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Synthesis of novel dinucleosides via tandem cross-metathesis and ring-closing metathesis

S. Zhong,[a] M. Mondon,[a] S. Pilard[b] and C. Len[a,*]

[a]*Synthèse et Réactivité des Substances Naturelles, UMR 6514 CNRS, FR 2703, Université de Poitiers, 40 Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*
[b]*Plate-Forme Analytique, 33 rue Saint Leu, F-80039 Amiens, France*

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Abstract—Two novel cyclic dinucleosides having two butylene linkers between the 5′-OH and N-3 positions (thereby generating a 24-membered ring) were synthesized from uridine via tandem cross-metathesis and ring-closing metathesis. Selective synthesis of one dinucleoside with a link between the two N-3 atoms and a link between the two 5′-OH groups was achieved.
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The biochemical importance of the equilibrium conformation of nucleosides[1] (involving N-type and S-type, *anti* and *syn*, +sc, ap and −sc conformations) has motivated the synthesis of conformationally restricted nucleosides and nucleotides.[2] These novel nucleoside and/or nucleotide analogues can be classified in to three families: bicyclonucleosides (e.g., **1**) obtained by bridging two atoms of the furanose moiety with an alkyl chain or analogous ether; cyclic phosphorus esters (e.g., **2**) in which a similar bridge is formed between the phosphate group and the furanose moiety or the nucleobase; cyclonucleosides (e.g., **3**) in which the bridge is formed between the furanose moiety and the nucleobase (Fig. 1). These types of conformationally restricted nucleosides have been intensively investigated as building blocks in nucleic acid analogues, for the study of enzymes and receptors with nucleoside or nucleotide substrates[3] and/or as potential antiviral agents.[3a,c,d,4] Several reports extend this idea to different di- and trinucleotides with large cyclic structures.[2e,f,5] Metathesis[6] is an extremely useful method in organic chemistry due to the development of efficient and selective catalysts such as the ruthenium carbenes **4** (Grubbs first generation catalyst)[7] and **5** (Grubbs second generation catalyst),[8] which offer a good compromise between efficiency and tolerance to functional groups (Fig. 1). The use of metathesis reactions in the nucleoside field[9–11] has been developed over the last decade and we now report a novel application of cross-metathesis (CM)[6a,b] and ring-closing metathesis (RCM)[6c,d] to the formation of cyclic dinucleosides **6** and **7** in which the conformation is constrained by being part of a 24-membered ring. Compounds **6** and **7** having no hydrogen bonding differ from the regular conformational states of double-stranded DNA and RNA molecules and could adopt biologically disparate structures such as bulges, hairpin loops, and U-turns.

Starting from uridine (**8**) (Scheme 1), selective N-allylation was performed with K_2CO_3 and allyl bromide, in

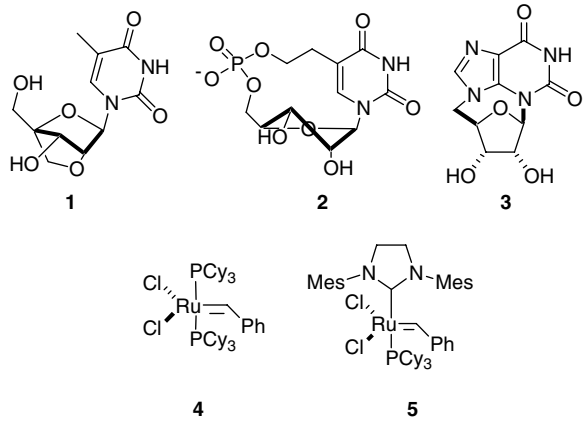

Figure 1. Restricted conformational nucleoside analogues **1**–**3** and Grubbs catalysts **4** and **5**.

* Corresponding author. Tel.: +33 5 49 36 63 89; fax: +33 5 49 45 35; e-mail: christophe.len@univ-poitiers.fr

