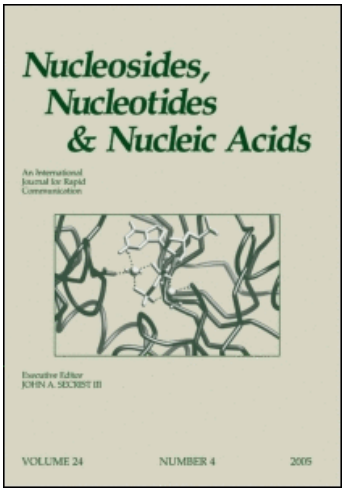

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Foldamers Derived From Nucleoside β-Amino Acids: Pna Or Dna? Can We Have Both In One Place?

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FOLDAMERS DERIVED FROM NUCLEOSIDE β-AMINO ACIDS: PNA OR DNA? CAN WE HAVE BOTH IN ONE PLACE?

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□ *The synthesis of a modified thymidine (nucleoside β-amino acid) monomer and preliminary investigations into the solid phase peptide synthesis of PNA/DNA chimeras containing a neutral, internucleoside amide linkage are described.*

Keywords Peptide nucleic acid; chimera; foldamers; nucleoside beta-amino acid

INTRODUCTION

The majority of natural biological processes rely on macromolecules with defined tertiary structures, the most obvious examples being RNA and protein catalysis. The specificity of these macromolecules is derived from their ability to adopt compact folded architectures, which, in turn, are assemblies of secondary structure motifs, such as helices and sheets. Unnatural oligomers that display similar propensity to adopt conformers are termed "foldamers".[1] Even with the emergence of peptide nucleic acid (PNA),[2] there has only been limited exploration into combining the structural potential of nucleosides (predictable nucleobase association) and the peptide bond. The synthesis of a novel nucleoside β-amino acid has been completed. Derived from thymidine, the compound contains a 5′-carboxylic acid moiety and a 3′-amino function to enable the construction of peptide bonds by standard solid-phase peptide synthesis procedures. Investigation into the synthesis of an amide-backboned oligonucleotide/polypeptide hybrid is currently underway.

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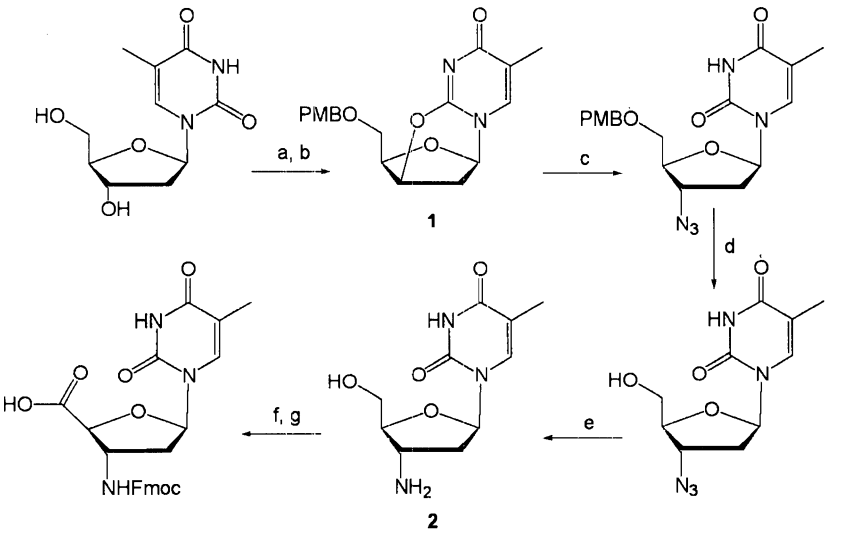


