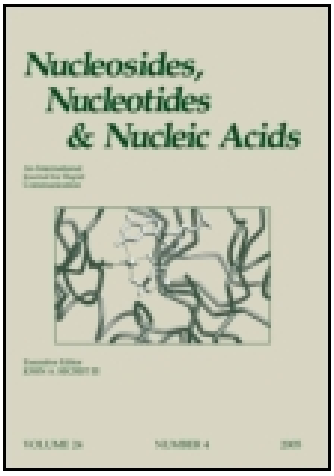

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A New Synthetic Approach Towards α- and β-LNA (Locked Nucleic Acids)

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A NEW SYNTHETIC APPROACH TOWARDS α- AND β-LNA (LOCKED NUCLEIC ACIDS)

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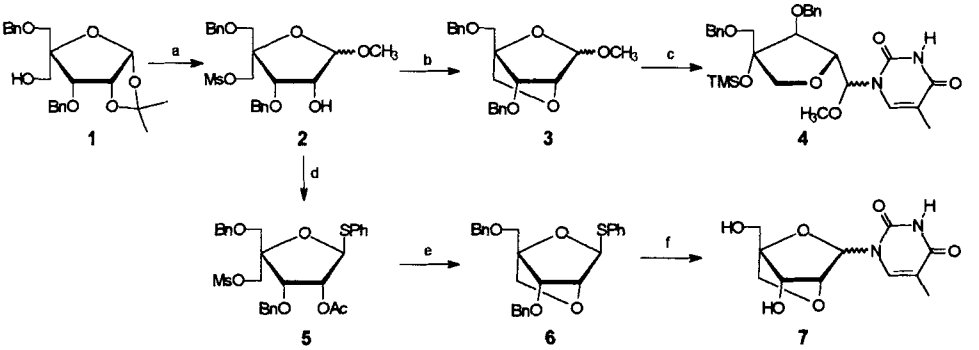
ABSTRACT: A bicyclo[2.2.1] phenyl thioglycoside was efficiently synthesised and introduced as the key synthon in a novel method for convergent synthesis of β-LNA-nucleosides as well as their α-configurated isomers. An acid-induced ring-opening reaction on the corresponding bicyclo[2.2.1] methyl furanoside is also described.

LNA (Locked Nucleic Acids) has been recently introduced as a promising novel class of preorganized oligonucleotide analogues[1,2] containing one or more LNA monomers, which are bicyclo[2.2.1] nucleosides preorganized into a C-3'-*endo* conformation.[1-3] LNA has demonstrated unprecedented high-affinity recognition of both single stranded DNA and RNA in all-modified LNA-oligomers as well as in oligoribo- or oligodeoxynucleotide contexts.[1,2] In our initial synthetic approaches, monomeric β-configurated LNA-nucleosides were synthesized by stereoselective condensation of appropriately protected 4-*C*-hydroxymethyl furanoses with silylated nucleobases and subsequent ring-closure and deprotection;[1,2] linear syntheses of LNA nucleosides were also accomplished.[4] Here a novel synthetic strategy is introduced, involving the use of a bicyclic carbohydrate precursor for nucleobase coupling reactions thus revealing a favourable route towards the β-LNA nucleosides as well as their α-configurated isomers.

The furanose **1**[5] was easily converted to the isomeric bicyclic methyl furanosides **3** (Scheme 1). However, coupling of thymine using a modified Vorbrüggen methodology afforded only the ring-opened product **4** as a mixture of diastereomers. The considerable

ring strain in the bicyclic structure is a plausible explanation for the favoring of the Lewis acid mediated ring-opening reaction over the cleavage of the anomeric bond. As an attempt to overcome this problem, a better leaving group was introduced at the anomeric center and the bicyclic phenyl thioglycoside **6** was easily obtained (Scheme 1). Condensation of **6** with silylated thymine using NBS as a thiophilic activator gave after deprotection a mixture of anomeric nucleosides **7** (α:β ~ 2:1); the known LNA-nucleoside and its α-LNA nucleoside analogue. The general use of **6** as a precursor for synthesis of other nucleobase analogues of α- and β-LNA nucleosides is currently under investigation leading eventually to the introduction of α-LNA oligomers.



Scheme 1. a) i. MsCl, Pyridine (99%), ii. 20% HCl in MeOH, H_2O (95%); b) NaH, DMF (90%); c) Thymine, BSA, TMS-Tf, CH_3CN (59%); d) i. Ac_2O, Pyr. (97%), ii. TMSSPh, TMS-Tf, DCM (66%); e) i. NH_3, MeOH, ii. NaH, DMF (95%); f) i. Thymine, HMDS, 4Å MS, DCM (61%), ii. H_2, $Pd(OH)_2$-C, EtOH, DCM (37%).

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