Tetrahedron 64 (2008) 7828–7836

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and structure of novel cyclonucleoside analogues of uridine

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ARTICLE INFO

Article history:
Received 18 March 2008
Received in revised form 9 May 2008
Accepted 23 May 2008
Available online 29 May 2008

ABSTRACT

Novel cyclonucleoside analogues of uridine having pentylene and hexylene linker between the 5′-O and 3-N positions (thereby generating a 13- and 14-membered ring, respectively) were synthesized from uridine via ring-closing metathesis. An example of cyclic dinucleosides having two butylene linkers between the 5′-O and 3-N positions (24-membered ring) was synthesized from uridine via tandem cross-metathesis and ring-closing metathesis.

1. Introduction

Nucleoside analogues display a large range of biological activities as antiviral agent analogues[1] and as antitumoral agents.[2] Such nucleoside analogues normally are prodrug forms of active pharmaceutical agents. They must undergo interactions with proteins in cellular and compartmental membranes, nucleoside kinases, and mono- and/or dinucleotide kinases and then bind with target proteins (e.g., DNA polymerases, reverse transcriptases, and/or other nucleoside triphosphate metabolizing enzymes). In solution, nucleos(t)ide analogues can adopt a number of conformations, which can be determined with four parameters:[3] (i) the glycosyl torsion angle χ, which determines the *syn* or *anti* disposition of the base relative to the sugar moiety; (ii) the torsion angle γ, which determines the orientation of 5′-OH with respect to C3′ as represented by the three main rotamers +sc, ap, −sc; (iii) the puckering of the furanose ring described by the phase angle of pseudorotation *P*;[4,5] and (iv) the degree of deviation from planarity of the furanose ring indicated by the maximum out-of-plane pucker ν_{max}.[4,5] The conformations of nucleoside described by these three-state models (χ, γ, *P*) are in interdependent equilibria and the energy barrier between the preferred conformational state is usually low. The majority of nucleos(t)ide target enzymes appears to have strict conformational requirements for substrate binding. Moreover, the nucleotides adopt distinctive conformations when they are in DNA/DNA and DNA/RNA duplexes (*South* conformation in B-DNA and *North* conformation in A-RNA).[3] These properties have motivated the synthesis of conformationally restricted nucleos(t)ides for the search of novel nucleoside analogues in the area of antitumoral and antiviral agents,[6] and novel oligomers in the antisense technology.[7]

Four families of constrained nucleoside and/or nucleotide analogues have been developed: bicyclonucleosides[8] (e.g., **1**) obtained by bridging two atoms of the furanose moiety with an alkyl chain or analogous ether; cyclic phosphorus esters[9] (e.g., **2**) in which a similar bridge is formed between the phosphate group and the furanose moiety or the nucleobase; cyclonucleosides[10] (e.g., **3**) in which the bridge is formed between the furanose moiety and the nucleobase; and nucleotide di(tri)mers[11] (e.g., **4**) (Fig. 1).

Metathesis[12] is an extremely useful method in organic chemistry due to the development of efficient and selective catalysts such as the ruthenium carbenes **5** (first generation Grubbs catalyst)[13] and **6** (second generation Grubbs catalyst),[14] which offer a good compromise between efficiency and tolerance to functional groups (Fig. 2). The use of metathesis reactions such as Ring-Closing Metathesis (RCM) and Cross-Metathesis (CM) in the nucleoside field[15] has been developed over the last decade for the synthesis

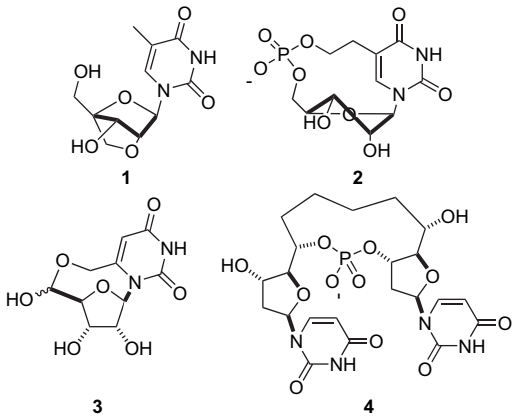

Figure 1. Nucleoside analogues **1**–**4**.

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doi:10.1016/j.tet.2008.05.112

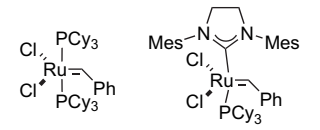


Figure 2. Ruthenium catalysts **5** and **6** for metathesis.

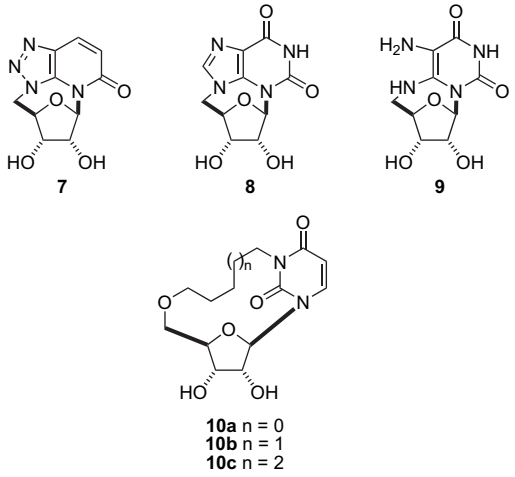


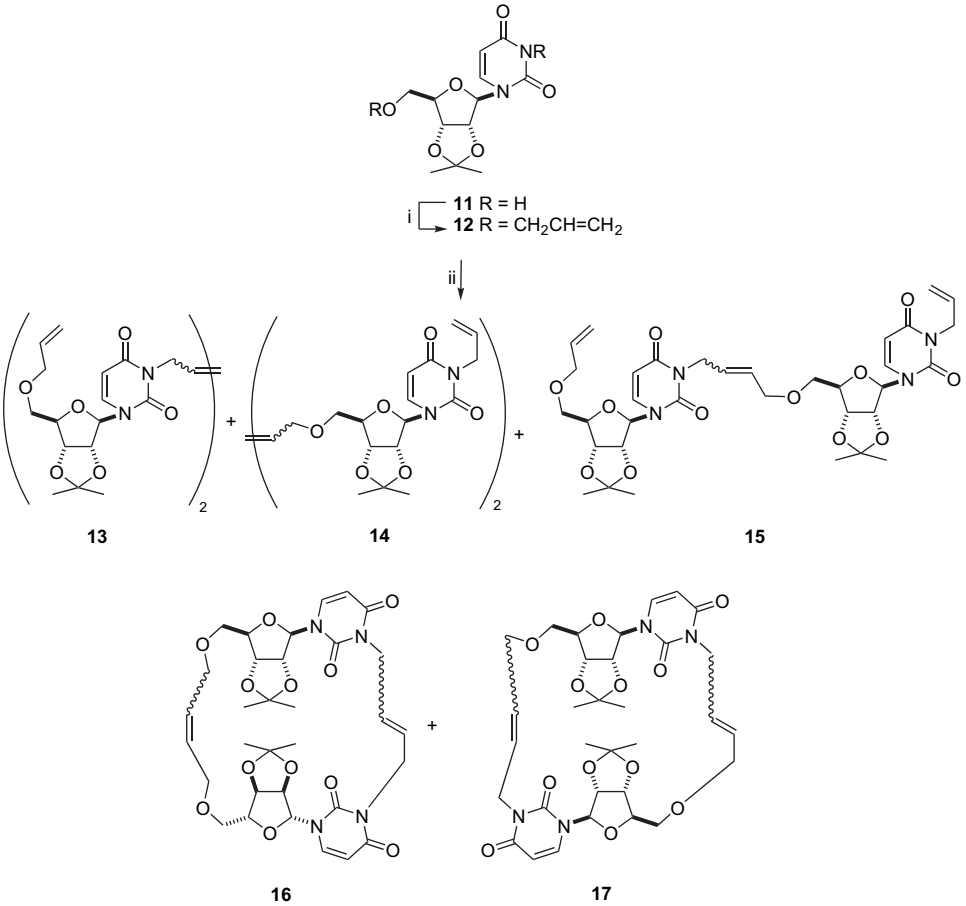
Figure 3. Nucleoside analogues **7**–**9** and **10a**–**c**.

of: (i) known antiviral agents such as Stavudine;[16] (ii) carbocyclic nucleosides;[17] (iii) acyclonucleosides;[18] and (iv) polycyclic nucleosides.[11c,d,i,19]

Recent papers described the synthesis of cyclonucleosides **7**–**9** having anti-hepatitis C virus activity in the HCV subgenomic RNA replicon.[10c–e] The mode of action of these novel compounds **7**–**9** was the subject of studies because the lack of 5′-OH does not permit the phosphorylation to furnish the corresponding nucleotide as required in the classical metabolism pathway. In this paper, we describe the synthesis of cyclonucleoside analogues of **7**–**9** via RCM reaction; the target nucleosides **10** having a saturated alkylidene bridge between the O5′-oxygen atom and the N3-nitrogen atom (Fig. 3).