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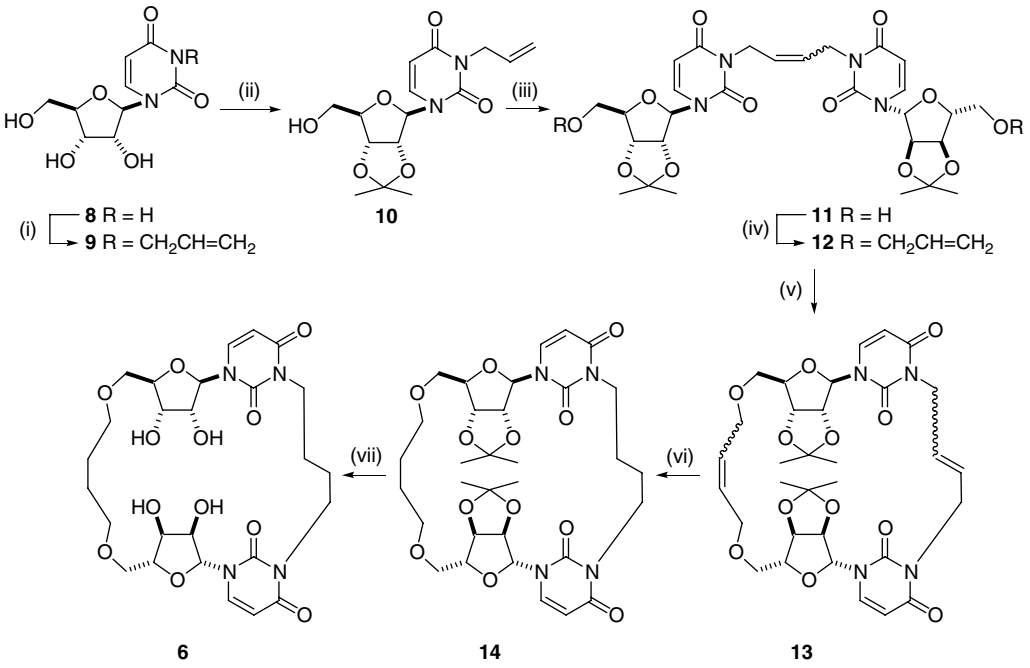
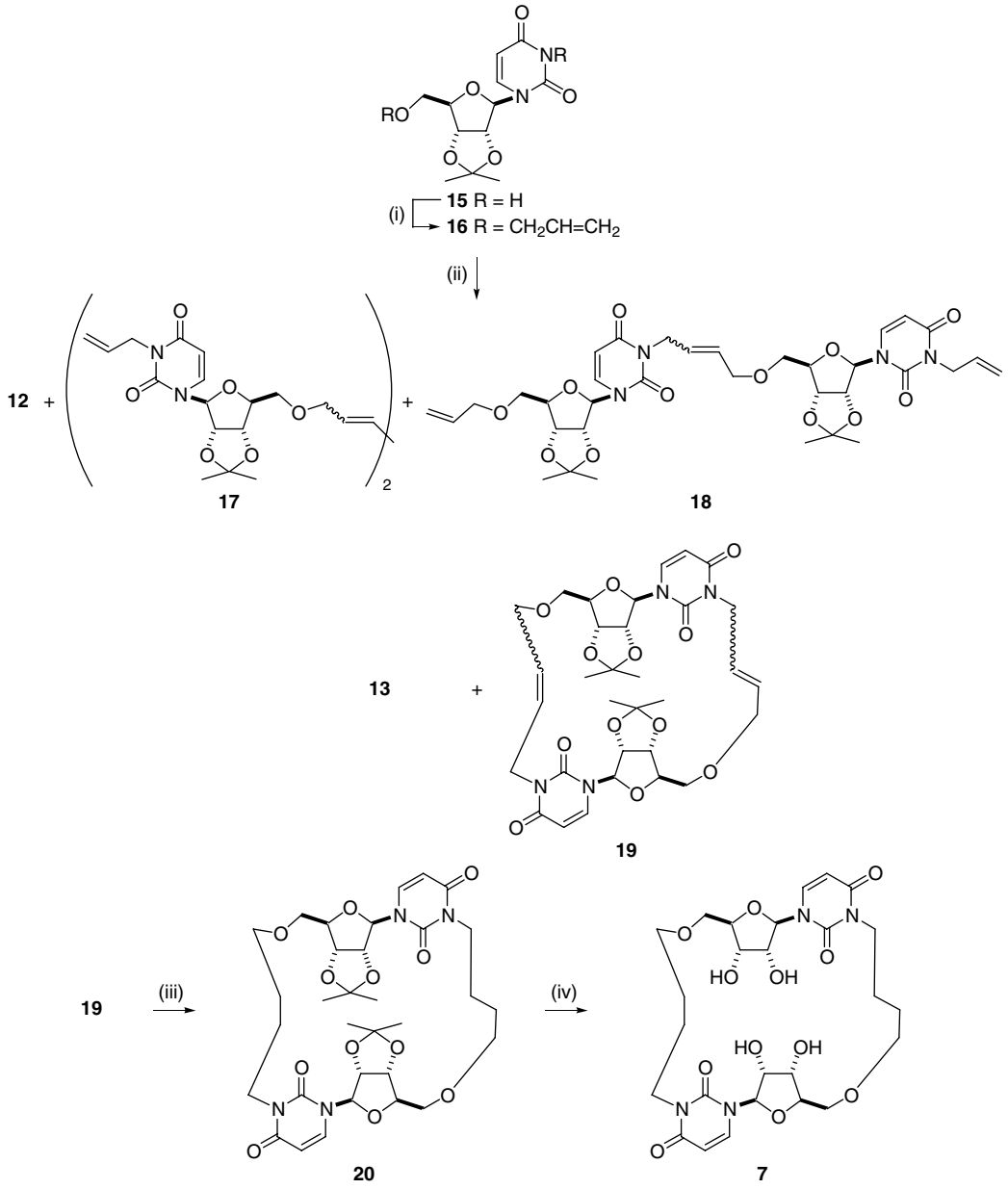


