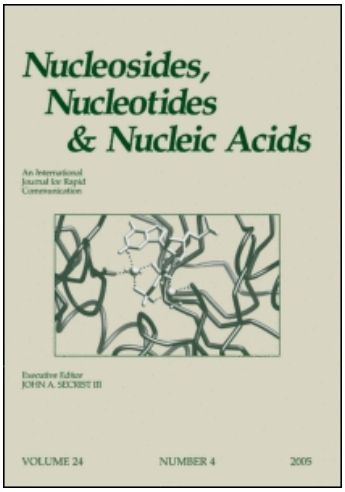

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Synthesis and Hybridization Properties of Oligodeoxynucleotides Containing 3'-Deoxy-3'-*C*-methyleneuridine

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Synthesis and Hybridization Properties of Oligodeoxynucleotides Containing 3′-Deoxy-3′-*C*-methyleneuridine

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ABSTRACT

3′-Deoxy-3′-*C*-methyleneuridine nucleoside **1**[1] has been incorporated into oligodeoxynucleotides. Relative to the unmodified references, oligomers containing nucleoside **1** displayed reduced binding affinities towards complementary DNA and RNA with a tendency towards RNA-selective hybridization.

Key Words: Oligonucleotides; Oligodeoxynucleotides; 3′-Methyleneuridine; Hybridization.

We have studied the effect of incorporating 3′-deoxy-3′-*C*-methyleneuridine (**1**)[1] into oligodeoxynucleotides. Nucleoside **1** was synthesized by a convergent strategy starting from 1,2-*O*-isopropylidene-α-D-xylofuranose (Sch. 1).[1–3] Coupling between the tri-*O*-acyl furanose derivative and uracil by the Vorbrüggen method followed by deactylation afforded nucleoside **1**. The corresponding phosphoramidite **2** was obtained and used for automated synthesis of oligomers **B**, **D** and **E** (Table 1).

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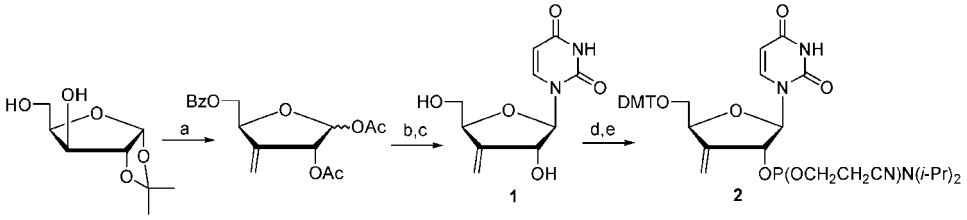

Scheme 1. a) Ref. 2–3; b) Uracil, BSA, TMS-triflate, CH_3CN; c) MeONa, MeOH (48%, two steps); d) DMTCl, DMAP, pyridine; e) $NCCH_2CH_2OP(Cl)N(i\text{-}Pr)_2$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2 (52%, two steps).

Table 1. Hybridization data.[a]

	Complementary ssDNA		Complementary ssRNA	
Oligonucleotide	T_m/°C	ΔT_m/°C	T_m/°C	ΔT_m/°C
A: 5′-GTGATATGC	28.0	Ref.	26.0	Ref.
B: 5′-GTGA**X**ATGC	21.0	−7.0	24.0	−2.0
C: 5′-T_{14}	32.5	Ref.	29.0	Ref.
D: 5′-$T_7\mathbf{X}T_6$	24.0	−8.5	25.0	−4.0
E: 5′-$T_5\mathbf{X}_4T_5$	< 5.0		15.0	−3.5

[a]A_{260} as a function of temperature was recorded in a medium salt buffer (100 mM sodium chloride, 10 mM sodium phosphate, 0.1 mM EDTA, pH = 7.0) with 1.5 μM concentration of each of the two complementary strands. **X** = 2′,5′-linked nucleotide monomer derived from **1**.

The possibility of forming an allylic carbocation during the iodine oxidation of a standard oligonucleotide synthesis cycle made us replace the usual oxidation reagent, iodine/water/pyridine, with *tert*-butyl hydroperoxide.[4] The cyanoethyl group was selectively deprotected with diisopropylamine to limit the cleavage of internucleotide bonds known to be a problem for similar compounds.[5]

Due to the presence of the exocyclic double bond, the furanose ring of nucleoside **1**[1] is restricted into a C1′-*exo* type furanose conformation as shown by molecular modeling. However, hybridization studies towards complementary DNA and RNA showed reduced melting temperatures for oligomers **B**, **D** and **E** compared to the oligodeoxynucleotide references **A** and **C** (Table 1). As for oligonucleotides containing 2′,5′-linked RNA,[6,7] a selectivity towards complementary RNA was found.

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REFERENCES

1. Samano, V.; Robins, M.J. Nucleic acid related compounds. 62. Stereoselective addition of a Wittig reagent to give at single nucleoside oxaphosphetane diastereoisomer. Synthesis of 2′(and 3′)-deoxy-2′(and 3′)-methyleneuridine (and cytidine) derivatives from uridine ketonucleosides. Synthesis **1991**, 283 pp.
2. Johnson, C.R.; Bhumralkar, D.R. 3′-*C*-Trifluoromethyl ribonucleosides. Nucleosides Nucleotides **1995**, *14*, 185 pp.
3. Giradet, J.; Gunic, E.; Esler, C.; Cieslak, D.; Pietzkowski, Z.; Wang, G. Synthesis and cytotoxicity of 4-amino-5-oxopyrido[2,3-*d*]pyrimidine nucleosides. Phosphoramidites derived from tertiary alcohols. Why do they sometimes couple with low efficiency? J. Med. Chem. **2000**, *43*, 3704 pp.
4. Scheuer-Larsen, C.; Dahl, B.M.; Wengel, J.; Dahl, O. Synthesis and properties of some (2′,5′) linked dinucleoside monophosphates modified with 3′-difluoromethylene groups. Tetrahedron Lett. **1998**, *39*, 8361 pp.
5. Brown, C.A.; Barnes, C.L.; Serafinowski, P.J. Oligoribonucleotides containing 2′,5′-phosphodiester linkages exhibit binding selectivity for 3′,5′-RNA over 3′,5′-ssDNA. Nucleosides Nucleotides **1999**, *18*, 1249 pp.
6. Giannaris, P.A.; Dahma, M.J. Oligoribonucleotides containing 2′,5′-phosphordiester linkages exhibit binding selectivity for 3′,5′-RNA over 3′,5′-ssDNA. Nucleic Acids Res. **1993**, *21*, 4742 pp.
7. Kandimalla, E.R.; Manning, A.; Zhao, Q.; Shaw, D.R.; Byrn, R.A.; Sasisekharan, V.; Agrawal, S. Mixed backbone antisense oligonucleotides: design, biochemical and biological properties of oligonucleotides containing 2′-5′-ribo- and 3′-5′-deoxyribonucleotide segments. Nucleic Acids Res. **1997**, *25*, 370 pp.

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