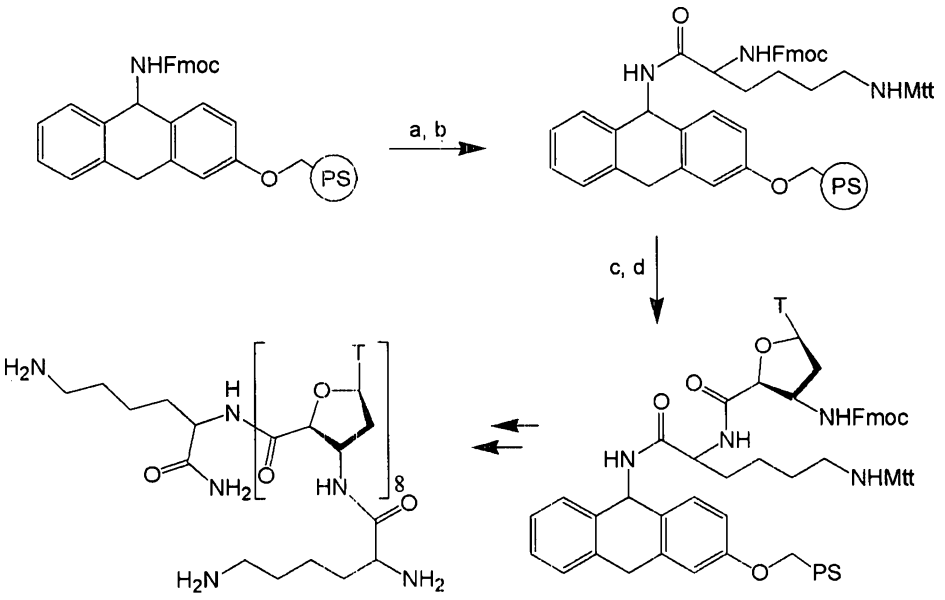
a) PPh_3, DIAD, Anisic acid, DMF; b) PPh_3, DIAD, DMF; c) LiN_3, DMF 125 °C; d) NaOMe, MeOH; e) Pd/C, H_2 MeOH; f) FmocCl, K_2CO_3, 1,4-dioxane/H_2O; g) TEMPO, BAIB, MeCN/H_2O

SCHEME 1

RESULTS AND DISCUSSION

The synthesis of the target Fmoc-protected nucleoside β-amino acid (mT, see Scheme 1) was achieved beginning with the 3′-azido-3′-deoxythymidine (AZT) synthesis of Czernecki *et al.*[3]. Starting from thymidine, two Mitsunobu style reactions performed in tandem allowed sequential, one-pot protection of 5′-OH with a PMB group whilst stereoselectively displacing 3′-OH by forming the anhydro compound (**1**) using neighboring group participation from the heterocyclic base. Yields of the anhydro species were improved by more than 10% over that obtained at room temperature by cooling the reaction mixture to a constant 15°C in a water bath during exothermic DIAD additions. The anhydro species was then opened from the α-face by N_3^- in DMF at 125°C. Little difference in yield was observed using either NaN_3 or LiN_3, both giving around 50% yield after purification. Attempts to improve the yield by the addition of a proton source (benzoic acid) to assist in the reprotonation of thymine N3 also made very little difference to the overall yield.

By far the simplest method for reduction of the 3′-azide was catalytic hydrogenation over Pd/C giving the 3′-amino compound a 97% yield. Fmoc protection of the 3′-amine was afforded by treatment of (**2**) with FmocCl and K_2CO_3 in aqueous 1,4-dioxane. From many available, the method chosen for oxidation of the 5′-OH was using free radical TEMPO and hypervalent iodine complex (bis-acetoxy)-iodobenzene (BAIB).[4] In the standard



a) 2 % DBU/DMAc; b) Fmoc-Lys-(Mtt)-OH, HBTU, DIPEA, DMAc;
c) 2 % DBU/DMAc, Compound (**3**), HBTU, DIPEA, DMAc

SCHEME 2

solvent for this reaction (aqueous acetonitrile) the Fmoc-protected nucleoside is only sparingly soluble, leading to reaction times of greater than 24 hours and low yields of around 45%.

It was believed that these neutral-backboned oligomers would not be readily soluble in aqueous media and that natural α-amino acids should be included in an attempt to improve aqueous solubility. Therefore, it was decided that lysine residues should be included at both *C*- and *N*-terminals (see Scheme 2). Initial studies on oligomerisation of the Fmoc-protected nucleoside β-amino acid were based on the method of Gude *et al.*[5] Loading of Fmoc-Lys-(monomethyltrityl)-OH onto the solid support (Sieber amide resin) was determined by UV assay of dibenzofulvene at $\lambda = 294$ and 304 nm liberated during the deblocking step.

The technique was also extended to the first two couplings of mT to inspect the coupling efficiencies with the natural amino acid and with itself. This qualitative method was sufficient to show that little difference was observed for the coupling of lysine to mT when using either Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) or 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HBTU) as the coupling reagent. However, NMP and DMF were particulary poor solvents. The mT to mT couplings were also solvent dependent. In this case, coupling yields were significantly reduced using the

combination of HBTU with DMF but increased greatly with the addition of 20% DMSO. The superior solvent/coupling reagent combination was found to be *N*,*N*,-dimethylacetamide with HBTU.

CONCLUSIONS

The modified thymidine monomer, mT, has been synthesized successfully in reasonable yield from thymidine and the production of oligomers via solid-phase peptide synthesis protocols is currently under investigation.

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