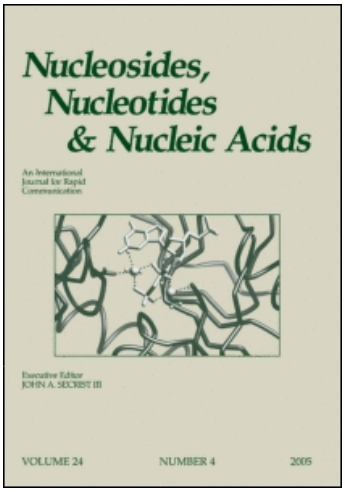

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Hrdlicka, Patrick J. , Kumar, T. Santhosh and Wengel, Jesper(2005) 'Synthesis of a 2'-Amino-α-l-LNA-T Phosphoramidite', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 1101 — 1104
To link to this Article: DOI: 10.1080/15257770500276866
URL: http://dx.doi.org/10.1080/15257770500276866

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):1101–1104, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1080/15257770500276866

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SYNTHESIS OF A 2′-AMINO-α-L-LNA-T PHOSPHORAMIDITE

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▫ *A convergent route to 2′-amino-α-L-LNA-T phosphoramidite building block* ***16*** *has been developed. Key steps include 1) introduction of a C2-azido group prior to nucleobase-coupling, 2) tandem Staudinger and intramolecular nucleophilic substitution reaction, and 3) separation of α-L- and β-L-configured intermediates.*

INTRODUCTION

The high-affinity hybridizations of β-D-LNA **1** (locked nucleic acid),[1–3] 2′-amino-β-D-LNA **2**[4] (R = H) and α-L-LNA **3**[5] (Figure 1) towards complementary DNA and RNA sequences are well established. When incorporated into an oligodeoxyribonucleotide (ODN), β-D-LNA **1** tunes duplexes towards DNA and RNA complements towards A/B-type and A-type helix geometry, respectively.[6,7] Conversely, when α-L-LNA **3** is incorporated into an ODN, duplexes towards DNA and RNA adopt B-type and A/B-type helix geometries, respectively, globally similar to unmodified duplexes.[8,9] N-substituted 2′-amino-β-D-LNA monomers have recently been introduced as building blocks to generate functional nucleic acid architectures with groups at the brim of the minor groove capable of signalling assembly processes.[10–12] In contrast, the secondary amine group of a 2′-amino-α-L-LNA **4** (Figure 1) would allow introduction of functional groups that are predictably positioned in the major groove of nucleic acid duplexes having similar global duplex geometries as unmodified DNA:DNA or DNA:RNA duplexes. Due to the potential of using N-substituted 2′-amino-α-L-LNA monomers in bottom up Ångström-scale chemical engineering[13] we set out to synthesize the protected 2′-amino-α-L-LNA-T phosphoramidite building block **16** (Scheme 2).

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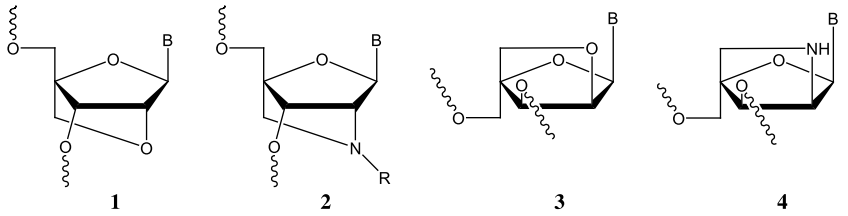
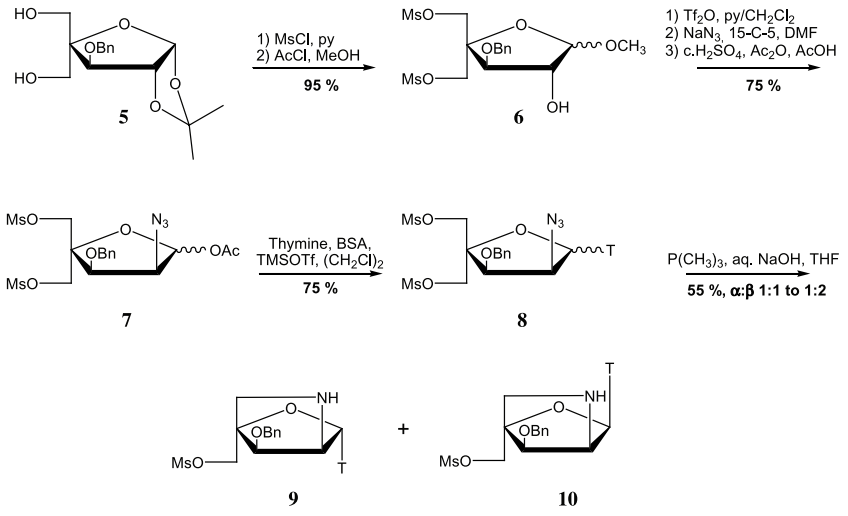


