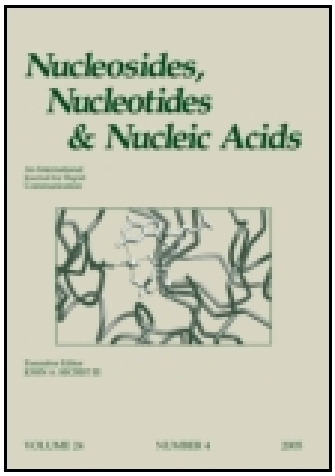

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NOVEL MACROCYCLES DERIVED FROM NUCLEOSIDES

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NOVEL MACROCYCLES DERIVED FROM NUCLEOSIDES

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ABSTRACT

A novel nucleoside-derived macrocycle formed from three thymidine 5′-carboxylic acid monomer units is described.

Although cyclic oligonucleotides had previously been isolated as by-products in oligonucleotide condensation reactions, the direct synthesis of cyclic oligonucleotides attracted attention in the early 1980s. In particular Hsu *et al*. described the synthesis of cyclic diribonucleotides such as r(cUpUp), r(cApAp) and r(cApUp) and reported that these cyclic ribonucleotides act as inhibitors of DNA dependent *E. coli* RNA polymerase (1,2). The synthesis of longer cyclic nucleotides has been facilitated by the use of polyethylene glycol (PEG) as soluble polymer support (3) and new approaches to solid-phase synthesis (4). More recently circular oligonucleotides have been shown to bind very strongly to single-stranded nucleic acids through formation of a triple helical complex (5).

We now describe our first efforts towards the synthesis of a nucleoside-derived macrocycle (**1**, Fig. 1) formed from three thymidine 5′-carboxylic acid monomer units (**2**).

Modelling studies have shown that this 12-membered lactone ring forms a relatively strain free system with the carbonyl groups of the ester bonds well disposed to co-ordinate metal ions. Additionally, hydrogen bonding interactions between the complementary nucleobases potentially allows for the formation of supramolecular complexes.

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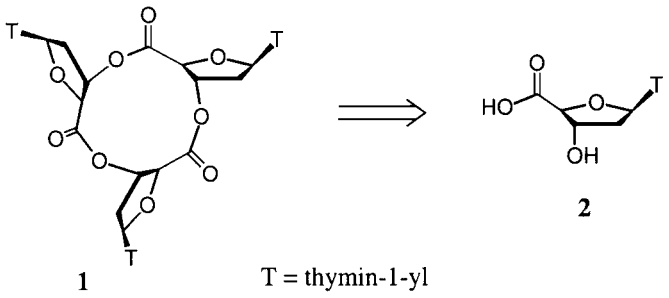

Figure 1.

For the synthesis of the hydroxy acid monomers, oxidation of 3′-*O*-*t*-butyldimethylsilylthymidine was accomplished in two steps. An initial Moffat oxidation to give the aldehyde was followed by treatment with $NaClO_2$ in the presence of KH_2PO_4 and 2-methyl-2-butene in aqueous *t*-butanol, to give the hydroxy-protected acid (**3**), which would serve as one of the building blocks for synthesis of the linear trimer (Fig. 2). The benzhydryl protected monomer (**4**) was prepared by alkylation with diphenyldiazomethane and subsequent desilylation with triethylamine trihydrogen fluoride.

