



# Synthesis of a bicyclic double-headed nucleoside



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## ABSTRACT

An attempt of preparing a carbocyclic LNA-analogue using different RCM-methods failed. However, a compound with a hemiacetal linker between the C2' and the C4'-positions was isolated and found to be a suitable substrate for making a conformationally restricted double-headed nucleoside. This contains two uracil nucleobases organized on a bicyclic skeleton and is locked in an *N*-type conformation.

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## 1. Introduction

Chemically modified nucleotide analogues are essential for the design of therapeutically active nucleic acids.<sup>1–3</sup> A large number of modifications have been prepared leading to oligonucleotides that are both physiologically stable and recognize complementary DNA and RNA with high affinity and selectivity.<sup>1–4</sup> Bicyclic nucleoside monomers, which covalently bridge the C2' with the C4'-position (Fig. 1), have gained particular interest as these are locked in the C3'-*endo* conformation and preorganised for forming thermally very strong duplexes.<sup>4–6</sup> As the first and prime example, the monomer **1** is the building block in LNA (locked nucleic acid),<sup>7–10</sup> which is now a well-established nucleic acid analogue for numerous applications.<sup>11</sup> A number of close analogues of LNA have been investigated,<sup>4–6,12</sup> for instance the 2'-amino-LNA, **2**, which has been used to introduce various groups into nucleic acids via the amino-group leading to interesting components in DNA nanotechnology.<sup>13–15</sup> Recently, carbocyclic analogues of LNA have gained some interest.<sup>4,16–21</sup> As the first of these, we introduced the monomer **3** (B=U),<sup>16</sup> and later some analogues of this,<sup>17</sup> which all contain an all-carbon C2'–C4' linker, which is one atom longer than the oxymethylene linker in LNA (**1**). The synthesis of **3** was based on ring-closing metathesis (RCM)<sup>22–24</sup> as the key step and was performed in 13 steps and 7% overall yield from uridine.<sup>16</sup> Chattopadhyaya and co-workers have later developed a general method to

carbocyclic LNA-analogues based on radical cyclizations.<sup>4</sup> Hence, a series of analogues of both **3** and of the carba-LNA monomer **4** with various substituents at the C2'–C4' linker have been obtained.<sup>4,18,19</sup> The unsubstituted nucleoside **4** (B=T) was obtained in 20 steps starting from *D*-allose.<sup>19</sup> Herein, we present our attempts of making **4** (B=U) from a shorter route based on the RCM-strategy. This was absolutely unsuccessful but led to the development of a hemiacetal bicyclic nucleoside structure **5** (in a protected form), that is, a potentially very useful precursor for other analogues, for instance for placing various entities in the DNA duplex in a similar

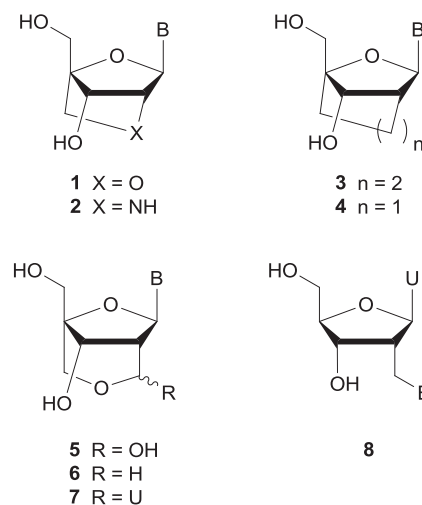


Fig. 1. Bicyclic and double-headed nucleosides. B=any nucleobase, U=uracil-1-yl.

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way as from amino-LNA. Analogues made from **5** will be substituted analogues of **6**, which was originally studied by Wang and co-workers.<sup>25</sup> We decided to use **5** as a precursor for a double-headed nucleoside **7**.

