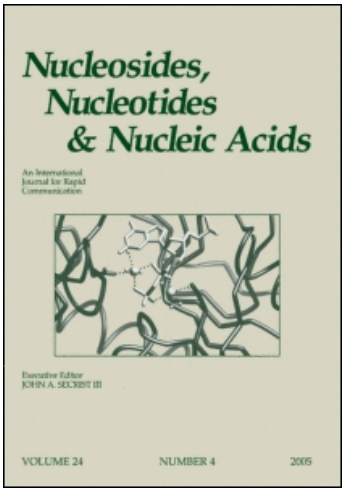

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THE SYNTHESIS OF, AND STUDIES ON, 2′-*C*-MODIFIED NUCLEOTIDES

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ABSTRACT

The synthesis of uridine monomers containing either a 2′-deoxy-2′-*C*-methylcyano or ethylcyano group is described. These monomers are intended for incorporation into oligonucleotides to investigate a proposed duplex-stabilising effect exerted by 2′-tethered amide groups.

Previously we have investigated the synthesis of several functionalized 2′-*C*-branched nucleosides with the long term aim of constructing ribozymes with enhanced functionality and nuclease resistance. Encouragingly, preliminary studies have shown that the incorporation of these 2′-*C*-modified residues into dinucleoside monophosphates confers considerable resistance to nucleases (1). Related to this work Sproat and co-workers have shown that 2′-*O*-carbamoylmethyl containing oligonucleotides show higher affinity for RNA than those which contain the simple 2′-*O*-alkyl or allyl modification (2). These results suggest, that in addition to the known beneficial effect of the 2′-oxygen, the amide group itself has some stabilising effect on the duplex. To further investigate this effect we describe here the synthesis of monomers that will enable the incorporation of 2′-*C*-branched nucleosides containing an amide functionality appended to either a 1 or 2 carbon alkyl chain (Fig. 1).

We have previously experienced difficulties in incorporating amide-functionalised nucleoside monomers into oligonucleotides due to either poor phosphitylation

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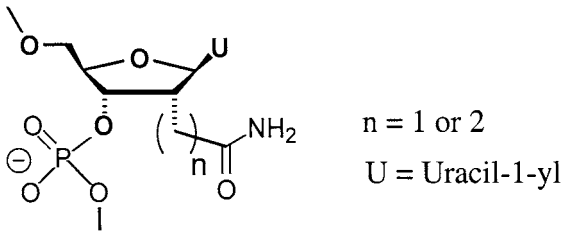

Figure 1.

to generate the amidite or dehydration of the amide to the nitrile during the iodine oxidation step (1). It seemed appropriate therefore to prepare the amidite monomers containing a nitrile group which could be converted by aminolysis to the amide. This approach has been successfully developed by Sproat and coworkers (2).

The synthesis of the required 2′-*C*-cyanoethyl- (**1**) and 2′-*C*-cyanomethyl- (**2**) uridine mononucleosides, from a common aldehyde precursor (3), is shown in Figure 2.

Model studies have shown that the cyanoethyl derivative **1** is cleanly converted to the corresponding amide by treatment with concentrated aqueous ammonia at 60°C. Following dimethoxytritylation and phosphitylation the cyanoethyl derivative **1** has been incorporated into oligonucleotides using standard automated procedures.

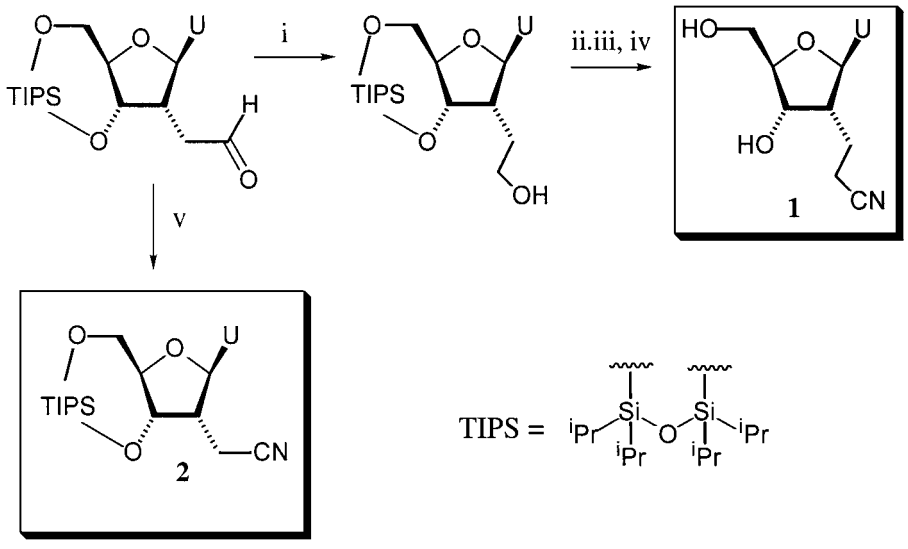

Figure 2. *Reagents and Conditions* i) $NaBH_4$, MeOH, 81%; ii) $MeSO_2Cl$, pyridine, 87%; iii) NaCN, DMSO, 120°C, 71%; iv) $NEt_3 \cdot 3HF$, THF, 80%; v) $NH_2OH \cdot HCl$, $CHCl_3$, SeO_2.

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REFERENCES

1. Lawrence, A.J.; Pavey, J.B.J.; O'Neil, I.A.; Cosstick, R. *J. Org. Chem.*, **1996**, *61*, 9213.
2. Grøtli, M.; Beijer, B.; Sproat, B. *Tetrahedron*, **1999**, *55*, 4299.
3. De Mesmaeker, A.; Lebreton, J.; Hoffman, P.; Freir, S.M. *Synlett*, **1993**, 677.

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