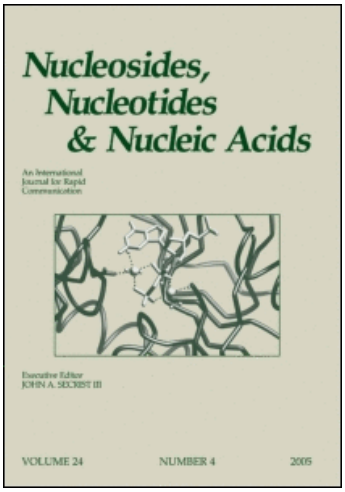

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Synthesis of a Base-Protected *xylo*-LNA Adenine Nucleoside

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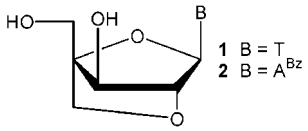
ABSTRACT

Synthesis of (1*S*,3*R*,4*R*,7*R*)-7-hydroxy-1-hydroxymethyl-3-(6-*N*-benzoyl-adenin-9-yl)-2,5-dioxabicyclo[2.2.1]heptane (**2**), a base-protected *xylo*-LNA adenine nucleoside, has been accomplished using a convergent synthetic strategy starting from 1,2-di-*O*-acetylfuranose **3**.

Key Words: LNA (locked nucleic acid); *xylo*-LNA; Xylonucleoside.

Synthesis of the *xylo*-LNA thymine nucleoside **1** has been previously reported.[1–3] Incorporation of nucleoside **1** into oligodeoxynucleotides induced lowered affinity for a partly modified *xylo*-LNA/DNA oligonucleotide, but enhanced affinity for a fully modified *xylo*-LNA oligonucleotide. Herein we present our efforts towards synthesis of the *xylo*-LNA adenine nucleoside **2**.



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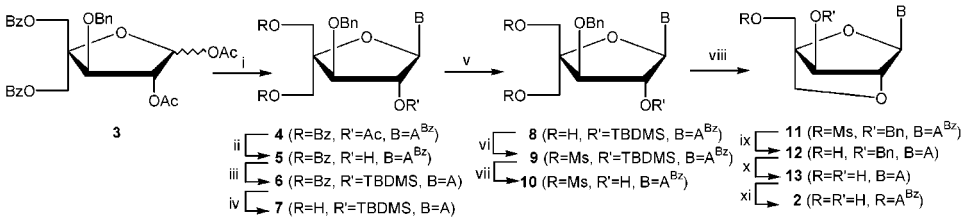

Scheme 1. i) A^{Bz}, $SnCl_4$, CH_3CN (52%) or A^{Bz}, TMS-triflate, BSA, CH_3CN (43%); ii) 50% sat. NH_3 in MeOH (85%); iii) TBDMSCl, imidazole, DMF (72%); iv) sat. NH_3 in MeOH (94%); v) a) TMSCl, pyridine, b) BzCl, pyridine, c) 10% sat. aq. NH_3 in MeOH; vi) MsCl, pyridine (79% from **7**); vii) TBAF, THF (87%); viii) NaH, DMF (83%); ix) KOH, EtOH (90%); x) H_2, 10% Pd/C, EtOH (76%); xi) a) TMSCl, pyridine, b) BzCl, pyridine, c) 16% sat. NH_3 in H_2O (81%).

The known furanose **3**[3] was subjected to base coupling with 6-N-benzoylated adenine under various conditions. Standard Vorbrüggen conditions (TMS-triflate, BSA) required heating for several hours and yielded both the N7- and the N9-isomers of nucleoside **4**. A better 52% yield, shorter reaction time, and regioselective formation of the N9-isomer were the results when using $SnCl_4$ instead of BSA and TMS-triflate.

A series of protection group manipulations (see Sch. 1) was performed in order to obtain selective introduction of mesyl groups at the two primary hydroxy groups and a free hydroxy group at the 2′-position (nucleoside **10**). Base-induced ring closure yielded the bicyclic nucleoside **11**, which was deprotected to give the unprotected nucleoside **13**. Eventually, the benzoyl group was reintroduced at the N6-position of the adenine moiety.

In spite of many synthetic steps leading to a relatively low overall yield, a viable strategy for the preparation of the 6-*N*-benzoyl-protected *xylo*-LNA nucleoside of adenine has been developed. We are currently studying the synthesis and properties of adenine-containing *xylo*-configured oligonucleotides.

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