2. Results and discussion

The strategy developed for the synthesis of 5′,3-cyclonucleosides **10** required to start from the readily available nucleoside acetonide **11**.[20] 3-N and 5′-O bisallylation was realized with KOH, allyl bromide, and 18-crown-6, in THF at rt, to give the key diene **12** in 88% yield. The diene **12** was subjected to a metathesis reaction using catalyst **5** in dichloromethane at 40 °C. Under these conditions only the presence of dimers and starting material was observed.[21] The crude product was separated by flash column chromatography into two mixtures: (i) linear dimers **13**–**15** in 22% yield and (ii) cyclic dimers **16** and **17** in 28% yield (Scheme 1). The use of catalyst **6** at 40 °C gave a mixture of dimers **13**–**15** in 20% yield and a mixture of dimers **16** and **17** in 41% yield. The complex mixture did not permit to determine the ratio of *E* and *Z* isomers. The use of diluted conditions (c=0.2 mM vs c=1.9 mM) was not



Scheme 1. Reagents and conditions: (i) KOH, 18-crown-6, CH_2=$CHCH_2Br$, THF, rt, 3 h, 88%; (ii) 10 mol % **6**, CH_2Cl_2, 40 °C, 12 h.

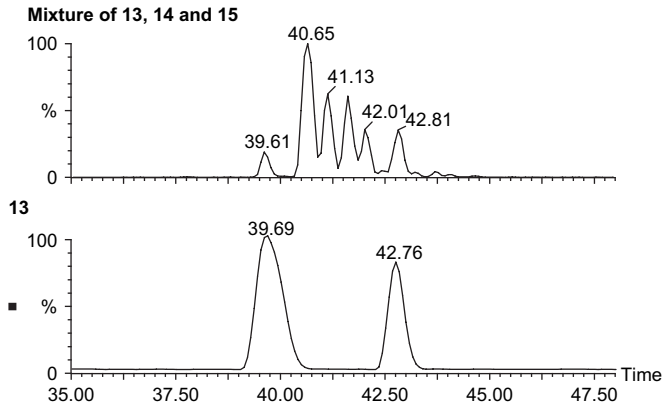


Figure 4. LC/ESI-MS profiles (RIC *m*/*z* 701) of linear dimers **13**–**15** mixture (top) and of pure **13** (bottom) obtained following Scheme 1 and Scheme 2 strategies, respectively.

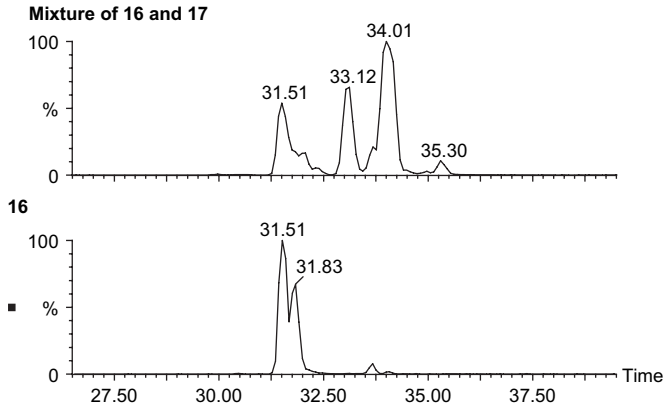
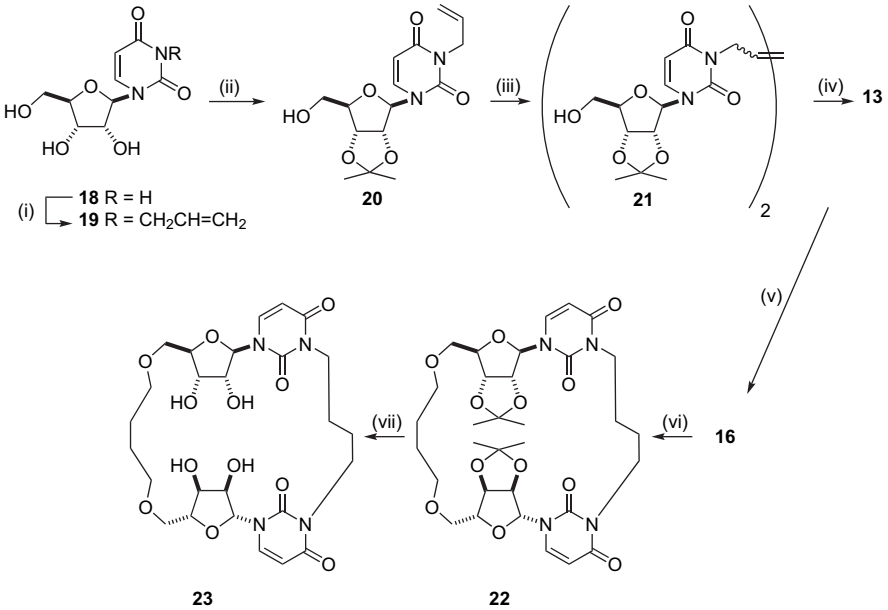


Figure 5. LC/ESI-MS profiles (RIC *m*/*z* 673) of cyclic dimers **16** and **17** mixture (top) and of pure **16** (bottom) obtained following Scheme 1 and Scheme 2 strategies, respectively.

found to be essential to prevent the formation of dimerization byproducts **13**–**17**. LC/ESI-MS analysis of both the mixture of linear compounds **13**–**15** (Fig. 4) and the mixture of cyclic compounds **16** and **17** (Fig. 5) indicated the expected loss of one ethylene and two ethylenes during the metathesis process, leading to compounds having molecular weight of 700 (**13**–**15**, MH^+ *m*/*z* 701) and 672 (**16** and **17**, MH^+ *m*/*z* 673), respectively. ^1H NMR spectroscopy of compounds **16** and **17** indicated the complete loss of terminal double bond by the disappearance of the signal around δ=5.2 ppm. Starting from the diene **12** tandem CM and RCM reactions occurred, leading first to dimerization (*head-to-tail*, *head-to-head* or *tail-to-tail*) followed by ring closure.

In order to determine the structure of linear and cyclic compounds **13**–**17**, selective synthesis of cyclic dinucleoside having exclusively a tail-to-tail (i.e., base-to-base) has been developed. Starting from uridine (**18**) (Scheme 2), selective N-allylation was performed with K_2CO_3 and allyl bromide, in DMF and acetone at 55 °C, to produce the alkene **19** in 82% yield.[22] Protection of the ribose ring in **19** was realized by acetonide formation using 2,2-dimethoxypropane with *p*-TsOH as catalyst to afford compound **20** in 90% yield. The key alkene **20** was subjected to CM reaction in dichloromethane at 40 °C, using the ruthenium carbene **5** as catalyst, to afford the linear dimer **21** in 61% yield as a mixture of two isomers *E* and *Z* (9:1). A similar result was found using catalyst **6**. MS and NMR analyses confirmed the expected loss of ethylene and the loss of the terminal double bond (disappearance of the signal around δ=5.2 ppm in the ^1H NMR spectra). After classical O-allylation of both 5′-hydroxyl groups, the triene **13** was obtained as a mixture of *Z* and *E* isomers (see LC/ESI-MS profile Fig. 4) and was later subjected to an RCM reaction in dichloromethane with catalyst **6** at 40 °C to give compound **16** as a mixture of mainly two geometric isomers in 50% yield (see LC/ESI-MS profile Fig. 5). It was not possible to determine the ratio of the various *Z* and *E* isomers. To the best of our knowledge this is the first time that a cyclic dinucleoside structure of this type has been described. Reduction of the diene **16** by hydrogenation using Pd/C in methanol gave only one species, the dimer **22** in 55% yield. Removal of the two ribose protecting groups in compound **22** by hydrolysis in acetic acid produced the pure desired free cyclic dinucleoside **23** in 74% yield (Fig. 6, t_R=15.40 min and $[M+H]^+$ *m*/*z* 597). This strategy, shown in



Scheme 2. Reagents and conditions: (i) K_2CO_3, CH_2=$CHCH_2Br$, DMF, acetone, 55 °C, 12 h, 82%; (ii) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, acetone, rt, 4 days, 90%; (iii) 10 mol % **5**, CH_2Cl_2, 40 °C, 12 h, 61%; (iv) KOH, 18-crown-6, CH_2=$CHCH_2Br$, THF, rt, 6 h, 50%; (v) 10 mol % **6**, CH_2Cl_2, 40 °C, 12 h, 50%; (vi) H_2, Pd/C, MeOH, rt, 12 h, 55%; (vii) AcOH, H_2O, 90 °C, 5 h, 74%.

