

This article was downloaded by: [DUT Library]

On: 07 October 2014, At: 05:56

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides and Nucleotides

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/Incn19>

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

Poul Nielsen ^a & Jesper Wengel ^b

^a Department of Chemistry, Odense University, DK-5230, Odense M, Denmark

^b Center for Synthetic Bioorganic Chemistry, Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100, Copenhagen, Denmark

Published online: 04 Oct 2006.

To cite this article: Poul Nielsen & Jesper Wengel (1999) A New Synthetic Approach Towards α - and β -LNA (Locked Nucleic Acids), Nucleosides and Nucleotides, 18:4-5, 701-702, DOI:

[10.1080/15257779908041546](https://doi.org/10.1080/15257779908041546)

To link to this article: <http://dx.doi.org/10.1080/15257779908041546>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

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

Poul Nielsen^{a,*} and Jesper Wengel^b

^aDepartment of Chemistry, Odense University, DK-5230 Odense M, Denmark

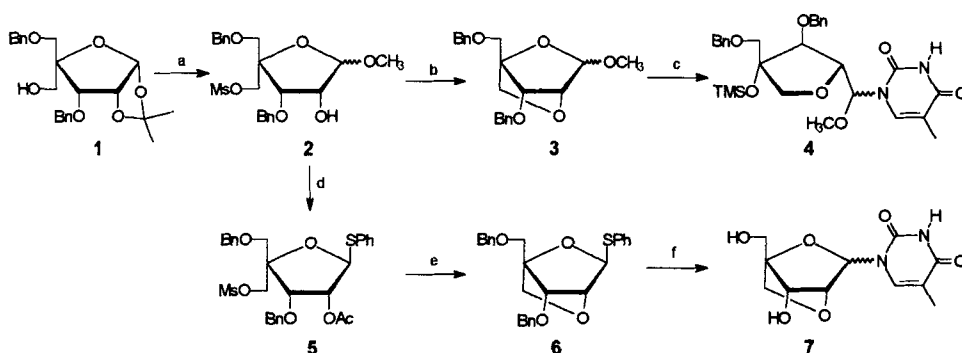
^bCenter for Synthetic Bioorganic Chemistry, Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

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 -configured 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 -configured 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 -configured 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** ($\alpha:\beta \sim 2:1$); 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, H₂O (95%); b) NaH, DMF (90%); c) Thymine, BSA, TMS-Tf, CH₃CN (59%); d) i. Ac₂O, Pyr. (97%), ii. TMSSPh, TMS-Tf, DCM (66%); e) i. NH₃, MeOH, ii. NaH, DMF (95%); f) i. Thymine, HMDS, 4Å MS, DCM (61%), ii. H₂, Pd(OH)₂-C, EtOH, DCM (37%).

ACKNOWLEDGEMENTS

The Danish Natural Science Research Council, The Danish Technical Research Council and Exiqon A/S, Denmark are thanked for financial support.

REFERENCES AND NOTES

1. Singh, S. K.; Nielsen, P.; Koshkin, A. A.; Wengel, J. *Chem. Commun.* **1998**, 455-456.
2. Koshkin, A. A.; Singh, S. K.; Nielsen, P.; Rajwanshi V. K.; Kumar, R.; Meldgaard, M.; Olsen, C. E.; Wengel, J. *Tetrahedron* **1998**, *54*, 3607-3630.
3. Obika, S.; Nanbu, D.; Hari, Y.; Morio, K.; In, Y.; Ishida, T.; Imanishi, T. *Tetrahedron Lett.* **1997**, *38*, 8735-8738.
4. Koshkin, A. A.; Rajwanshi, V. K.; Wengel, J. *Tetrahedron Lett.* **1998**, *39*, 4381-4384.
5. Waga, T.; Nishizaki, T.; Miyakawa, I.; Ohnui, H.; Meguro, H. *Biosci. Biotech. Biochem.* **1993**, *57*, 1433-1438.