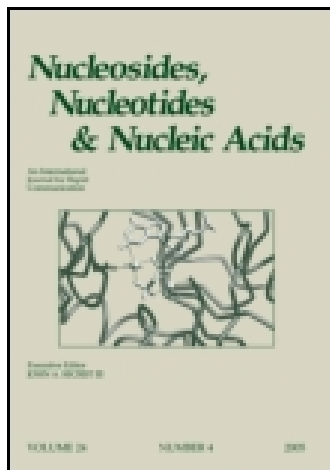


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## Nucleosides, Nucleotides and Nucleic Acids

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### Improved Synthesis of 2'-Amino-LNA

Signe M. Christensen<sup>a d</sup>, Christoph Rosenbohm<sup>a</sup>, Mads Sørensen<sup>b</sup>, Lotte-Emilie Larsen<sup>a</sup>, Jesper Wengel<sup>c</sup> & Troels Koch<sup>a</sup>

<sup>a</sup> Cureon A/S, Copenhagen, Denmark

<sup>b</sup> Department of Chemistry, University of Copenhagen, Copenhagen, Denmark

<sup>c</sup> Department of Chemistry, Nucleic Acid Center, University of Southern Denmark, Odense M, Denmark

<sup>d</sup> Cureon A/S, Fruebjergvej 3, DK-2100, Copenhagen, Denmark

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## Improved Synthesis of 2'-Amino-LNA

Signe M. Christensen,<sup>1,\*</sup> Christoph Rosenbohm,<sup>1</sup> Mads Sørensen,<sup>2</sup>  
Lotte-Emilie Larsen,<sup>1</sup> Jesper Wengel,<sup>3</sup> and Troels Koch<sup>1</sup>

<sup>1</sup>Cureon A/S, Copenhagen, Denmark

<sup>2</sup>Department of Chemistry, University of Copenhagen,  
Copenhagen, Denmark

<sup>3</sup>Department of Chemistry, Nucleic Acid Center,  
University of Southern Denmark,  
Odense M, Denmark

### ABSTRACT

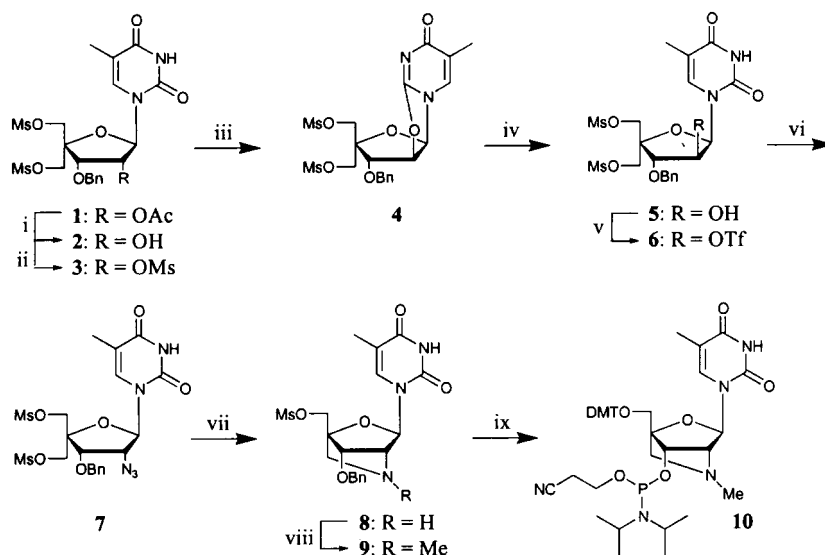
2'-Amino-LNA phosphoramidite (**10**) was synthesised by means of a new strategy, which is convergent with the synthesis of 2'-oxy-LNA up until a late stage intermediate (**1**).

*Key Words:* 2'-Amino-LNA; Convergent strategy; Gram-scale synthesis.