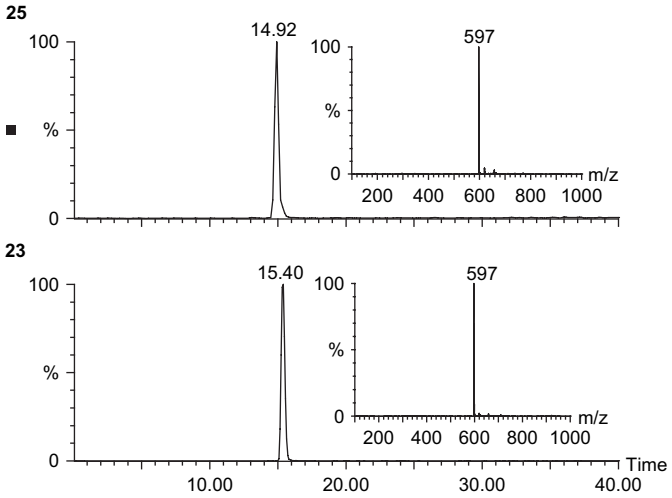
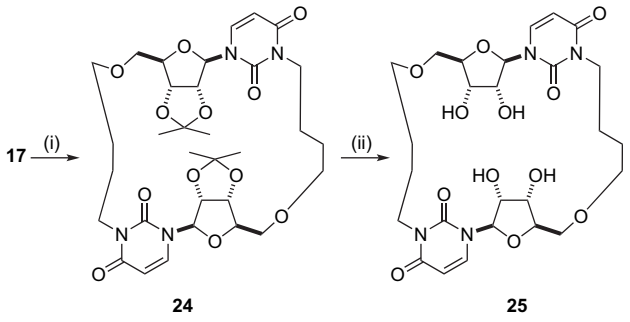


Figure 6. LC/ESI-MS profiles (RIC *m*/*z* 597) and corresponding no fragmented mass spectra (CV 20 V) of compounds **25** (top) and **23** (bottom).

Scheme 2, results in the synthesis of a cyclic dinucleoside having exclusively a tail-to-tail (i.e., base-to-base) connection. The comparison of the LC/ESI-MS profiles (Figs. 4 and 5) obtained for compounds **13** and **16** (Scheme 2 strategy) with those of the linear dimers mixture **13**–**15** and cyclic dimers mixture **16** and **17** (Scheme 1 strategy) clearly evidenced that the dinucleosides **13** and **16** were present in the first strategy.

In order to obtain the dimer nucleoside **25**, compound **17** was subjected to hydrogenation followed by deprotection to furnish the target cyclic dinucleoside **25** (57% over two steps, Scheme 3). The LC/ESI-MS analysis clearly shows that **25** is different (head-to-tail instead of tail-to-tail) but isomeric to **23** (Fig. 6, t_R=14.92 min and $[M+H]^+$ *m*/*z* 597). The fragmentation pathways obtained for these two compounds under Collision Induced Dissociation (CID) conditions are in accordance with the proposed structures. All the dinucleosides except the linear dimer **15** showed symmetrical structures as determined by ^1H and ^{13}C NMR studies. It was notable that, for compound **15**, two sets of signals were observed for the H-5 and H-6 protons.

Since it was not possible to obtain the cyclonucleoside **10a** via the RCM reaction, enhancement of the number of carbon atoms was envisaged for the synthesis of the cyclonucleosides **10b** and **10c**. Starting from acetonide **11**, regioselective allylation of the primary hydroxyl group without prior protection of the more acidic proton in 3 position was effected using allyl bromide in presence of sodium hydride with microwave activation[23] to give the alkene **26** in 76% yield (Scheme 4). N-Alkenylation was performed with KOH and alkenyl bromide in toluene and DMSO to produce the alkenes **27** and **28** in 75% and 68% yields, respectively. Compounds **27** and **28** were studied as substrates for RCM reactions using Grubbs catalyst **6** in refluxing dichloromethane. In this case, the dienes **27** and **28** did not afford any dimers but only cyclonucleosides **29** and **30** have been obtained in 74% and 59% yields, respectively, as a mixture of two *Z* and *E* stereoisomers as deduced from the LC/ESI-MS profiles. It was clear that the enhancement of only one carbon atom was enough to disfavor totally the formation of the corresponding dimers. Hydrogenation of alkenes **29** and **30** using PtO_2 in ethyl acetate afforded the alcano derivatives **31** and **32** in 80% and 68% yields. Surprisingly the reduction of the diene **29** by hydrogenation using Pd/C in methanol gave only the 3-*N*-pentyl derivative, although the hydrogenation of the cyclic dimers **16** and **17** using Pd/C furnished the alcano cyclic derivatives **22** and **24** without isolation of the byproducts having a free hydroxyl group. Classical deprotection of the diol in compounds **31** and **32** by hydrolysis in acetic acid produced the desired free cyclonucleosides **10b** and **10c** in 62% and 55% yields, respectively. The LC/ESI-MS analysis (Fig. 7) clearly evidenced the difference of one methylene



Scheme 3. Reagents and conditions: (i) H_2, Pd/C, MeOH, rt, 12 h, 67%; (ii) AcOH, H_2O, 90 °C, 5 h, 85%.

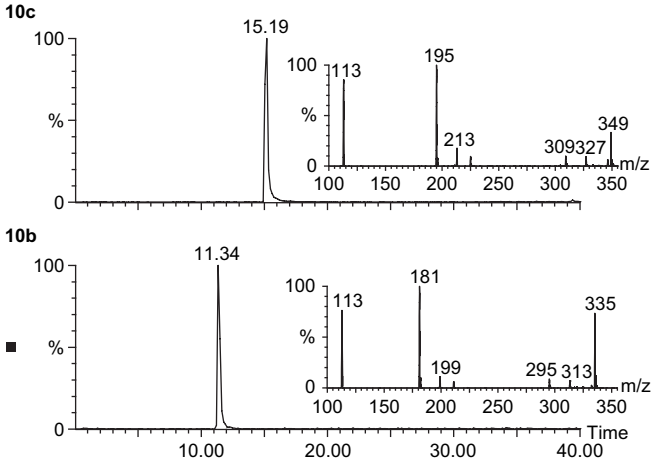
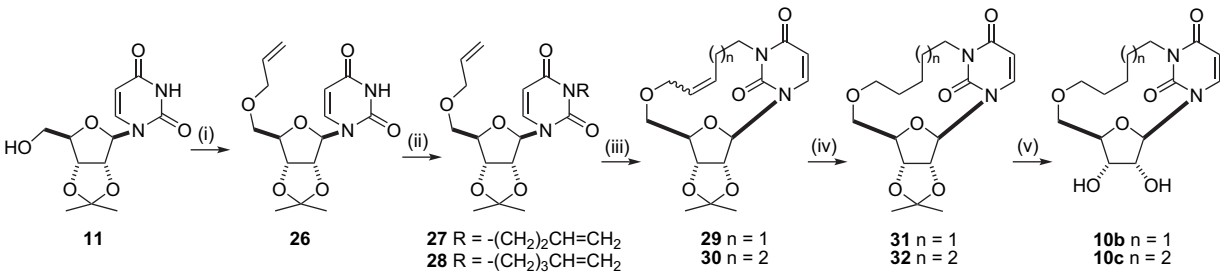


Figure 7. LC/ESI-MS profiles (RIC *m*/*z* 327 and *m*/*z* 313) and corresponding fragmented mass spectra (CV 40 V) of compounds **10c** (top) and **10b** (bottom).



Scheme 4. Reagents and conditions: (i) NaH, DMF, MW (100 W, 40 °C), 3 min then CH_2=$CHCH_2Br$, MW (100 W, 40 °C), 3 min, 76%; (ii) KOH, RBr, DMSO, toluene, TA, 12 h (for **27**, 75%; for **28**, 68%); (iii) 10 mol % **6**, CH_2Cl_2, 40 °C, 12 h (for **29**, 74%; for **30**, 59%); (iv) H_2, PtO_2, ethyl acetate (for **31**, 80%; for **32**, 68%); (v) H_2O, CH_3COOH, 110 °C, 4 h (for **10b**, 62%; for **10c**, 55%).

between **10b** (t_R=11.34 min, $[M+Na]^+$ *m/z* 335, $[M+H]^+$ *m/z* 313, $[M+H-H_2O]^+$ *m/z* 295, $[M+H-C_5H_6O_3]^+$ *m/z* 199, and $[M+H-C_5H_8O_4]^+$ *m/z* 181) and **10c** (t_R=15.19 min, $[M+Na]^+$ *m/z* 349, $[M+H]^+$ *m/z* 327, $[M+H-H_2O]^+$ *m/z* 309, $[M+H-C_5H_6O_3]^+$ *m/z* 213, and $[M+H-C_5H_8O_4]^+$ *m/z* 195).

As expected, the fragment corresponding to the uracil moiety ($C_4H_5N_2O_2^+$ *m/z* 113) remains unchanged.

3. Conclusion

In summary, we have demonstrated a concise method using RCM reaction for the synthesis of the 3,5′-*O*-pentano- and 3,5′-*O*-hexanouridine. The practicality of using LC/ESI-MS for the stepwise control of RCM and CM reactions in the nucleoside field was also demonstrated. Unfortunately, this strategy did not permit the synthesis of the cyclonucleoside having a butyl linker. In this case, the formation of cyclic dinucleosides having two butylene linkers between the 5′-O and N-3 positions was observed.

