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## Nucleosides, Nucleotides and Nucleic Acids

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## Conformationally Locked Nucleoside Analogs. Synthesis of 2'-Deoxy-2'-C, 4'-C-Bridged Bicyclic Nucleosides

Guangyi Wang\* and Esmir Gunic

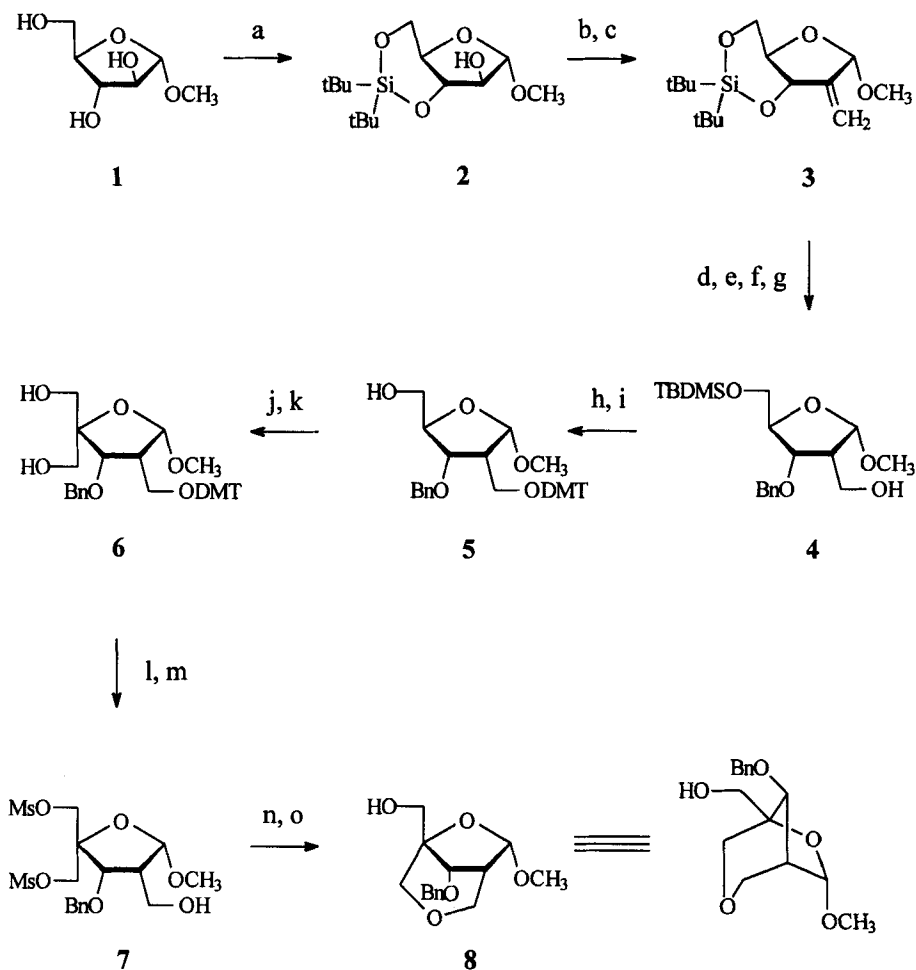
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**Abstract:** 1- $\alpha$ -Methylarabinose was converted, in three steps, to 2-deoxy-2-methylenetribose derivative **3**, which was subjected to hydroboration to give 2- $\alpha$ -hydroxymethyl derivative **4** exclusively. **4** was converted to 2,4-bis(hydroxymethyl)ribose derivative **6** in four steps. Mesylation, detritylation, and ring closure, followed by hydrolysis of the mesyl group at O5, gave 3,6-dioxabicyclo[3,2,1]octane derivative **8**. After acetylation, **8** was coupled with silylated 6-chloropurine to give desired  $\alpha$ - and  $\beta$ -bicyclic-sugar nucleosides.

Recently, conformationally locked nucleosides have drawn considerable attention since these nucleosides adopt certain desired, fixed, geometrical shape and are potentially useful as inhibitor of certain enzymes.<sup>1-8</sup> It was reported that certain conformationally locked nucleosides having 3'-endo (the Northern) bicyclo[3,1,0]hexane as sugar moiety demonstrated activities against HSV, HCMV and EBV.<sup>2-3</sup> Apparently, conformationally locked nucleosides, especially those having 3'-endo conformation, are promising candidates as antiviral drugs and deserve further exploration. In addition, the nucleosides having the fixed sugar pucker are potentially useful as the building blocks of antisense oligonucleotide.<sup>9-17</sup> The sugar pucker in DNA-RNA double helix tends to adopt 3'-endo conformation while the 2'-endo sugar pucker predominates in the DNA-DNA duplex. It is anticipated that oligonucleotides having 3'-endo sugar pucker would have good binding affinity to the complementary RNA.