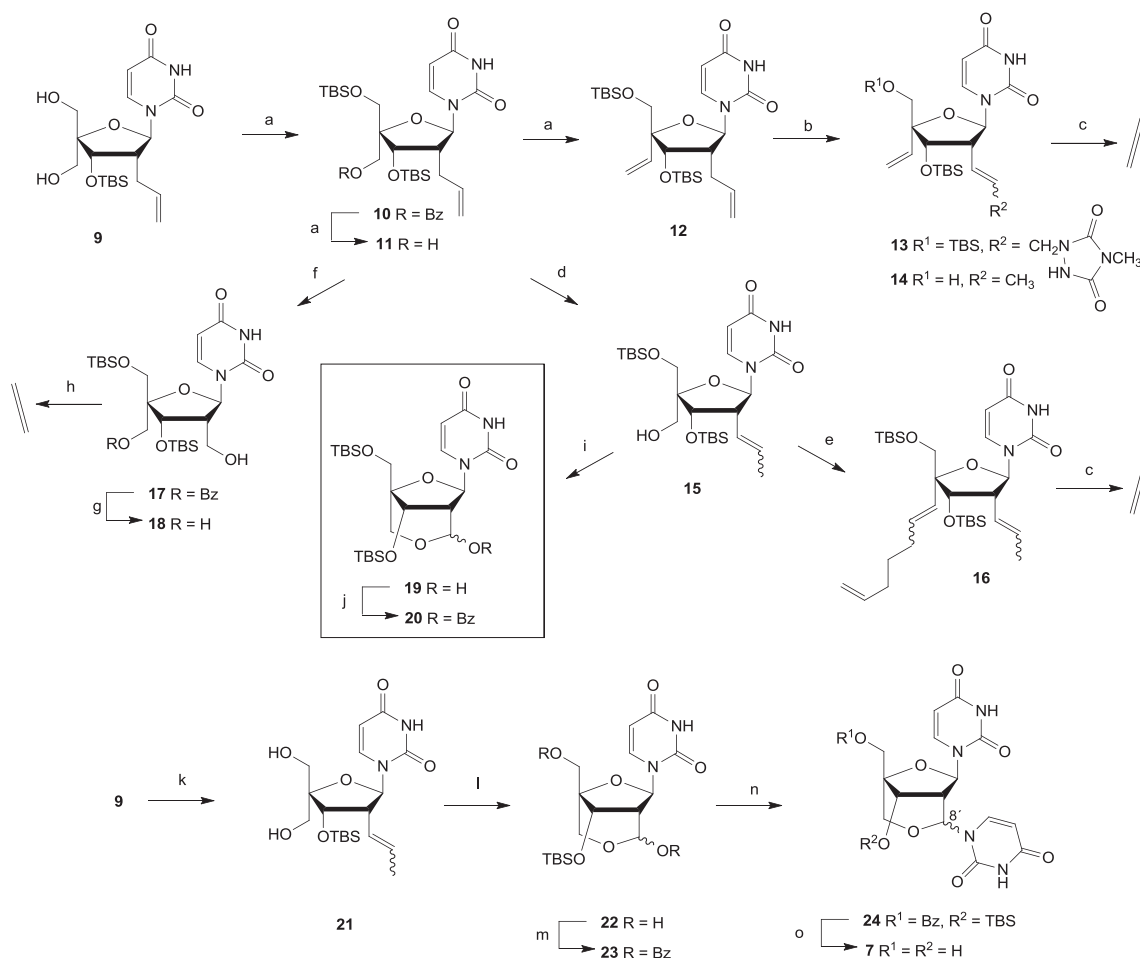
Double-headed nucleosides are defined as nucleoside analogues bearing two nucleobases. We<sup>26–33</sup> and others<sup>34–36</sup> have recently studied these as building blocks for oligonucleotides that can either target nucleic acid secondary structures, form interesting new nucleic acid motifs or potentially transfer molecular information in new ways. Recently, the double-headed nucleosides **8** (B=T/A) were synthesized and found to form base-pairs in the core of a duplex hereby extending the duplex with an additional base pair.<sup>31,32</sup> The bicyclic analogue **7** is a conformationally restricted analogue of **8**, but, whereas **8** is preferring a C2'-endo conformation,<sup>31</sup> **7** would be conformationally locked in a C3'-endo conformation. It is of great interest to study how the restriction itself and the different positioning of the additional nucleobase will influence the properties in forming artificial nucleic acid motifs and targeting other nucleic acids.