4. Experimental

4.1. General

Melting points were determined on a digital melting-point apparatus (Electrothermal) and were uncorrected. Optical rotations were recorded in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (JASCO) using a 1 dm cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 (internal Me_4Si) at 300.13 MHz and at 75.47 MHz, respectively (Bruker Advance-300). TLC was performed on Silica F_{254} (Merck) and detection was by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was carried out on Silica Gel 60 (Merck, 230 mesh). EtOAc and petroleum ether were distilled before use. Bases and solvents were used as supplied. The Liquid Chromatography/Electrospray Ionization Mass Spectrometry (LC/ESI-MS) was carried out on an Alliance HPLC system (Waters 2695) equipped with a photodiode array detector (Waters 2996 PDA detector). In this study, absorbances were monitored between 190 and 400 nm. The presence of the target cyclonucleosides was confirmed using their specific response at 261 nm. The reaction mixtures (5 μL) were loaded on a YMC-Pack Pro 120-5C18 column (YMC, 250×4.6 mm). The elution was performed using a 1 mL/min mobile phase gradient programmed from water (A), acetonitrile (B), and acetonitrile containing 10% acetic acid (C) as follows (A/B/C): 90:0:10 (*t*=0 min), 40:50:10 (*t*=40 min), 0:90:10 (*t*=50 min), and 0:90:10 (*t*=55 min). The effluent was flow-split via a peek tee with 1/5 of the flow directed toward the electrospray (ESI) source of a simple quadrupole mass spectrometer (Waters-Micromass ZQ 4000) and the residual 4/5 directed toward the PDA detector. LC/ESI-MS data were recorded in the positive and negative ion modes with capillary voltages of ±2.5 kV and cone voltages from 20 to 80 V. Scanning was performed in the range 100–1500 Da at a scan rate of 1 s/scan and spectra were collected in the profile mode. The source and desolvation temperatures were 120 and 250 °C, respectively. Nitrogen was used as a drying and nebulizing gas at flow rates of 450 and 100 L/h, respectively. Data acquisition and processing were performed with MassLynx 4.0 software. High-resolution electrospray mass spectra (ESI-HRMS) in the positive ion mode were obtained on a Q-TOF *Ultima Global* hybrid quadrupole time-of-flight instrument (Waters-Micromass), equipped with a pneumatically assisted electrospray (Z-spray) ionization source and an additional sprayer (Lock Spray) for the reference compound. The purified compounds were dissolved in methanol (0.01 mg/mL) and the solutions were directly introduced (5 μL/min) through an integrated syringe pump into the electrospray source. The source and desolvation temperatures were 80 and 150 °C, respectively. Nitrogen was used as the drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. Typically, the capillary voltage was 3.5 kV and the cone voltage 110 V. Lock mass correction, using appropriate cluster ions of an orthophosphoric acid solution (0.1% in H_2O/CH_3CN, 50:50, v/v), was applied for accurate mass measurements. The mass range was 50–2000 Da and spectra were recorded at 2 s/scan in the profile mode at a resolution of 10,000 (FWMH). Data acquisition and processing were performed with MassLynx 4.0 software.

4.2. Synthesis of symmetrical and dissymmetrical cyclic dimers 23 and 25

*4.2.1. 3-N,5′-O-Diallyl-2′,3′-O-isopropylideneuridine (**12**)*

To a solution of 2′,3′-*O*-isopropylideneuridine (**11**) (2.0 g, 7.04 mmol) in dry THF (30 mL) were added KOH (1.2 g, 21 mmol), 18-crown-6 (80 mg, 0.3 mmol), and allyl bromide (1.8 mL, 21 mmol). The reaction mixture was stirred for 6 h at rt. The solvent was removed in vacuo and the residue was partitioned between H_2O and CH_2Cl_2. The organic phase was separated and the aqueous solution extracted with CH_2Cl_2. The combined organic solutions were washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to furnish **12** (2.3 g, 88%) as a colorless oil; R_f 0.6 (MeOH/CH_2Cl_2, 2:98); $[\alpha]_D^{20}$ −24.3 (*c* 0.4 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, *J*=8.1 Hz, 1H, H-6), 5.91 (d, *J*=2.5 Hz, 1H, H-1′), 5.96–5.77 (m, 2H, OCH_2CH= and NCH_2CH=), 5.73 (d, *J*=8.1 Hz, 1H, H-5), 5.30–5.16 (m, 4H, $2CH_2$=), 4.80 (dd, *J*=6.2, 2.5 Hz, 1H, H-3′), 4.77 (dd, *J*=6.2, 2.5 Hz, 1H, H-2′), 4.52 (m, 2H, NCH_2), 4.44 (m, 1H, H-4′), 3.95 (dt, *J*=5.7, 1.3 Hz, 2H, OCH_2CH=), 3.70 (dd, *J*=10.6, 2.5 Hz, 1H, H-5′), 3.62 (dd, *J*=10.6, 3.6 Hz, 1H, H-5′), 1.55 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.8 (C-4), 151.0 (C-2), 139.2 (C-6), 134.0 (OCH_2CH=), 131.9 (NCH_2CH=), 118.32 and 118.16 ($2CH_2$=), 114.2 ($C(CH_3)_2$), 101.7 (C-5), 94.3 (C-1′), 86.1 (C-4′), 85.9 (C-2′), 81.4 (C-3′), 72.7 (OCH_2CH=), 70.5 (C-5′), 43.3 (NCH_2CH=), 27.6 (CH_3), 25.7 (CH_3). HRMS (ESI) $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_6Na$: 387.1532, found 387.1523.

*4.2.2. Protected unsaturated disymmetrical acyclic dinucleoside **15** and protected unsaturated disymmetrical cyclic dinucleoside **17***

Grubbs second catalyst **6** (24 mg, 10 mol %) was added to a solution of **12** (102 mg, 0.28 mmol) in CH_2Cl_2 (150 mL) and the mixture was stirred at 40 °C overnight. The solvent was removed in vacuo and the residue was purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to give two fractions. The less polar one was constituted of a mixture of linear dimers **13**–**15** (19.6 mg, 20%); the second fraction was constituted of a mixture of cyclic dimers **16** and **17** (38.6 mg, 41%). A second flash chromatography furnished the cyclic dimer **17** (23.5 mg, 25%). *Major linear dimer **15***: R_f 0.6 (EtOAc/petroleum ether, 60:40); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57 (d, *J*=8.1 Hz, 1H, H-6a), 7.52 (d, *J*=8.1 Hz, 1H, H-6b), 5.70 (d, *J*=8.1 Hz, 1H, H-5a), 5.68 (d, *J*=8.1 Hz, 1H, H-5b), 5.86–5.7 (m, 4H, CH=CH, $2CH$=CH_2), 5.90 (s, 2H, 2H-1′), 5.23–5.09 (m, 4H, $2CH_2$=), 4.75–4.66 (m, 4H, 2H-2′, 2H-3′), 4.51–4.30 (m, 6H, 2H-4′, $2NCH_2$), 3.94–3.85 (m, 4H, $2OCH_2CH$=), 3.70–3.48 (m, 4H, 4H-5′), 1.56 (s, 6H, $2CH_3$), 1.33 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 162.7 (2C-4), 151.0 and 150.9 (2C-2), 139.1 and 139.2 (2C-6), 134.0, 131.9, 130.0 and 127.6 (4CH=), 118.3 and 118.4 ($2CH_2$=), 114.4 and 114.3 ($2C(CH_3)_2$), 101.9 and 101.8 (2C-5), 94.0, 93.5 (2C-1′), 86.0, 85.9, 85.7, and 85.6 (2C-2′, 2C-4′), 81.4 and 81.3 (2C-3′), 72.8 and 71.8 ($2OCH_2CH$=), 70.53 and 70.46 (2C-5′), 43.4 and 42.2 ($2NCH_2CH$=), 27.2 ($2CH_3$), 25.3 ($2CH_3$). HRMS (ESI) $[M+Na]^+$ calcd for $C_{34}H_{44}N_4O_{12}Na$: 723.2853, found 723.2854. *Major cyclic dimer **17***: R_f 0.5 (EtOAc/petroleum ether, 60:40); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, *J*=8.1 Hz, 2H, 2H-6), 5.86 (d, *J*=2.5 Hz, 2H, 2H-1′), 5.80 (d,

J=8.1 Hz, 2H, 2H-5), 5.74 (m, 4H, 2CH=CH), 4.84 (dd, J=6.2, 3.1 Hz, 2H, 2H-3′), 4.76 (dd, J=6.2, 2.5 Hz, 2H, 2H-2′), 4.60 (dd, J=14.6, 5.4 Hz, 2H, NC*HaH*bCH=), 4.52 (dd, J=14.6, 4.0 Hz, 2H, NC*HaH*bCH=), 4.39 (m, 2H, 2H-4′), 4.08 (dd, J=12.3, 5.1 Hz, 2H, OC*HaH*bCH=), 4.00 (dd, J=12.3, 5.3 Hz, 2H, OC*HaH*bCH=), 3.76 (dd, J=10.6, 3.0 Hz, 2H, 2H-5′a), 3.64 (dd, J=10.6, 4.5 Hz, 2H, 2H-5′b), 1.55 (s, 6H, $2CH_3$), 1.32 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 162.5 (2C-4), 150.9 (2C-2), 139.6 (2C-6), 129.2 and 127.9 (2CH=), 114.4 ($2C(CH_3)_2$), 102.3 (2C-5), 94.7 (2C-1′), 86.4 (2C-4′), 85.7 (2C-2′), 81.7 (2C-3′), 71.6 ($2OCH_2CH$=), 70.8 (2C-5′), 41.6 ($2NCH_2CH$=), 27.6 ($2CH_3$), 25.7 ($2CH_3$). HRMS (ESI) $[M+Na]^+$ calcd for $C_{32}H_{40}N_4O_{12}Na$: 695.2540, found 695.2533.