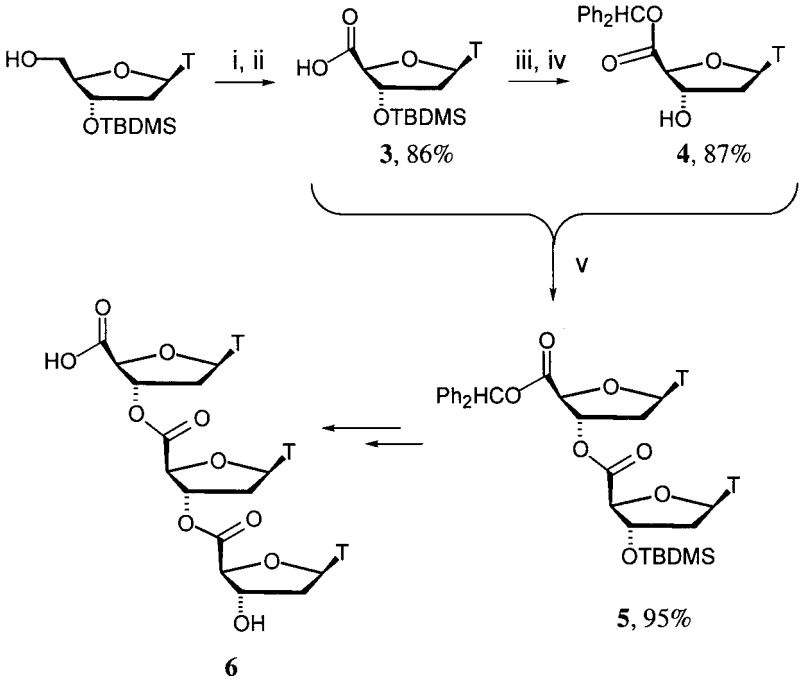

Figure 2. *Reagents and Conditions* i) Dicyclohexylcarbodiimide, dichloroacetic acid, dimethylsulfoxide; ii) $NaClO_2$, H_2O, *t*-butanol, iii) diphenyldiazomethane in acetone; iv) $NEt_3 \cdot 3HF$ in THF; v) HBTU, hydroxybenzotriazole, diisopropyldiethylamine in CH_3CN.

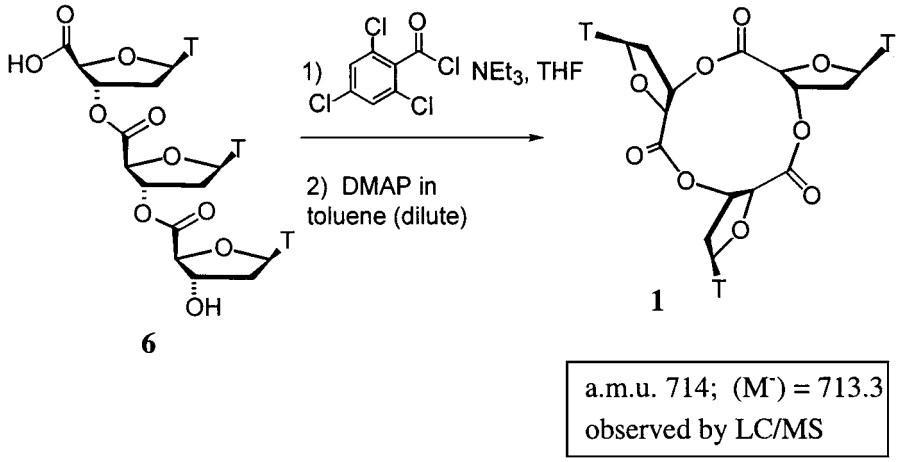

Figure 3.

In the key ester-forming reaction between the monomers **3** and **4** to generate the fully protected dimer (**5**), an extensive range of condensing agents was investigated. Most success was achieved using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexaflurophosphate (HBTU) (6). This commercially available condensing reagent, originally developed for peptide synthesis, gave the dimer in 95% yield. The linear trimer (**6**) was obtained by removal of the benzhydryl group from the dimer followed by a further condensation reaction with monomer (**4**) and subsequent deprotection ($NEt_3 \cdot 3HF$, H_2/Pd). Although this linear trimer was fully characterised it was found to be unexpectedly susceptible to hydrolysis/transesterification, which greatly hindered its isolation.

Our attempts to perform the cyclisation step (Fig. 3) with HBTU, which had proved very effective in the synthesis of the linear esters, were unsuccessful. However, activation with 2,4,6-trichlorobenzoyl chloride (7) (Yamaguchi's reagent) in THF followed by dilution into a solution of *N*,*N*-dimethylaminopyridine in toluene gave a mixture of products, from which the cyclic trimer (**1**) was identified by LC/MS. A pseudomolecular ion of 713.3 was observed in the electrospray spectrum corresponding to M^-.

In conclusion, an efficient synthesis of the thymidine-derived hydroxy acid monomers has been developed and HBTU has proved very effective in condensing these monomer units. Cyclisation has been achieved using Yamaguchi's reagent although the macrolactonisation procedure requires further optimisation.

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