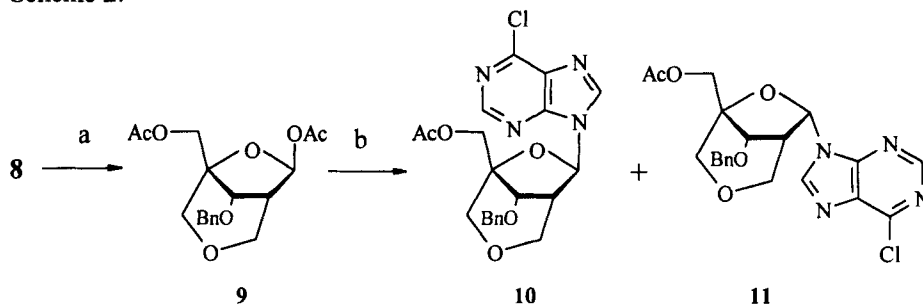
Nucleosides having 2'-O, 4'-C-methylenetribofuranose sugar moiety were recently synthesized.<sup>14</sup> Oligonucleotides containing these nucleosides have shown excellent

Scheme 1.



a)  $(\text{tBu})_2\text{Si}(\text{OTf})_2$ , DMAP, pyridine, r.t., 12 h, 71%; b) DMSO, DCC, TFA, pyridine, r.t., 16 h; c)  $\text{Ph}_3\text{P}=\text{CH}_2$ , ether;  $-10^\circ\text{C}$ , 1 h, 56%; d) TBAF, THF, r.t., 48 h, 100%; e) TBDMS-Cl, pyridine; f) Bn-Br, NaH, THF, r.t., 5 h, 71% (two steps); g) 1. 9-BBN, THF,  $40^\circ\text{C}$ , 14 h; 2.  $\text{NaBO}_3$ ,  $\text{H}_2\text{O}$ ,  $50^\circ\text{C}$ , 4 h, 93%; h) DMT-Cl, pyridine, r.t., 16 h; i) TBAF, THF, r.t., 0.5 h, 94% (two steps); j) DMSO, DCC, TFA, pyridine, r.t., 6 h, 90%; k)  $\text{CH}_2\text{O}$ , NaOH, dioxane,  $\text{H}_2\text{O}$ , r.t., 48 h, 95%; l) Ms-Cl, pyridine, r.t., 0.25 h; m) AcOH,  $\text{H}_2\text{O}$ , r.t., 2 h, 90% (two steps); n) NaH, THF,  $55^\circ\text{C}$ , 28 h; o) NaOH,  $\text{H}_2\text{O}$ , reflux, 24 h, 89% (two steps).

Scheme 2.



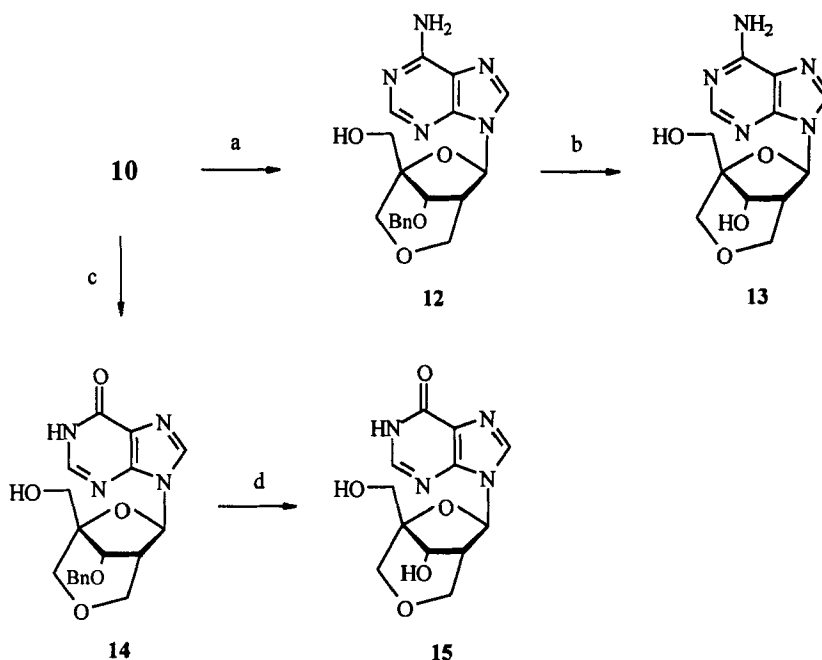
a)  $\text{Ac}_2\text{O}$ ,  $\text{AcOH}$ ,  $\text{H}_2\text{SO}_4$ , r.t., 2 h, 96%; b) 6-chloropurine-TMS,  $\text{Me}_3\text{SiOSO}_2\text{CF}_3$ ,  $\text{Cl}(\text{CH}_2)_2\text{Cl}$ , reflux, 1 h, 75% (ratio of  $\beta$  and  $\alpha$  ~1:1).

binding affinity to both complementary DNA and RNA.<sup>15-17</sup> Conformationally locked nucleosides offered a new reservoir of building blocks for antisense oligonucleotides. Recently, we have independently explored conformationally locked nucleosides as potential small molecule therapeutics as well as building blocks for antisense oligonucleotides. In this communication, synthesis of 2'-deoxy-2'-C, 4'-C-bridged bicyclic nucleosides is described.