*4.2.3. 3-Allyluridine (**19**)*

To a solution of uridine (**18**) (4.9 g, 20 mmol) in DMF (25 mL) and acetone (25 mL) was added K_2CO_3 (5 g, 36 mmol) at rt. After 20 min of stirring, allyl bromide (2.6 mL, 30 mmol) was added and the reaction mixture was stirred for 12 h at 55 °C before filtration and concentration in vacuo. The crude compound was purified by flash column chromatography (MeOH/CH_2Cl_2, 3:97) to give **19** as a colorless oil (4.7 g, 82%). R_f 0.2 (MeOH/CH_2Cl_2, 20:80); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.05 (d, J=8.2 Hz, 1H, H-6), 5.92 (d, J=3.8 Hz, 1H, H-1′), 5.85 (ddt, J=17.2, 10.3, 5.6 Hz, 1H, CH_2CH=), 5.78 (d, J=8.2 Hz, 1H, H-5), 5.18 (dq, J=17.2, 1.5 Hz, 1H, $1CH_2$=), 5.14 (dq, J=10.2, 1.5 Hz, 1H, $1CH_2$=), 4.52 (dt, J=5.6, 1.4 Hz, 2H, NCH_2), 4.15 (m, 2H, H-2′ and H-3′), 4.01 (dt, J=4.5, 2.8 Hz, 1H, H-4′), 3.86 (dd, J=12.2, 2.6 Hz, 1H, H-5′), 3.74 (dd, J=12.2, 3.1 Hz, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.1 (C-4), 151.2 (C-2), 141.5 (C-6), 133.5 (NCH_2CH=), 118.1 (CH_2=), 102.2 (C-5), 92.1 (C-1′), 86.8 (C-4′), 76.1 and 71.2 (C-2′ and C-3′), 62.7 (C-5′), 43.1 (NCH_2CH=). The physical data were in accordance with those previously described by Watanabe.[22]

*4.2.4. 3-Allyl-2′,3′-O-isopropylideuridine (**20**)*

To a solution of **19** (5.5 g, 19.3 mmol) in acetone (170 mL) were added 2,2-dimethoxypropane (20 mL, 162 mmol) and *p*-TsOH (150 mg, 0.79 mmol). The reaction mixture was stirred for 4 days at rt and then concentrated in vacuo. The crude compound was purified by flash column chromatography (MeOH/CH_2Cl_2, 2:98) to give **20** as a white solid (5.63 g, 90%). Mp 92 °C; R_f 0.5 (MeOH/CH_2Cl_2, 2.5:97.5); $[\alpha]_D^{20}$ −31.6 (c 0.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, J=8.0 Hz, 1H, H-6), 5.84 (ddt, J=17.4, 10.5, 5.8 Hz, 1H, CH_2CH=), 5.75 (d, J=8.0 Hz, 1H, H-5), 5.59 (d, J=2.5 Hz, 1H, H-1′), 5.23 (d, J=17.4 Hz, 1H, $1CH_2$=), 5.17 (d, J=10.5 Hz, 1H, $1CH_2$=), 4.98 (dd, J=6.4, 2.5 Hz, 1H, H-2′), 4.94 (dd, J=6.4, 3.0 Hz, 1H, H-3′), 4.50 (d, J=5.8 Hz, 2H, NCH_2), 4.31 (m, 1H, H-4′), 3.84 (dd, J=11.9, 2.5 Hz, 1H, H-5′a), 3.78 (m, 1H, H-5′b), 2.84 (br s, 1H, OH), 1.56 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 162.2 (C-4), 150.7 (C-2), 140.7 (C-6), 131.1 (NCH_2CH=), 118.4 (CH_2=), 114.3 ($C(CH_3)_2$), 102.0 (C-5), 96.9 (C-1′), 87.0 (C-4′), 83.7 (C-2′), 80.3 (C-3′), 62.7 (C-5′), 43.1 (NCH_2CH=), 27.2 (CH_3), 25.2 (CH_3). HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{20}N_2O_6Na$: 347.1219, found 347.1218. The physical data were in accordance with those previously described by Walker et al.[24]

*4.2.5. 1,4-Bis-(uridin-3-yl)but-2-ene (**21**)*

Grubbs first catalyst **5** (64 mg, 10 mol %) was added to a solution of **20** (250 mg, 0.77 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred at 40 °C overnight. The solvent was removed in vacuo and the residue was purified by flash column chromatography (MeOH/CH_2Cl_2, 1:99) to give **21** (146 mg, 61%) as a mixture of *Z* and *E* isomers. *Major isomer*: R_f 0.4 (MeOH/CH_2Cl_2, 2.5:97.5); ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 7.36 (d, J=8.0 Hz, 2H, 2H-6), 5.77 (m, 2H, –HC=CH–), 5.74 (d, J=8.0 Hz, 2H, 2H-5), 5.55 (d, J=2.4 Hz, 2H, 2H-1′), 5.04 (dd, J=6.4, 2.4 Hz, 2H, 2H-2′), 4.93 (dd, J=6.4, 3.4 Hz, 2H, 2H-3′), 4.52 (dd, J=14.5, 3.0 Hz, 2H, NCH_a), 4.44 (dd, J=14.5, 3.0 Hz, 2H, NCH_b), 4.30 (q-like, J=3.3, 2.8 Hz, 2H, 2H-4′), 3.80 (br d, J=11.9 Hz, 2H, 2H-5′a), 3.70 (dm, J=11.9 Hz, 2H, 2H-5′b), 3.18 (br s, 2H, 2OH), 1.57 (s, 6H, $2CH_3$), 1.36 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 162.7 (2C-4), 151.0 (2C-2), 141.4 (2C-6), 127.9 (2CH=), 114.6 ($2C(CH_3)_2$), 102.3 (2C-5), 97.3 (2C-1′), 88.0 (2C-4′), 84.6 (2C-2′), 80.9 (2C-3′), 63.1 (2C-5′), 42.2 ($2NCH_2$), 27.6 ($2CH_3$), 25.7 ($2CH_3$).

*4.2.6. 1,4-Bis-(5′-O-allyluridin-3-yl)but-2-ene (**13**)*

To a solution of **21** (192 mg, 0.31 mmol) in dry THF (12 mL), were added KOH (101 mg, 1.8 mmol), 18-crown-6 (8 mg, 0.03 mmol), and allyl bromide (0.16 mL, 1.86 mmol). The reaction mixture was stirred for 6 h at rt. Then, the solvent was removed under reduced pressure and the residue was partitioned between H_2O and CH_2Cl_2. The organic phase was separated and the aqueous solution extracted with CH_2Cl_2. The combined organic solutions were washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to furnish **13** (107 mg, 50%) as a colorless oil and as a mixture of *Z* and *E* isomers with one major isomer. *Major isomer*: R_f 0.6 (MeOH/CH_2Cl_2, 2.5:97.5); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, J=8.0 Hz, 2H, H-6), 5.92–5.80 (m, 4H, 4=CH–), 5.87 (s, 2H, 2H-1′), 5.68 (d, J=8.0, 2H, 2H-5), 5.22 (m, 4H, $2CH_2$=), 4.80 (br s, 4H, 2H-2′, 2H-3′), 4.49 (m, 4H, $2NCH_2$), 4.43 (br s, 2H, 2H-4′), 4.0 (d, J=5.2 Hz, 4H, $2OCH_2CH$=), 3.70 (d, J=10.5 Hz, 2H, 2H-5′a), 3.62 (br d, J=10.5 Hz, 2H, 2H-5′b), 1.58 (s, 6H, $2CH_3$), 1.37 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2 (2C-4), 150.5 (2C-2), 138.7 (2C-6), 133.7 (OCH_2CH=$CHCH_2O$), 127.6 (NCH_2CH=$CHCH_2N$), 117.9 ($2CH_2$=), 114.0 ($2C(CH_3)_2$), 101.4 (2C-5), 94 (2C-1′), 85.9 and 85.7 (2C-2′, 2C-4′), 81.0 (2C-3′), 72.4 ($2OCH_2CH$=), 70.1 (2C-5′), 41.9 ($2NCH_2CH$=), 27.2 ($2CH_3$), 25.3 ($2CH_3$). HRMS (ESI) $[M+Na]^+$ calcd for $C_{34}H_{44}N_4O_{12}Na$: 723.2853, found 723.2846.

