (CH_3). HRMS calcd for $[C_{20}H_{30}N_2O_6 + H]^+$ *m/z* 395.2202, found 395.2182. Anal. ($C_{20}H_{30}N_2O_6$) C, H, N.

3-(2-C-β-Methyl-β-D-ribofuranosyl)-6-decyl- 2,3-dihydrofurano[2,3-d]-pyrimidin-2(1H)-one (12)

Treatment of **10** (372 mg, 0.51 mmol) with methanolic ammonia (7 mL) as described above gave **12** (126 mg, 59%) as a white solid foam. ^{1}H NMR 8.87 (s, 1H, H4), 6.41 (s, 1H, H5), 6.03 (s, 1H, H1′), 5.36 (t, J = 4.8, 1H, 5′OH), 5.24 (s, 1H, 2′OH), 5.14 (d, J = 7.2, 1H, 3′OH), 3.89–3.84 (m, 2H, H3′, H4′), 3.74–3.64 (m, 2H, H5′), 2.63 (t, J = 6.9, 2H, αCH_2), 1.61 (m, 2H, βCH_2), 1.29–1.24 (m, 10H, 5 × CH_2), 0.94 (s, 3H, 2′CH_3), 0.85 (t, J = 6.2, 3H, CH_3). ^{13}C NMR 171.1 (C7a), 158.7 (C6), 154.2 (C2), 136.8 (C4), 106.6 (C4a), 99.6 (C5), 92.8 (C1′), 82.3 (C4′), 78.5 (C2′), 71.2 (C3′), 58.7 (C5′), 31.3 (αCH_2), 28.9, 28.8, 28.7, 28.6, 28.3, 27.3, 26.2, 22.1 (8 × CH_2), 19.7 (2′CH_3), 13.9 (CH_3). HRMS calcd for $[C_{22}H_{34}N_2O_6 + H]^+$ *m/z* 423.2522, found 423.2495. Anal. ($C_{22}H_{34}N_2O_6$) C, H, N.

4-O-Methyl-5-(2-oxodecyl)-2′-C-β-methyl-D-uridine (13)

A sample of **9** (353 mg, 0.5 mmol) was stirred in 0.1 M MeONa (20 mL) at room temperature for 24 hours. After this time the reaction mixture contained two products (TLC). The mixture was neutralized with acetic acid, methanol was evaporated, and the products were separated on a silica gel column in chloroform-methanol 9:1. First UV-absorbing fractions

contained compound **13** (87 mg of an oil, 41%), and further elution gave the already known nucleoside **11** (78 mg, 40%). The product **13** was crystallized from hexane-methanol, m.p. 115°C. ^{1}H NMR 11.96 (s, 1H, NH), 8.19 (s, 1H, H6), 5.91 (s, 1H, H1′), 5.22 (t, J = 4.8, 1H, 5′OH), 5.16 (s, 1H, 2′OH), 5.12 (d, J = 7.2, 1H, 3′OH), 3.78 (s, 3H, OCH_3), 3.82–3.87 (m, 2H, H3′, H4′), 3.68–3.59 (m, 2H, H5′), 3.40 (s, 2H, C5-CH_2), 2.45 (t, J = 7.5, 2H, αCH_2), 1.46 (m, 2H, βCH_2), 1.27–1.23 (m, 10H, 5 × CH_2), 0.94 (s, 3H, 2′CH_3), 0.85 (t, J = 6.9, 3H, CH_3). ^{13}C NMR 206.9 (C = O), 169.4 (C4), 154.9 (C2), 142.9 (C6), 101.6 (C5), 91.7 (C1′), 82.2 (C4′), 78.4 (C2′), 71.5 (C3′), 58.9 (C5′), 41.4 (C5-CH_2), 31.3 (αCH_2), 28.8, 28.8, 28,7, 28.6, 28.5, 23.3, 22.1 (7 × CH_2), 19.8 (2′CH_3), 14.0 (CH_3). HRMS calcd for $[C_{21}H_{34}N_2O_7 + H]^+$ *m/z* 427.2451, found 427.2444. Anal. Calc. for $C_{21}H_{34}N_2O_7$ (426.51): C, 59.15; H, 7.98; N, 6.57. Found: C, 58.88; H, 8.32; N, 6.46.