1- $\alpha$ -Methylarabinose **1**, prepared according to a published procedure,<sup>18</sup> was protected with (di-*t*-butyl)silyl at O3 and O5 and converted to a ketone. Wittig reaction afforded 2-deoxy-2-methylene derivative **3**. After removal of the silyl group and protection with TBDMS at O5 and Bn at O3, hydroboration of the double bond was conducted with 9-BBN to give exclusively the 2- $\alpha$ -hydroxymethyl derivative **4** in excellent yield. The 2-hydroxymethyl of **4** was protected with DMT and the TBDMS at O5 was removed to give **5**. 5-Hydroxy of **5** was oxidized to an aldehyde, which was treated with formaldehyde and sodium hydroxide to yield the 4-hydroxymethyl derivative **6** in good yield. **6** was converted to the methanesulfonate and DMT subsequently removed to give **7**. The ring closure was effected with NaH in THF and the subsequent removal of the mesyl group at the O5 yielded the 2-deoxy-2- $\alpha$ -C, 4- $\alpha$ -C-bridged 1- $\alpha$ -methylribofuranose **8** as shown in Scheme 1.

Treatment of **8** with acetic acid/anhydride in the presence of sulfuric acid yielded the 1- $\beta$ , 5-diacetate **9** in high yield and a small amount of the 1- $\alpha$ -isomer. Coupling reaction of **9** with silylated 6-chloropurine afforded a mixture of **10** and **11** in good yield.

Scheme 3.

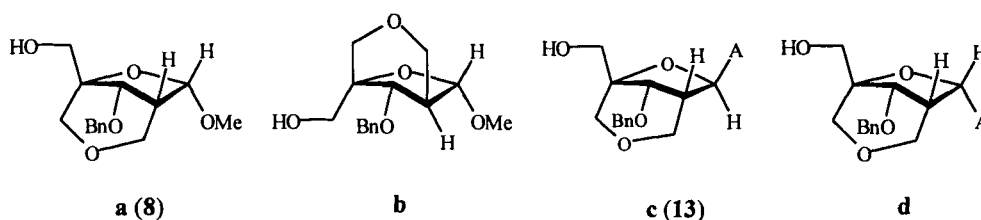


a)  $\text{NH}_4\text{OH}$ , dioxane,  $100^\circ\text{C}$ , overnight; b)  $\text{H}_2$ , 20%  $\text{Pd}(\text{OH})_2/\text{C}$ , r.t., 3 days, 60% (two steps); c)  $\text{HS}(\text{CH}_2)_2\text{OH}$ ,  $\text{NaOMe}$ ,  $\text{MeOH}$ , reflux, 7 h, 84%; d) same as b, 80%.

Treatment of **10** with ammonia afforded **12**, which was hydrogenolyzed to give the bicyclic nucleoside **13**. Treatment of **10** with mercaptoethanol in the presence of base yielded **14**, which was hydrogenolyzed to **15**. Similarly, the  $\alpha$ -isomer **11** was converted to the  $\alpha$ -isomers of **13** and **15**, respectively (not shown).

The stereochemistry was the major concern from the very beginning. The key step concerning stereochemistry is the hydroboration. Both benzyl at O3 and methyl at O1 of **3** adopt  $\alpha$ -conformation, which leaves the space above the double bond open while it is crowded below the double bond. When the bulky 9-BBN is chosen as reagent, the highly selective reaction is anticipated. In fact, the reaction gave the 2- $\alpha$ -hydroxymethyl product **4** exclusively. As can be seen from Scheme 1, the subsequent reactions after **4** do not change the conformation of the hydroxymethyl at C2 and hence the hydroxymethyl will have the same conformation in the bicyclic ring system. Conformational determination of the bicyclo[3,2,1]octane **8** (a) was straightforward. As indicated by a stick-ball model, the

rigid bicyclo[3,2,1]octane ring system forces the protons at C1 and C2 near parallel. The dihedral angle of H1-C1-C2-H2 after geometry optimization (Alchemy) is  $34^\circ$ . In consistence to these, a coupling constant of 3.9 Hz was observed. The result also confirms that the hydroxymethyl at C2 of **4** has  $\alpha$ -conformation. If the hydroxymethyl had  $\beta$ -conformation, it would yield a different bicyclic compound (b). The two protons at C1 and C2 are nearly orthogonal ( $102^\circ$  after geometry optimization) and would not show any appreciable coupling. The stereochemistry of the nucleosides formed from reaction of the bicyclic sugar with the silylated base can be assigned by the same token. In the  $\beta$ -isomer **13** (c), no coupling was observed between the protons at C1 and C2 while a coupling constant of 4.2 Hz was observed in the  $\alpha$ -isomer of **13** (d).



In summary, we have demonstrated synthesis and conformational assignments of a 3,6-dioxabicyclo[3,2,1]octane derivative and the nucleosides composed of. The synthetic approach is useful for preparation of novel nucleosides having locked 3'-endo conformation and allows introduction of desired nucleoside bases. The detailed studies on chemistry and biological evaluation will be reported elsewhere.

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