## 2. Results and discussion

### 2.1. Chemical synthesis

In the original synthesis of the bicyclic nucleoside **3**, the key intermediate **9** (Scheme 1) was first prepared from uridine in six

steps.<sup>16</sup> Benzoylation and subsequent silylation gave **10**, debenzoylation afforded **11**, and an oxidation/Wittig sequence gave the nucleoside **12**.<sup>16</sup> With its two terminal alkenes this constituted a perfect substrate for an RCM-reaction, which proceeded in 96% yield affording after hydrogenation and deprotection the bicyclic nucleoside **3**.<sup>16</sup> We envisioned that a similar strategy might also afford the one atom shorter analogue **4** even though ring-closing metathesis might have its limitation in the formation of very constrained ring-systems.<sup>24</sup> Nevertheless, it was relatively straightforward to convert **12** into a substrate for this using a modified en-reaction.<sup>37</sup> Hence, treatment of **12** with a triazolinedione afforded compound **13** as exclusively the *E*-isomer in a reasonable yield, whereas treatment with RhCl<sub>3</sub> mediated a rearrangement of the allyl group<sup>38</sup> and 5'-deprotection to afford **14** as an *E/Z*-mixture. However, neither **13** nor **14** worked as substrates for an RCM reaction using Grubbs second generation catalyst. The problem could be the problematic combination of a sterically hindered terminal alkene in the 4'-position and internal alkenes in the 2'-position. In a former study on cyclic dinucleotides, we found a dinucleotide with two 4'-C-vinyl groups to be unreactive towards RCM, whereas cyclizations between a 4'-C-vinyl group and a more reactive 5'-allyl group were possible.<sup>39</sup> Therefore, we could either introduce a terminal alkene (a vinyl group) at the 2'-C-position, where it is expected to be less sterically hindered, or attempt the so-called relay-RCM method.<sup>40,41</sup> The latter strategy was followed by first rearranging the alkene of compound **11** to give **15** (this time optimized



**Scheme 1.** Reagents and conditions. (a) Ref. 16; (b) 4-methyl-1,2,4-triazoline-3,5-dione, CH<sub>2</sub>Cl<sub>2</sub> (65%) or RhCl<sub>3</sub>·xH<sub>2</sub>O, EtOH; (c) Grubbs second generation catalyst, CH<sub>2</sub>Cl<sub>2</sub>; (d) RhCl<sub>3</sub>·xH<sub>2</sub>O, K<sub>2</sub>CO<sub>3</sub>, EtOH, MW, 80 °C, 61%; (e) i. DMP, CH<sub>2</sub>Cl<sub>2</sub>; ii. CH<sub>2</sub>=CH(CH<sub>2</sub>)<sub>4</sub>PPh<sub>3</sub>Br, *n*-BuLi, Et<sub>2</sub>O; (f) i. 4-methyl-1,2,4-triazolidine-3,5-dione, CH<sub>2</sub>Cl<sub>2</sub> (47%); ii. O<sub>3</sub>, MeOH, -70 °C; iii. MeOH, NaBH<sub>4</sub>, 60% (2 steps); (g) NaOCH<sub>3</sub>, MeOH, 64%; (h) DMP, CH<sub>2</sub>Cl<sub>2</sub>; (i) i. OsO<sub>4</sub>, NMO, acetone, H<sub>2</sub>O; ii. NaIO<sub>4</sub>, dioxane, H<sub>2</sub>O, 52%; (j) BzCl, pyridine, 85%; (k) RhCl<sub>3</sub>·xH<sub>2</sub>O, K<sub>2</sub>CO<sub>3</sub>, EtOH, MW, 75 °C, 55%; (l) i. OsO<sub>4</sub>, NMO, acetone, H<sub>2</sub>O; ii. NaIO<sub>4</sub>, dioxane, H<sub>2</sub>O, 62%; (m) BzCl, pyridine, 65%; (n) Uracil, BSA, TMS-OTf, CH<sub>3</sub>CN, 58%; (o) i. NH<sub>3</sub>, CH<sub>3</sub>OH; ii. TBAF, THF, 72%. NMO=*N*-methylmorpholine-*N*-oxide, DMP=Dess–Martin periodinane, TBS=*tert*-butyldimethylsilyl.

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