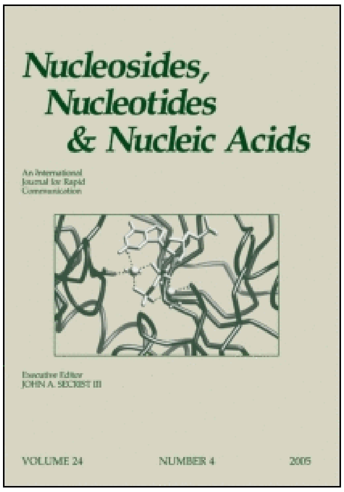

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Synthesis of Thymine Derivatives of 4-Hydroxyvaline

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ABSTRACT

A synthetic route to thymine derivatives of (2*S*,3*R*)- and (2*S*,3*S*)-4-hydroxyvaline has been developed starting from commercially available *L*-aspartic acid.

Key Words: PNA; Hydroxyvaline analogues; α-Amino acids.

Polyamide nucleic acid (PNA) analogues of DNA (**1**) have attracted much interest as potential regulators of gene expression through their ability to invade double-stranded DNA.[1] However, one limitation that is hindering the development of PNA is that strand invasion is generally restricted to homopurine and homopyrimidine PNA.[1] Thus, there is the need to explore other PNA analogues for the purpose of expanding the strand invasion alphabet. Recently, we have reported the design and synthesis of a true peptide mimic of DNA, designated L-α-PNA (**2**).[2] Surprisingly, L-α-PNA oligomers failed to bind to complementary ssDNA. We believe that the most likely explanation for this is side chain flexibility and so we are currently examining side chain restricted analogues. As part of this research programme, we are interested in evaluating β-substituted-L-α-PNAs such as **3**.

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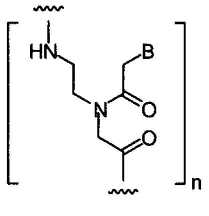

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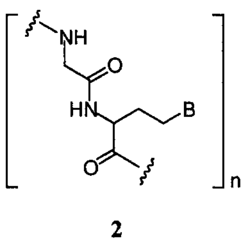

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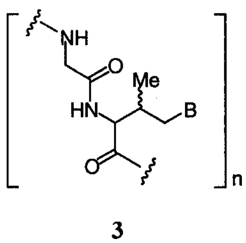
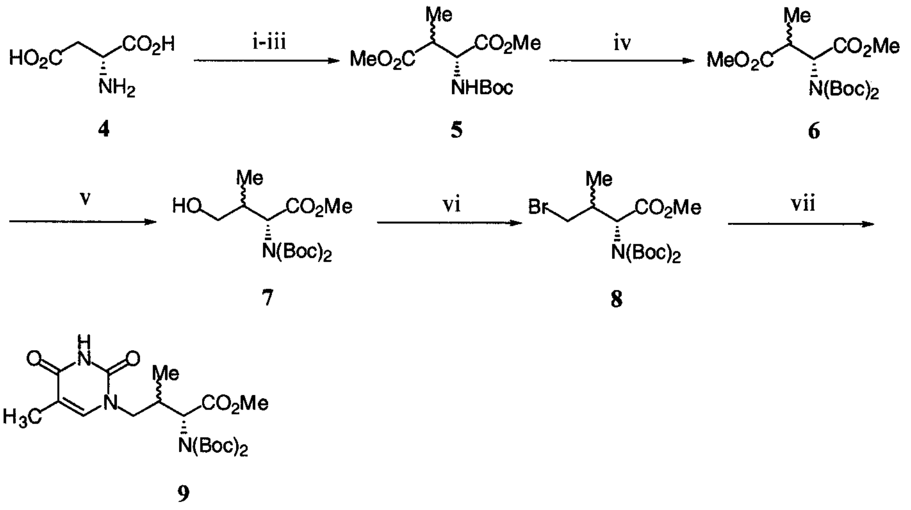


3

The 4-hydroxyvaline derivative **7** is the key intermediate in the synthesis of the thymine monomers required for construction of the β-methyl-L-α-PNA oligomers. This has been prepared as an inseparable mixture of diastereoisomers in five steps from commercially available *L*-aspartic acid (**4**) as shown in Scheme 1.

Treatment of **7** with *N*-bromosuccinimide and triphenylphosphine yielded the bromo derivative **8**. Finally, alkylation of thymine with **8** in the presence of sodium hydride gave the thymine monomer **9** in reasonable yields. We are currently working on separating the two diastereoisomers of **9**.



Scheme 1. Reagents: i. $SOCl_2$, MeOH; ii. $(Boc)_2O$, Et_3N, MeOH;[3] iii. (a) LiHMDS, THF, −78°C (b) MeI, −7°C;[4] iv. $(Boc)_2O$, DMAP, CH_3CN;[3] v. DIBAL-H, diethyl ether, −78°C;[3] vi. NBS, PPh_3, pyridine, DCM; vii. Thymine, NaH, DMF

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