LNA (Locked Nucleic Acid) was introduced in 1998<sup>[1–3]</sup> as a novel class of conformationally restricted oligonucleotide analogues: The first LNA monomer was based on the 2'-OCH<sub>2</sub>-4' bicyclic structure (LNA/2'-oxy-LNA). Later similar high affinity/specificity LNA monomers such as 2'-NHCH<sub>2</sub>-4', 2'-N(CH<sub>3</sub>)CH<sub>2</sub>-4' (2'-amino-LNA)<sup>[4,5]</sup> and 2'SCH<sub>2</sub>-4' (2'-thio-LNA)<sup>[4,6]</sup> were synthesised.

\*Correspondence: Signe M. Christensen, Cureon A/S, Fruebjergvej 3, DK-2100 Copenhagen, Denmark; Fax: +45 70 26 00 97; E-mail: smc@cureon.com.





**Scheme 1.** i) half sat.  $\text{NH}_3$  in MeOH (97%); ii) MsCl, pyridine (93%); iii) DBU, MeCN (91%); iv) acetone, 0.1M  $\text{H}_2\text{SO}_4$  (98%); v)  $\text{TF}_2\text{O}$ , DMAP, pyridine,  $\text{CH}_2\text{Cl}_2$  (80%); vi)  $\text{NaN}_3$ , 15-crown-5, DMF (91%); vii)  $\text{PMe}_3$ , NaOH(aq), THF (93%); viii)  $\text{CH}_2\text{O}$ ,  $\text{HCO}_2\text{H}$  (90%); ix) a) NaOBz, b) MeONa, DMF (98%), c) 20%  $\text{Pd}(\text{OH})_2/\text{C}$ ,  $\text{H}_2$ , AcOH (97%), d) DMTCl, pyridine (92%), e)  $\text{NC}(\text{CH}_2)_2\text{OP}(\text{N}(\text{iPr})_2)_2$ , 4,5-dicyanoimidazole, MeCN,  $\text{CH}_2\text{Cl}_2$  (98%).

Scale up of the original synthesis of 2'-amino-LNA proved to be difficult in our hands, and we therefore developed a new synthetic approach, which converges the syntheses of 2'-oxy-LNA and 2'-amino-LNA. The 2'-*O*-acetyl dimesylated nucleoside **1** (Sch. 1), used in the improved and recently published synthesis of 2'-oxy-LNA nucleosides,<sup>[7]</sup> was deacetylated using half-saturated methanolic ammonia to afford nucleoside **2** in quantitative yield. Subsequent reaction with mesyl chloride in pyridine gave the trimesylate **3** in 96% on a 20 g scale. The 2,2'-anhydro intermediate **4** was synthesised quantitatively by treatment of **3** with 1.1 equivalents of DBU in anhydrous acetonitrile. Opening of the 2,2'-anhydro intermediate by refluxing it in a mixture of aqueous sulfuric acid (0.1M) and acetone (1:1, v/v) resulted in a clean reaction giving the *threo*-configured nucleoside **5** in 91%. Treatment of **5** with trifluoromethanesulfonic anhydride, pyridine and DMAP in anhydrous dichloromethane at 0°C gave the desired triflate **6** in 80% after chromatography. Subsequent treatment with sodium azide afforded the 2'-azido-2'-deoxynucleoside **7** in 91%. Reduction of the azide using trimethylphosphine and aqueous NaOH in THF gave the nucleoside **8** with the desired 2-oxa-5-azabicyclo [2.2.1] heptane skeleton in 93%. Methylation using Eschweiler-Clarke conditions gave the 2'-*N*-methyl derivative **9** in 90% yield. Nucleophilic replacement of the mesylate on C5' with benzoate followed by transesterification with methoxide afforded the 5'-hydroxy nucleoside in 98% yield. Reductive debenzoylation with hydrogen and 20%  $\text{Pd}(\text{OH})_2/\text{C}$  in acetic acid yielded the deprotected nucleoside in 97%. 4,4'-Dimethoxytritylation

of the 5'-hydroxygroup and phosphitylation of the 3'-hydroxy group gave the amidite **10** in 90% yield ready for the automated incorporation into oligonucleotides.

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