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Aryl- β -C-LNA Monomers as Universal Hybridization Probes^[1,2]

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ABSTRACT

High-affinity universal hybridization is demonstrated for oligonucleotides containing the pyrenyl-LNA monomer **6b**, 2'-O-Me-RNA monomers and LNA monomers.

Key Words: Universal bases; Universal hybridization; LNA, locked nucleic acid.

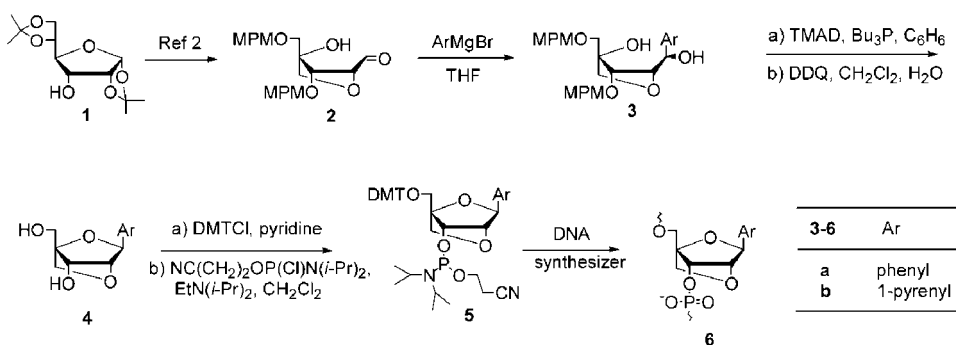
Universal monomers that bind isoenergetically with each of the natural nucleotides include non-hydrogen bonding, hydrophobic nucleotides.^[3] Although there has been some success in the design of universal base analogues, examples that are able to hybridize without significant duplex destabilization are rare. We decided to synthesize the LNA^[4] derivatives **6a** and **6b**, both based on the 2'-O,4'-C-methylene- β -D-ribofuranosyl moiety known to be preorganized in a locked C3'-*endo* (*N*-type) RNA-like furanose conformation.

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Table 1. Thermal denaturation experiments (T_m values shown) for **ON1-ON5** towards DNA complements with each of the four natural bases in the central position.

DNA target:	3'-d(CACTYTACG)	Y:	A	C	G	T
ON1	5'-d(GTGATATGC)		28	11	12	19
ON2	5'-d(GTGA 6a ATGC)		12	5	6	7
ON3	5'-d(GTGA 6b ATGC)		18	17	18	19
ON4	5'-d[2'-OMe(GTGATATGC)]		35	14	19	21
ON5	5'-d[2'-OMe(GT ^L GA 6b AT ^L GC)]		39	38	37	40



Compared to the DNA reference **ON1**, introduction of the phenyl-LNA monomer **6a** (**ON2**) leads to reduced thermal stability of the resulting duplexes, and universal hybridization is not achieved due to the preferential binding to the target DNA with the central adenine monomer (Table 1). The pyrene-LNA monomer **6b** (**ON3**) displays more encouraging properties, i.e., increased binding affinity compared to **6a** (**ON2**) and universal hybridization (the four T_m values = 17–19°C). We then constructed **ON5** as a mixture of six 2'-*O*-Me-RNA monomers, one central pyrenyl-LNA monomer **6b**, and two affinity-enhancing LNA thymine monomers **T^L**. Indeed, the 2'-*O*-Me-RNA/LNA chimera **ON5** displays universal hybridization with binding affinities exceeding those of the references **ON1** and **ON4** (the T_m values of **ON5** = 37, 38, 39 and 40°C).

The obtained results show that high-affinity universal hybridization can be obtained by use of a combination of the pyrenyl-LNA monomer **6b**, 2'-*O*-Me-RNA monomers and LNA monomers.

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