FIGURE 1

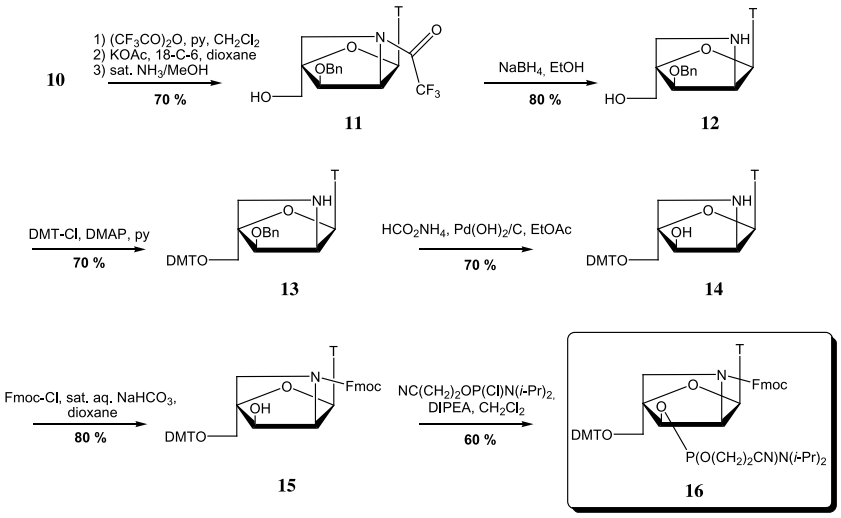
RESULTS AND DISCUSSION

Preliminary attempts to synthesize α-L-*ribo*-configured key intermediate **10** (Scheme 1) via an stereoselective route in which a thymine moiety was installed diastereospecifically (via anchimeric assistance from an O2-acetyl group) during nucleobase-coupling prior to introduction of a C2′-azido group, failed.[14] Instead, the first successful synthesis of phosphoramidite **16** initiated from diol **5**,[15] which was converted into an anomeric mixture of methyl furanoside **6** in two steps (Scheme 1).

Subsequent O2-triflation of the anomeric mixture followed by selective nucleophilic displacement of the O2-triflate and acetolysis, furnished glycosyl donor **7**. Glycosylation of **7** with persilylated thymine using modified Vorbrüggen conditions, furnished an inseparable anomeric mixture of nucleosides **8** which was reacted further in a tandem Staudinger and intramolecular nucleophilic substitution reaction to afford a separable mixture of β-L-*ribo*-configured nucleoside **9** and α-L-*ribo*-configured nucleoside **10** (α:β∼1:2).



SCHEME 1



SCHEME 2

Displacement of the O5′-methanesulfonyl group of nucleoside **10** necessitated protection of the 2′-amino group as a trifluoroacetamide (TFA) since tricyclic products, resulting from Michael addition of the C2′-amino group to C-6, were otherwise formed. Remarkably, deacylation using basic conditions did not cleave the TFA group but rather furnished nucleoside **11** (Scheme 2). However, nucleoside **11** could readily be converted into amino alcohol **12** using mildly reducing conditions. After chemoselective O5′-DMT protection to give nucleoside **13**, transfer hydrogenolysis afforded nucleoside **14** that constitutes a suitable intermediate for N-functionalization. Standard Fmoc-protection of nucleoside **14** followed by phosphitylation of nucleoside **15** afforded 2′-amino-α-L-LNA-T phosphoramidite **16**.

Incorporation of phosphoramidite **16** into ODNs and biophysical studies hereof are ongoing.

ACKNOWLEDGMENT

We thank The Danish National Research Foundation for financial support.

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