3-(2-C-β-Methyl-β-D-ribofuranosyl)-6-octyl- 2,3-dihydropyrrolo[2,3-d]-pyrimidin-2(3H,7H)-one (14)

Method A. A solution of **11** (118.2 mg, 0.3 mmol) in saturated methanolic ammonia (50 mL) was placed in a pressure glass tube and heated in an oil bath at 50°C for 48 hours. The solvent was evaporated, and the residue was chromatographed on a silica gel column in chloroform-methanol (4:1) to give **14** (87 mg, 74%) as a colorless oil. The product was crystallized from a mixture of hexane, methanol and ethyl acetate, m.p. 155°C.

Method B. The open-ring compound **13** (85.2 mg, 0.2 mmol) was treated with methanolic ammonia (20 mL) by method A to give **14** (47.3 mg, 60%), identical in all respects with the product of obtained from **11**. ^{1}H NMR 11.08 (s, 1H, N^7H) 8.66 (s, 1H, H4), 6.09 (s, 1H, H1′), 5.85 (s, 1H, H5), 5.29 (t, J = 3.6, 1H, 5′OH), 5.09 (s, 1H, 2′OH), 5.07 (d, J = 5.4, 1H, 3′OH), 3.88–3.83 (m, 2H, H3′, H4′), 3.75–3.67 (m, 2H, H5′), 2.52 (t, 2H, αCH_2), 1.59 (m, 2H, βCH_2), 1.27–1.24 (m, 10H, 5 × CH_2), 0.89 (s, 3H, 2′), 0.84 (t, J = 5.1, 3H, CH_3). ^{13}C NMR 159.1 (C7a), 154.3 (C2), 142.7 (C6), 134.6 (C4), 108.7 (C4a), 96.2 (C5), 92.3 (C1′), 82.1 (C4′), 78.4 (C2′), 71.4 (C3v), 58.8 (C5′), 31.3 (αCH_2), 28.9, 28.9, 28.8, 28.7, 28.6, 28.5, 27.4, 22.1 (8 × CH_2), 19.9 (2′CH_3), 13.9.0 (CH_3). HRMS calcd for $[C_{20}H_{31}N_3O_5 + H]^+$ *m/z* 394.2334, found 394.2342. Anal. ($C_{20}H_{31}N_3O_5$) C, H, N.

3-(2-C-β-Methyl-β-D-ribofuranosyl)-6-decyl- 2,3-dihydropyrrolo[2,3-d]-pyrimidin-2(3H,7H)-one (15)

Treatment of **12** (64 mg, 0.15 mmol) with methanolic ammonia (6 mL) as described above (Method A) gave **15** (30.5 mg, 48%) as a white solid. 11.08 (s, 1H, N^7H) 8.66 (s, 1H, H4), 6.09 (s, 1H, H1′), 5.85 (s, 1H, H5), 5.28 (t, J = 3.6, 1H, 5′OH), 5.10 (s, 1H, 2′OH), 5.08 (d, J = 5.7, 1H, 3′OH), 3.85–3.83 (m, 2H, H3′, H4′), 3.73–3.67 (m, 2H, H5′), 2.53 (t, 2H,

αCH_2), 1.58 (m, 2H, βCH_2), 1.27–1.24 (m, 14H, 7 x CH_2), 0.90 (s, $J = 5.1$, 3H, 2′CH_3), 0.85 (t, 3H, CH_3). ^{13}C NMR 159.1 (C7a), 154.3 (C2), 142.7 (C6), 134.6 (C4), 108.7 (C4a), 96.2 (C5), 92.3 (C1′), 82.1 (C4′), 78.4 (C2′), 71.4 (C3′), 58.8 (C5′), 31.2 (αCH_2), 28.7, 28.6, 28.5, 27.8, 27.5, 22.1 (6 × CH_2), 19.9 (2′CH_3), 14.0 (CH_3). HRMS calcd for $[C_{22}H_{35}N_3O_5 + H]^+$ *m/z* 422.2673, found 422.2655. Anal. ($C_{22}H_{35}N_3O_5$) C, H, N.

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