*4.2.7. Protected unsaturated symmetrical cyclic dinucleoside **16***

Grubbs second catalyst **6** (18 mg, 15 mol %) was added to a solution of **13** (100 mg, 0.14 mmol) in CH_2Cl_2 (180 mL), and the mixture was stirred at 40 °C overnight. The solvent was removed in vacuo and the residue was purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to give **16** (48 mg, 50%) as a mixture of *Z* and *E* isomers with one major isomer. *Major isomer*: R_f 0.5 (MeOH/CH_2Cl_2, 2:98); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J=8.1 Hz, 2H, 2H-6), 5.71 and 5.63 (2m, 4H, 2*H*C=C*H*–), 5.66 (d, J=8.1 Hz, 2H, 2H-5), 5.48 (d, J=1.6 Hz, 2H, 2H-1′), 4.95 (dd, J=6.0, 1.6 Hz, 2H, 2H-2′), 4.81 (dd, J=6.0, 2.7 Hz, 2H, 2H-3′), 4.55–4.33 (m, 6H, 2H-4′, $2NCH_2$), 3.94–3.83 (m, 4H, $2OCH_2CH$=), 3.62 (dd, J=10.2, 5.3 Hz, 2H, 2H-5′a), 3.57 (dd, J=10.2, 4.5 Hz, 2H, 2H-5′b), 1.53 (s, 6H, $2CH_3$), 1.33 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0 (2C-4), 150.7 (2C-2), 141.0 (2C-6), 129.0 and 126.9 (OCH_2CH=$CHCH_2O$ and NCH_2CH=$CHCH_2N$), 114.0 ($2C(CH_3)_2$), 101.5 (2C-5), 98.4 (2C-1′), 87.2 (2C-4′), 86.0 (2C-2′), 82.6 (2C-3′), 71.7 ($2OCH_2CH$=), 70.9 (2C-5′), 42.4 ($2NCH_2CH$=), 27.5 ($2CH_3$), 25.6 ($2CH_3$). HRMS (ESI) $[M+Na]^+$ calcd for $C_{32}H_{40}N_4O_{12}Na$: 695.2540, found 695.2563.

*4.2.8. Protected saturated symmetrical cyclic dinucleoside **22***

Dimer **16** (60 mg, 0.09 mmol) and 10% Pd/C (9 mg) in MeOH (5 mL), were stirred under a hydrogen atmosphere overnight. The mixture was filtered, the filtrate concentrated in vacuo and purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to give **22** (33 mg, 55%) as a colorless oil: R_f 0.5 (MeOH/CH_2Cl_2, 2:98); $[\alpha]_D^{20}$ +8.3 (c 0.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, J=8.0 Hz, 2H, 2H-6), 5.69 (d, J=8.0 Hz, 2H, 2H-5), 5.53 (s, 2H, 2H-1′), 4.93 (d, J=6 Hz, 2H, 2H-2′), 4.82 (m, 2H, 2H-3′), 4.44 (br s, 2H, 2H-4′), 3.91 (br s, 4H, $2NCH_2$), 3.63–3.53 (m, 4H, 4H-5′), 3.38 (br s, 4H, $2OCH_2$), 1.69–1.50 (m, 8H, $4CH_2$), 1.58 (s, 6H, $2CH_3$), 1.37 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 162.8 (2C-4), 150.8 (2C-2), 140.1 (2C-6), 113.5 ($2C(CH_3)_2$), 100.9 (2C-5), 97.4 (2C-1′), 87.8 (2C-4′), 86.1 (2C-2′), 81.9

(2C-3′), 71.7 (2OCH_2CH_2), 71.0 (2C-5′), 41.0 (2NCH_2CH_2), 27.1 (2CH_3), 26.4 (2CH_2), 25.3 (2CH_3), 24.8 (2CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{32}H_{44}N_4O_{12}Na$: 699.2853, found 699.2859.

*4.2.9. Unprotected saturated symmetrical cyclic dinucleoside **23***

A solution of **22** (81 mg, 0.12 mmol) in $CH_3COOH–H_2O$ (6 mL, v/v, 7:3) was stirred for 4 h with a bath at 110 °C. After cooling, the mixture was concentrated in vacuo, coevaporated twice with toluene and purified by flash column chromatography (MeOH/CH_2Cl_2, 3:97) to give **23** (53 mg, 74%) as a colorless oil; $[\alpha]_D^{20}$ +3.3 (*c* 0.3 in MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, *J*=8.0 Hz, 2H, 2H-6), 6.22 (d, *J*=6.0 Hz, 2H, 2H-1′), 5.92 (br s, 2OH), 5.51 (d, *J*=8.0 Hz, 2H, 2H-5), 4.33 (m, 4H, 2H-3′, 2H-4′), 4.27 (m, 2H, 2H-2′), 4.10 (m, 2H, 2NCHa), 3.70 (m, 6H, 2NCHb, 4H-5′), 3.59 (m, 2H, 2OCHa), 3.53 (m, 2H, 2OCHb), 3.26 (br s, 2OH), 1.92 (m, 4H, 2CH_2), 1.60 (m, 4H, 2CH_2); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 162.3 (2C-4), 151.4 (2C-2), 140.3 (2C-6), 100.5 (2C-5), 89.7 (2C-1′), 84.4 (2C-4′), 76.4 (2C-2′), 73.1 (2C-3′), 72.0 and 72.1 (2OCH_2CH_2 and 2C-5′), 42.5 (2NCH_2CH_2), 27.5 (2CH_2), 23.1 (2CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{26}H_{36}N_4O_{12}Na$: 619.2227, found 619.2205.

*4.2.10. Protected saturated disymmetrical cyclic dinucleoside **24***

Dimer **17** (101 mg, 0.15 mmol) and 10% Pd/C (9 mg) in MeOH (5 mL) were stirred under a hydrogen atmosphere overnight. The mixture was filtered, the filtrate concentrated in vacuo and purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to give **24** (67 mg, 67%) as a colorless oil. $[\alpha]_D^{20}$ −24.1 (*c* 0.5 in $CHCl_3$); R_f 0.5 (MeOH/CH_2Cl_2, 2:98); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, *J*=8.1 Hz, 2H, 2H-6), 5.72 (d, *J*=8.1 Hz, 2H, 2H-5), 5.62 (s, 2H, 2H-1′), 4.84 (m, 4H, 2H-2′, 2H-3′), 4.44 (br s, 2H, 2H-4′), 3.87 (m, 4H, 2NCH_2), 3.71 (dd, *J*=10.7, 2.2 Hz, 2H, 2H-5′a), 3.53 (dd, *J*=10.7, 3.3 Hz, 2H, 2H-5′b), 3.44 (m, 4H, 2OCH_2), 1.50 (m, 8H, 4CH_2), 1.53 (s, 6H, 2CH_3), 1.37 (s, 6H, 2CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 163.0 (2C-4), 151.0 (2C-2), 139.4 (2C-6), 113.7 (2*C*(CH_3)$_2$), 101.1 (2C-5), 96.7 (2C-1′), 87.6 (2C-4′), 86.7 (2C-2′), 81.9 (2C-3′), 71.7 and 71.5 (OCH_2CH_2 and 2C-5′), 40.6 (2NCH_2), 27.6 (2CH_3), 27.2 (CH_2), 25.8 (2CH_3), 24.7 (CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{32}H_{44}N_4O_{12}Na$: 699.2853, found 699.2849.

*4.2.11. Unprotected saturated disymmetrical cyclic dinucleoside **25***

A solution of dimer **24** (20 mg, 0.029 mmol) in $CH_3COOH–H_2O$ (3 mL, v/v, 7:3) was stirred for 4 h with a bath at 110 °C. The mixture was then concentrated in vacuo, coevaporated twice with toluene and purified by flash column chromatography (MeOH/CH_2Cl_2, 3:97) to give **25** (15 mg, 85%). $[\alpha]_D^{20}$ −187.5 (*c* 0.5 in $CHCl_3$); R_f 0.3 (MeOH/CH_2Cl_2, 2:98); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, *J*=8.1 Hz, 2H, 2H-6), 5.82 (d, *J*=5.3 Hz, 2H, 2H-1′), 5.75 (d, *J*=8.1 Hz, 2H, 2H-5), 5.06 (OH), 4.36 (br s, 2H, 2H-4′), 4.30 (dd, *J*=5.1, 1.2 Hz, 2H, 2H-3′), 4.24 (t-like, *J*=5.3, 5.1 Hz, 2H, 2H-2′), 4.02 (m, 2H, 2NC*H*aHb), 3.8 (m, 2H, NCHa*H*b), 3.71 (dd, *J*=10.6, 1.9 Hz, 2H, 2H-5′a), 3.58 (d, *J*=10.6 Hz, 2H, 2H-5′b), 3.50 (m, 2H, 2OC*H*aHb), 3.42 (m, 2H, 2OCHa*H*b), 1.62 (m, 8H, 4CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9 (2C-4), 152.3 (2C-2), 138.0 (2C-6), 102.0 (2C-5), 92.5 (2C-1′), 86.6 (2C-4′), 77.6 (2C-2′), 73.2 (2C-3′), 71.2 and 71.0 (OCH_2CH_2 and 2C-5′), 40.8 (2NCH_2CH_2), 28.3 (CH_2), 25.9 (CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{26}H_{36}N_4O_{12}Na$: 619.2227, found 619.2213.

