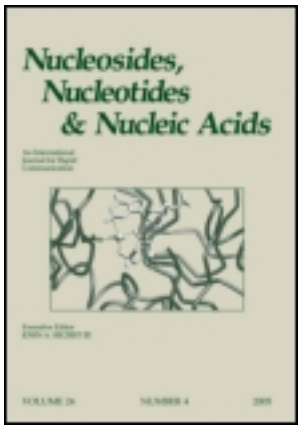

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Synthesis of a Base-Protected α-L-LNA Guanine Nucleoside

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ABSTRACT

Synthesis of (1*R*,3*R*,4*S*,7*R*)-7-hydroxy-1-hydroxymethyl-3-(2-*N*-isobutyroylguanin-9-yl)-2,5-dioxabicyclo[2.2.1]heptane (**12**), a protected α-L-LNA guanine nucleoside, has been accomplished using a convergent synthetic strategy starting from 1,2-di-*O*-acetylfuranose **4**.

Key Words: LNA (locked nucleic acids); α-L-LNA; Guanine nucleoside.

The unprecedented thermal stability of duplexes involving LNA[1] (Locked Nucleic Acid) and α-L-LNA[2] (α-L-*ribo* configured LNA; adenin-9-yl, 5-methylcytosin-1-yl and thymin-1-yl monomers) has stimulated us to synthesize the guanine α-L-LNA derivative **12** (Sch. 1).

Coupling between di-*O*-acetyl-di-*O*-mesyl furanose **4**[2] and per(trimethylsilyl)-2-*N*-acetyl-6-*O*-(diphenylcarbamoyl) guanine[3] afforded stereoselectively the desired *N*-9 regioisomer **5** in 59% yield. Treatment of nucleoside **5** with half-saturated methanolic ammonia gave chemoselectively the *O*-deacylated derivative **6** in 95% yield. To accomplish epimerisation at C2′, nucleoside **6** was reacted with trifluoromethanesulfonic anhydride in a mixture of pyridine and dichloromethane and

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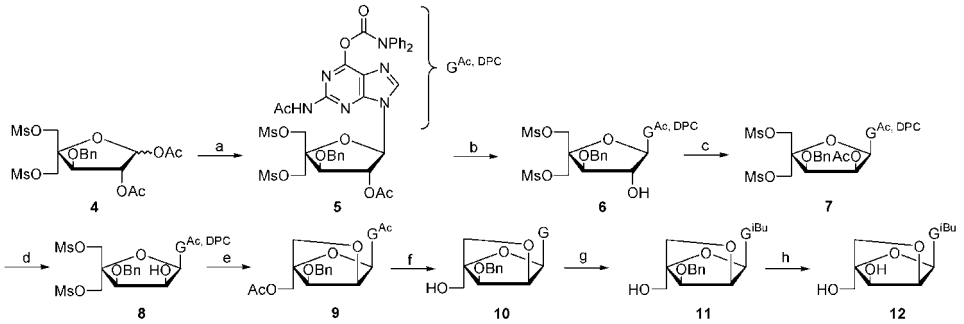

Scheme 1. Reagents and conditions: a) $G^{Ac,DPC}(SiMe_3)_2$, TMSOTf, toluene, 59%; b) half sat. NH_3, MeOH, 95%; c) 1) Tf_2O, pyridine, CH_2Cl_2, 2) AcOK, 18-crown-6, toluene, 63%; d) half sat. NH_3, MeOH, 96%; e) 1) NaH, THF; 2) AcOK, 18-crown-6, dioxane; f) NH_3, MeOH, 35%; g) 1) TMSCl, pyridine; 2) $^{i}Bu_2O$; 3) NH_4OH, 72%; h) HCO_2NH_4, Pd/C, MeOH, 46%.

subsequently with potassium acetate and 18-crown-6 in toluene to afford the desired derivative **7** in 46% yield. Selective O-deacylation of **7** using half-saturated methanolic ammonia gave in 96% yield nucleoside **8**, the C2′-epimer of nucleoside **6**. Nucleoside **8** was treated with sodium hydride in THF to induce cyclization, which was followed by substitution of the remaining mesyloxy group with an acetate group by reaction with potassium acetate and 18-crown-6 in dioxane at reflux, affording the bicyclic nucleoside derivative **9**. Complete deacetylation of **9** in saturated methanolic ammonia gave nucleoside **10** in 35% yield (from compound **8**). 2-*N*-Isobutyroyl protection of **10** was accomplished in 72% yield using transient protection[4] of the free hydroxy groups followed by acylation of the amine function giving nucleoside **11**. Debenzylation of this intermediate (ammonium formate, Pd/C, 46% yield) eventually afforded the desired 2-*N*-isobutyroyl α-L-LNA guanine nucleoside **12** (Sch. 1).

In spite of many synthetic steps leading to a relatively low overall yield, a viable strategy for the preparation of a α-L-LNA nucleoside of guanine has been developed.

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