Scheme 1. Reagents and conditions: (i) K_2CO_3, $CH_2{=}CHCH_2Br$, DMF, acetone, 60 °C, 4 h, 82%; (ii) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, acetone, rt, 4 d, 90% ; (iii) 10 mol % **4**, CH_2Cl_2, 40 °C, 12 h, 61% ; (iv) KOH, 18-crown-6, $CH_2{=}CHCH_2Br$, THF, rt, 6 h, 50% ; (v) 10 mol % **5**, CH_2Cl_2, 40 °C, 12 h, 50% ; (vi) H_2, Pd/C, MeOH, rt, 12 h, 55%; (vii) AcOH, H_2O, 90 °C, 5 h, 50%.

DMF and acetone at 60 °C, to produce alkene **9**[12] in 82% yield. Protection of the ribose ring in **9** was realized by acetonide formation using 2,2-dimethoxypropane with PTSA as catalyst to afford compound **10** in 90% yield. This key alkene was subjected to CM in dichloromethane at 40 °C, using the ruthenium carbene **4** as catalyst,[7] to afford the linear dimer **11** in 61% yield as a mixture of two isomers *E* and *Z* in a 9:1 ratio. A similar result was found using catalyst **5**.[8] MS and NMR spectra confirmed the expected loss of ethylene and the loss of the terminal double bond by the disappearance of the signal around $\delta = 5.2$ ppm. After classical O-allylation[13] of both 5′-hydroxyl groups, triene **12** was subjected to an RCM reaction in dichloromethane with catalyst **5** at 40 °C to give compound **13** as a mixture of geometric isomers in 50% yield. 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. The ring size is 24 using the shortest route and 30 using the longest route through the nucleoside moieties. Reduction of diene **13** by hydrogenation using Pd/C in methanol gave only one species, dimer **14**, in 55% yield. Removal of the two ribose protecting groups in compound **14** by hydrolysis in acetic acid produced the desired free cyclic dinucleoside **6**[14] in 50% yield. This strategy, shown in Scheme 1, results in the synthesis of a cyclic dinucleoside having exclusively a tail-to-tail (i.e., base-to-base) connection.

In order to prepare the cyclic dinucleoside **7**, a different strategy was developed. Starting from acetonide **15**, N-3- and O-5′ bisallylation were realized with KOH, allyl bromide and 18-crown-6, in THF at rt, giving the key diene **16** in 88% yield. This diene was subjected to a metathesis reaction using catalyst **5** in dichloromethane at 40 °C. Under these conditions tandem CM and RCM reactions can occur, leading first to dimerization (head-to-tail, head-to-head or tail-to-tail) followed by ring closure. The crude product was separated by flash chromatography into two mixtures: (i) linear dimer **18** with traces of compounds **12** and **17** in 22% yield; (ii) cyclic dimer **19** with traces of compound **13** in 28% yield (Scheme 2). The identity of these compounds was determined by NMR and LC/MS. It was notable that this second strategy afforded dinucleosides **18** and **19** as the major products, the result of head-to-tail metathesis suggesting that homodimerization is slower than heterodimerization. The use of catalyst **4** at 40 °C gave a mixture of dimers **12**, **17** and **18** in 40% yield and a mixture of dimers **13** and **19** in 20% yield. Mass spectroscopy of both the mixture of linear compounds **12**, **17** and **18** and the mixture of cyclic compounds **13** and **19** indicated the expected loss of one ethylene and two ethylenes, respectively. NMR spectroscopy of compounds **13** and **19** indicated the complete loss of terminal double bond by the disappearance of the signal around $\delta = 5.2$ ppm. After purification by flash chromatography, compound **19** was subjected to hydrogenation followed by deprotection to furnish the target cyclic dinucleoside **7**[15] (57% over two steps). Alkene isomerization[16] has been observed during different CM and RCM reactions but that complication was not found in the present work (Schemes 1 and 2). All the dinucleosides except the linear dimer **18** showed symmetrical structures as determined by ^1H and ^{13}C NMR study. It was notable that, for compound **18**, two sets of signals were observed for the H_5 and H_6 protons.[17]