4.3. Synthesis of cyclonucleosides 10b and 10c

*4.3.1. 5′-O-Allyl-2′,3′-O-isopropylideneuridine (**26**)*

To a solution of 2′,3′-*O*-isopropylideneuridine (**11**) (100 mg, 0.35 mmol) in dry DMF (3 mL) was added NaH (0.40 mmol) in an open reaction vessel. The solution was stirred under microwave activation for 3 min at 40 °C (monitored by IR sensor) in a CEM Discover instrument with a 100-W microwave power. Then, allyl bromide (0.038 mL, 0.40 mmol) was added and the reaction mixture was irradiated for an additional 5 min with the same conditions. After addition of MeOH (3 mL) and concentration in vacuo, the residue was purified by flash column chromatography (MeOH/CH_2Cl_2 1:99) to give **26** (86 mg, 76%) as a colorless oil: R_f 0.3 (MeOH/CH_2Cl_2, 2:98); $[\alpha]_D^{20}$ −30.3 (*c* 0.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (br s, NH), 7.56 (d, *J*=8.1 Hz, 1H, H-6), 5.85 (d, *J*=2.2 Hz, 1H, H-1′), 5.96–5.79 (m, 1H, OCH_2C*H*=), 5.62 (d, *J*=8.1 Hz, 1H, H-5), 5.22–5.13 (m, 2H, CH_2=), 4.76 (dd, *J*=6.2, 2.8 Hz, 1H, H-3′), 4.72 (dd, *J*=6.2, 2.2 Hz, 1H, H-2′), 4.33 (m, 1H, H-4′), 3.95 (d, *J*=5.4 Hz, 2H, OC*H*$_2$CH=), 3.64 (dd, *J*=10.5, 2.7 Hz, 1H, H-5′), 3.57 (dd, *J*=10.5, 3.6 Hz, 1H, H-5′), 1.52 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8 (C-4), 150.5 (C-2), 141.7 (C-6), 134.2 (OCH_2*C*H=), 118.4 (CH_2=), 114.6 (*C*(CH_3)$_2$), 102.5 (C-5), 93.2 (C-1′), 86.0 (C-4′), 85.5 (C-2′), 81.3 (C-3′), 72.8 (OCH_2CH=), 70.5 (C-5′), 27.4 (CH_3), 25.7 (CH_3).

*4.3.2. 5′-O-Allyl-3-(but-3-enyl)-2′,3′-O-isopropylidene uridine (**27**)*

To a stirred solution of **26** (500 mg, 1.55 mmol) in DMSO–toluene (5 mL, v/v, 1:4) were added KOH (520 mg, 9.3 mmol) and 4-bromobut-1-ene (0.95 mL, 9.3 mmol), and the reaction mixture was stirred overnight at rt. A saturated aqueous solution of NH_4Cl was then added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to furnish **27** (440 mg, 75%) as a colorless oil: R_f 0.6 (MeOH/CH_2Cl_2, 2:98); $[\alpha]_D^{20}$ −21.2 (*c* 0.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, *J*=8.0 Hz, 1H, H-6), 5.88 (s, 1H, H-1′), 5.91–5.74 (m, 2H, 2CH_2C*H*=CH_2), 5.70 (d, *J*=8.0 Hz, 1H, H-5), 5.23 (m, 2H, CH_2=CHCH_2O), 5.04 (m, 2H, CH_2=CH), 4.81 (d, *J*=6.2 Hz, 1H, H-3′), 4.76 (d, *J*=6.2 Hz, 1H, H-2′), 4.44 (br s, 1H, H-4′), 4.00 (m, 4H, NCH_2, =CHCH_2O), 3.70 (br d, *J*=10.5 Hz, 1H, H-5′), 3.62 (dd, *J*=10.5, 3 Hz, 1H, H-5′), 2.39 (q, *J*=7.0 Hz, CH_2), 1.59 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7 (C-4), 150.8 (C-2), 138.6 (C-6), 134.8 and 133.7 (2*C*H=CH_2), 117.9 and 116.9 (2CH_2=), 113.9 (*C*(CH_3)$_2$), 101.3 (C-5), 94.1 (C-1′), 85.8 and 85.7 (C-4′ and C-2′), 81.1 (C-3′), 72.4 (OCH_2CH=), 70.2 (C-5′), 40.2 (NCH_2), 27.2 (CH_3), 25.3 (CH_3). HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{26}N_2O_6Na$: 401.1689, found 401.1688.

*4.3.3. 5′-O-Allyl-3-N-(pent-4-enyl)-2′,3′-O-isopropylidene-uridine (**28**)*

To a stirred solution of **26** (500 mg, 1.55 mmol) in DMSO–toluene (5 mL, v/v, 1:4) were added KOH (520 mg, 9.3 mmol) and 5-bromopent-1-ene (1.1 mL, 9.3 mmol), and the reaction mixture was stirred overnight at rt. A saturated aqueous solution of NH_4Cl was then added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (MeOH/CH_2Cl_2, 0.5:99.5) to furnish **28** (412 mg, 68%) as a colorless oil: R_f 0.4 (MeOH/CH_2Cl_2, 2:98); $[\alpha]_D^{20}$ −17.5 (*c* 0.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, *J*=8.0 Hz, 1H, H-6), 5.89 (s, 1H, H-1′), 5.82 (m, 2H, 2C*H*=CH_2), 5.70 (d, *J*=8.0 Hz, 1H, H-5), 5.20 (m, 2H, CH_2=CHCH_2O), 5.05 (br d, *J*=17.0 Hz, 1H, CH_2=CH), 4.97 (br d, *J*=9.9 Hz, 1H, CH_2=CH), 4.76 (m, 2H, H-2′ and H-3′), 4.42 (br s, 1H, H-4′), 3.97 (d, *J*=5.5 Hz, 2H, =CHCH_2O), 3.90 (t, *J*=7.0 Hz, 2H, NCH_2), 3.71 (br d, *J*=10.5 Hz, 1H, H-5′), 3.62 (dd, *J*=10.5, 3.1 Hz, 1H, H-5′), 2.08 (q, *J*=7.0 Hz, CH_2), 1.72 (quint, *J*=7.0 Hz, CH_2), 1.57 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1 (C-4), 151.2 (C-2), 138.9 (C-6), 138.0 and 134.0 (2*C*H=CH_2), 118.1 and 115.2 (2CH_2=CH), 114.3 (*C*(CH_3)$_2$), 101.8 (C-5), 94.4 (C-1′), 86.1 and 85.9 (C-2′ and C-4′), 81.5 (C-3′), 72.8 (OCH_2CH=), 70.6 (C-5′), 41.1 (NCH_2), 31.5 (CH_2), 27.6 (CH_3), 26.9 (CH_2), 25.7 (CH_3). HRMS (ESI) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_6Na$: 415.1845, found 415.1852.

*4.3.4. 2′,3′-O-Isopropylidene-3,5′-O-(pent-2-eno)uridine (**29**)*

To a solution of **27** (220 mg, 0.58 mmol) in CH_2Cl_2 (320 mL) was added Grubbs second catalyst **6** (51 mg, 10 mol%). The resulting

mixture was stirred at 40 °C, under a nitrogen atmosphere, for 12 h. The reaction mixture was filtered through a short pad of silica gel ($MeOH/CH_2Cl_2$, 0.5:99.5) yielding the crude product **29** (151 mg, 74%) as a mixture of *Z* and *E* stereoisomers. *Major stereoisomer*: R_f 0.5 ($MeOH/CH_2Cl_2$, 2:98); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, J=7.8 Hz, 1H, H-6), 5.76 (d, J=7.8 Hz, 1H, H-5), 5.72 (ddd, J=15.2, 9.8, 5.2 Hz, 1H, CH_2CH_2CH=), 5.50 (d, J=6.2 Hz, 1H, H-2′), 5.40 (s, 1H, H-1′), 5.28 (ddd, J=15.2, 10.2, 4.6 Hz, 1H, OCH_2CH=), 4.69 (dd, J=6.2, 2.0 Hz, 1H, H-3′), 4.44 (dt, J=11.0, 2–3.2 Hz, 1H, H-4′), 4.16–4.03 (m, 3H, $2NCH_2$, 1=$CHCH_2O$), 3.89 (dd, J=11, 10.1 Hz, 1H, H-5′), 3.47 (dd, J=12.3, 10.2 Hz, 1H, 1=CH–CH_2O), 3.41 (dd, J=10.1, 3.2 Hz, 1H, H-5′), 2.38–2.19 (m, 2H, CH_2), 1.54 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7 (C-4), 151.8 (C-2), 143.7 (C-6), 136.0 (=$CHCH_2CH_2$), 128.5 (OCH_2CH=), 113.5 ($C(CH_3)_2$), 102.7 (C-5), 102.1 (C-1′), 88.3 (C-4′), 84.5 (C-2′), 83.4 (C-3′), 70.6 (OCH_2CH=), 67.7 (C-5′), 40.1 (NCH_2), 31.4 (CH_2), 26.9 (CH_3), 25.3 (CH_3). HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{22}N_2O_6Na$: 373.1376, found: 373.1366.

4.3.5. 2′,3′-O-Isopropylidene-3,5′-O-(hex-2-eno)uridine (**30**)

To a solution of **28** (140 mg, 0.35 mmol) in CH_2Cl_2 (180 mL) was added Grubbs second catalyst **6** (30 mg, 10 mol %). The resulting mixture was stirred at 40 °C, under a nitrogen atmosphere, for 12 h. The reaction mixture was filtered through a short pad of silica gel ($MeOH/CH_2Cl_2$, 0.5:99.5) to yield the crude product **30** (76 mg, 59%) as a mixture of *Z* and *E* stereoisomers. *Major stereoisomer*: R_f 0.5 ($MeOH/CH_2Cl_2$, 2:98); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, J=8.0 Hz, 1H, H-6), 5.65 (d, J=8.0 Hz, 1H, H-5), 5.51 (s, 1H, H-1′), 5.36 (m, 3H, H-2′, CH=CH), 4.76 (d, J=5.2 Hz, 1H, H-3′), 4.61 (br s, 1H, H-4′), 4.35 (ddd, J=13.2, 10.0, 4.4 Hz, 1H, $1NCH_2$), 3.88 (m, 2H, 1=$CHCH_2O$, $1NCH_2$), 3.74 (dd, J=10.7, 3.5 Hz, 1H, H-5′), 3.54 (br d, J=12.5 Hz, 1H, 1=$CHCH_2O$), 3.44 (dd, J=10.7, 1.3 Hz, 1H, H-5′), 2.3–1.6 (m, 4H, $2CH_2$), 1.57 (s, 3H, CH_3), 1.41 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.7 (C-4), 151.2 (C-2), 142.9 (C-6), 132.7 and 125.3 (CH=CH), 113.1 ($C(CH_3)_2$), 100.7 (C-5), 98.6 (C-1′), 89.9 (C-4′), 86.1 (C-2′), 82.5 (C-3′), 70.86 and 70.81 (OCH_2CH= and C-5′), 40.0 (NCH_2), 29.6 (CH_2), 27.5 (CH_3), 24.9 (CH_3), 23.7 (CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{18}H_{24}N_2O_6Na$: 387.1532, found: 387.1522.

4.3.6. 2′,3′-O-Isopropylidene-3,5′-O-pentanouridine (**31**)

Compound **29** (130 mg, 0.37 mmol) and PtO_2 (8 mg, 0.035 mmol) in EtOAc (5 mL) were stirred under a hydrogen atmosphere for 7 h at rt. The mixture was filtered, then concentrated in vacuo and purified by flash column chromatography ($MeOH/CH_2Cl_2$, 0.5:99.5) to give **31** (105 mg, 80%) as a white solid: mp 113–114 °C; R_f 0.4 (EtOAc/petroleum ether, 50:50); $[\alpha]_D^{20}$ +73.6 (*c* 0.2 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J=7.9 Hz, 1H, H-6), 5.70 (d, J=7.9 Hz, 1H, H-5), 5.57 (d, J=6.0 Hz, 1H, H-2′), 5.37 (s, 1H, H-1′), 4.84 (dd, J=6.0, 2.0 Hz, 1H, H-3′), 4.41 (m, 1H, H-4′), 4.26 (td, J=13.0, 3.2 Hz, 1H, $1NCH_2$), 3.97 (m, 2H, 1H-5′, $1NCH_2$), 3.47 (m, 2H, OCH_2CH_2), 3.36 (dd, J=9.5, 3.7 Hz, 1H, H-5′), 2.05 (m, 2H, CH_2), 1.56 (s, 3H, CH_3), 1.5–1.2 (m, 4H, $2CH_2$), 1.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4 (C-4), 151.2 (C-2), 142.8 (C-6), 113.3 ($C(CH_3)_2$), 102.0 (C-5), 101.6 (C-1′), 86.8 (C-4′), 83.8 (C-2′), 82.9 (C-3′), 69.9 (OCH_2CH_2), 67.7 (C-5′), 38.3 (NCH_2), 26.9 (CH_3), 26.2 (CH_2), 25.5 (CH_2), 25.1 (CH_3), 20.6 (CH_2); HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{24}N_2O_6Na$: 375.1532, found: 375.1527.

4.3.7. 2′,3′-O-Isopropylidene-3,5′-O-hexanouridine (**32**)

Compound **30** (140 mg, 0.38 mmol) and PtO_2 (8 mg, 0.035 mmol) in EtOAc (5 mL) were stirred under a hydrogen atmosphere for 7 h at rt. The mixture was filtered, then concentrated under reduced pressure and purified by flash column chromatography ($MeOH/CH_2Cl_2$, 0.5:99.5) to give **32** (96 mg, 68%) as a white solid: mp >180 °C; R_f 0.5 ($MeOH/CH_2Cl_2$, 2:98); $[\alpha]_D^{20}$ +55.3 (*c* 0.3 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, J=8.0 Hz, 1H, H-6), 5.68 (d, J=8.0 Hz, 1H, H-5), 5.41 (d, J=5.9 Hz, 1H, H-2′), 5.27 (s, 1H, H-1′), 5.05 (dd, J=5.9, 4.5 Hz, 1H, H-3′), 4.14 (td, J=4.5, 2.4 Hz, 1H, H-4′), 4.03 (m, 2H, NCH_2), 3.74 (dd, J=11.2, 4.5 Hz, 1H, H-5′a), 3.47 (m, 1H, $1OCH_2CH_2$), 3.46 (dd, J=11.2, 2.4 Hz, 1H, H-5′b), 3.37 (m, 1H, $1OCH_2CH_2$), 1.8–1.2 (m, 8H, $4CH_2$), 1.51 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.8 (C-4), 150.7 (C-2), 141.9 (C-6), 113.3 ($C(CH_3)_2$), 101.7 (C-5), 98.2 (C-1′), 87.2 (C-4′), 84.3 (C-2′), 80.2 (C-3′), 69.8 (OCH_2CH_2), 68.8 (C-5′), 39.9 (NCH_2), 29.1 (CH_2), 27.3 (CH_3), 26.2 (CH_2), 25.4 (CH_3), 24.9 (CH_2), 24.2 (CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{18}H_{26}N_2O_6Na$: 389.1689, found: 389.1698.

4.3.8. 3,5′-O-Pentanouridine (**10b**)

A solution of **31** (70 mg, 0.2 mmol) in $CH_3COOH–H_2O$ (3 mL, v/v, 7:3) was stirred for 4 h with a bath at 110 °C. The mixture was concentrated in vacuo, coevaporated twice with toluene and purified by flash column chromatography ($MeOH/CH_2Cl_2$, 3:97) to give **10b** (38.5 mg, 62%) as a colorless oil: R_f 0.2 ($MeOH/CH_2Cl_2$, 2.5:97.5); $[\alpha]_D^{20}$ +152.1 (*c* 0.3 in MeOH); ^1H NMR ($CD_3OD/CDCl_3$, 1:9; 300 MHz) δ 7.28 (d, J=8.0 Hz, 1H, H-6), 5.71 (d, J=8.0 Hz, 1H, H-5), 5.28 (dd, J=5.3, 2.8 Hz, 1H, H-2′), 5.22 (d, J=2.8 Hz, 1H, H-1′), 4.64 (t, J=5.3 Hz, 1H, H-3′), 4.26 (m, 1H, $1NCH_2$), 4.07 (td, J=5.3, 2.8 Hz, 1H, H-4′), 3.95 (ddd, J=13.0, 4.5, 2.8 Hz, 1H, $1NCH_2$), 3.80 (dd, J=10.5, 5.3 Hz, 1H, H-5′a), 3.51 (m, 1H, $1OCH_2CH_2$), 3.44 (dd, J=10.5, 2.8 Hz, 1H, H-5′b), 3.40 (m, 1H, $1OCH_2CH_2$), 1.98 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.29 (m, 2H, CH_2); ^{13}C NMR ($CD_3OD/CDCl_3$, 1:9; 75 MHz) δ 163.7 (C-4), 151.2 (C-2), 144.6 (C-6), 101.7 (C-5), 101.4 (C-1′), 84.8 (C-4′), 72.9 (C-2′), 71.0 (C-3′), 70.7 (C-5′), 68.1 (OCH_2CH_2), 39.1 (NCH_2), 27.9 (CH_2), 25.8 (CH_2), 21.4 (CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{20}N_2O_6Na$: 335.1219, found: 335.1223.

4.3.9. 3,5′-O-Hexanouridine (**10c**)

A solution of **32** (60 mg, 0.164 mmol) in $CH_3COOH–H_2O$ (3 mL, v/v, 7:3) was stirred for 4 h with a bath at 110 °C. The mixture was concentrated in vacuo, coevaporated twice with toluene and purified by flash column chromatography ($MeOH/CH_2Cl_2$) to give **10c** (29.6 mg, 55%) as a colorless oil: R_f 0.3 ($MeOH/CH_2Cl_2$, 2.5:97.5); $[\alpha]_D^{20}$ +109.7 (*c* 0.4 in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, J=8.0 Hz, 1H, H-6), 5.73 (d, J=8.0 Hz, 1H, H-5), 5.21 (d, J=2.1 Hz, 1H, H-1′), 4.93 (q like, J=5.3, 4.3 Hz, 1H, H-3′), 4.86 (m, 1H, H-2′), 4.19–4.0 (m, 3H, H-4′, NCH_2), 3.70 (m, 2H, 1H-5′, 1OH), 3.55 (dd, J=11.9, 1.9 Hz, 1H, 1H-5′), 3.42 (m, 2H, OCH_2CH_2), 3.20 (d, J=4.3 Hz, 1H, OH), 2.0–1.2 (m, 8H, $4CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9 (C-4), 151.4 (C-2), 141.5 (C-6), 101.8 (C-5), 98.5 (C-1′), 84.2 (C-4′), 74.6 (C-2′), 71.0 (OCH_2CH_2), 70.5 (C-3′), 68.8 (C-5′), 39.8 (NCH_2), 29.8 (CH_2), 25.9 (CH_2), 25.1 (CH_2), 24.8 (CH_2). HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{22}N_2O_6Na$: 349.1376, found: 349.1373.

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