Scheme 2. Reagents and conditions: (i) KOH, 18-crown-6, $CH_2{=}CHCH_2Br$, THF, rt, 3 h, 88% ; (ii) 10 mol % **5**, CH_2Cl_2, 40 °C, 12 h ; (iii) H_2, Pd/C, MeOH, rt, 12 h, 67%; (iv) AcOH, H_2O, 92 °C, 4 h, 85%.

In summary, we have described a short simple method for the synthesis of conformationally restricted cyclic dinucleosides incorporating a 24-membered ring using two strategies which combine sequential CM and RCM reactions. Our method can be extended to different positions of the nucleobase and the glycone moiety. Conformational analysis using molecular modeling and NMR and incorporation of compounds **6** and **7** at preselected positions in an oligonucleotide will be reported in due course.

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14. Selected physico-chemical data for compound **6**: R_f 0.36 (5% MeOH–CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.06 (d, 2H, $J = 8.0$ Hz, H_6); 6.22 (d, 2H, $J = 6.0$ Hz, $H_{1'}$); 5.92 (br s, 2H, OH); 5.51 (d, 2H, $J = 8.0$ Hz, H_5); 4.33 (m, 4H, $H_{3'}$ and $H_{4'}$), 4.27 (m, 2H, $H_{2'}$), 4.10 (m, 2H, NCH), 3.70 (m, 6H, $H_{5'a}$, and $H_{5'b}$ and NCH); 3.59 (m, 2H, OCH), 3.53 (m, 2H, OCH), 3.26 (br s, 2H, OH); 1.92 (m, 4H, NCH_2CH_2), 1.60 (m, 4H, OCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 162.3 (C_4); 151.4 (C_2); 140.3 (C_6); 100.5 (C_5); 89.7 ($C_{1'}$); 84.4 ($C_{4'}$); 76.4 ($C_{2'}$); 73.1 ($C_{3'}$); 72.0 ($C_{5'}$ and OCH_2); 42.5 (NCH_2); 27.5 (OCH_2CH_2); 23.1 (NCH_2CH_2). HRMS (ESI) ($M+Na^+$) calcd for $C_{26}H_{36}N_4O_{12}Na$: 619.2227, found 619.2205.
15. Selected physico-chemical data for compound **7**: R_f 0.20 (5% MeOH–CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.68 (d, 2H, $J = 8.1$ Hz, H_6); 5.82 (d, 2H, $J = 5.3$ Hz, $H_{1'}$); 5.75 (d, 2H, $J = 8.1$ Hz, H_5); 5.06 (br s, 2H, OH), 4.36 (br s, 2H, $H_{4'}$); 4.30 (dd, 2H, $J = 5.1$, 1.2 Hz, $H_{3'}$), 4.24 (dd, 2H, $J = 5.3$ Hz, $J = 5.1$ Hz, $H_{2'}$), 4.02 (m, 2H, NCH), 3.80 (m, 2H, NCH), 3.71 (dd, 2H, $J = 10.6$, 1.9 Hz, $H_{5'a}$); 3.58 (d, 2H, $J = 10.6$, $H_{5'b}$); 3.50 (m, 2H, OCH), 3.42 (m, 2H, OCH), 1.62 (m, 8H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 162.9 (C_4); 152.2 (C_2); 137.9 (C_6); 102.0 (C_5); 92.5 ($C_{1'}$); 86.6 ($C_{4'}$); 77.6 ($C_{2'}$); 73.4 ($C_{3'}$); 71.1 ($C_{5'}$ and OCH_2); 40.7 (NCH_2); 28.3 (OCH_2CH_2); 25.9 (NCH_2CH_2). HRMS (ESI) ($M+Na^+$) calcd for $C_{26}H_{36}N_4O_{12}Na$: 619.2227, found 619.2213.
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17. For compound **18**. H_{6a} 7.57, $J = 8.1$ Hz; H_{6b} 7.52, $J = 8.1$ Hz; H_{5a} 5.70, $J = 8.1$ Hz; H_{5b} 5.68, $J = 8.1$ Hz.