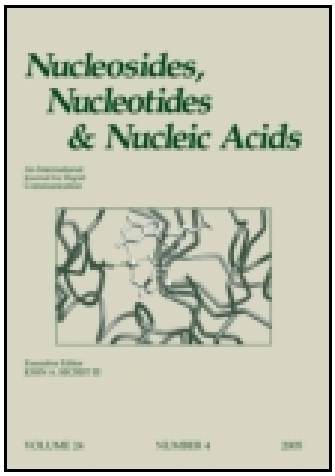

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α-cycloPNA: 1-Aminocylopentane-1-carboxylic Acid-Derived Peptide Nucleic Acid

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α-cycloPNA: 1-Aminocylopentane-1-carboxylic Acid-Derived Peptide Nucleic Acid

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ABSTRACT

All four diastereoisomers of 3-thymine-1-(^{t}butoxycarbonyl)aminocyclopentane-1-carboxylic acid have been synthesised from (*S*)-dimethyl malate and thymine monomer **12** has been incorporated into an α-cycloPNA oligomer.

Key Words: PNA; Cyclic α,α-disubstituted amino acids.

Polyamide analogues of DNA (**1**), termed PNA, have attracted much interest as potential regulators of gene expression as a consequence of their ability to invade ds-DNA.[1] However, one limitation hindering the development of PNA is that strand invasion by simple examples is generally restricted to homopurine and homopyrimidine sequences.[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, despite molecular models indicating structural complementarity,

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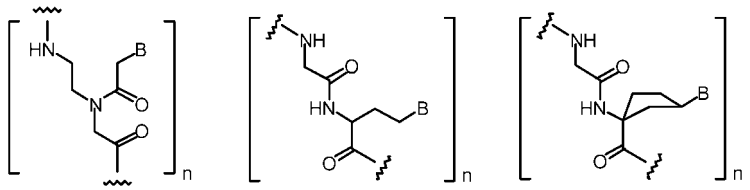
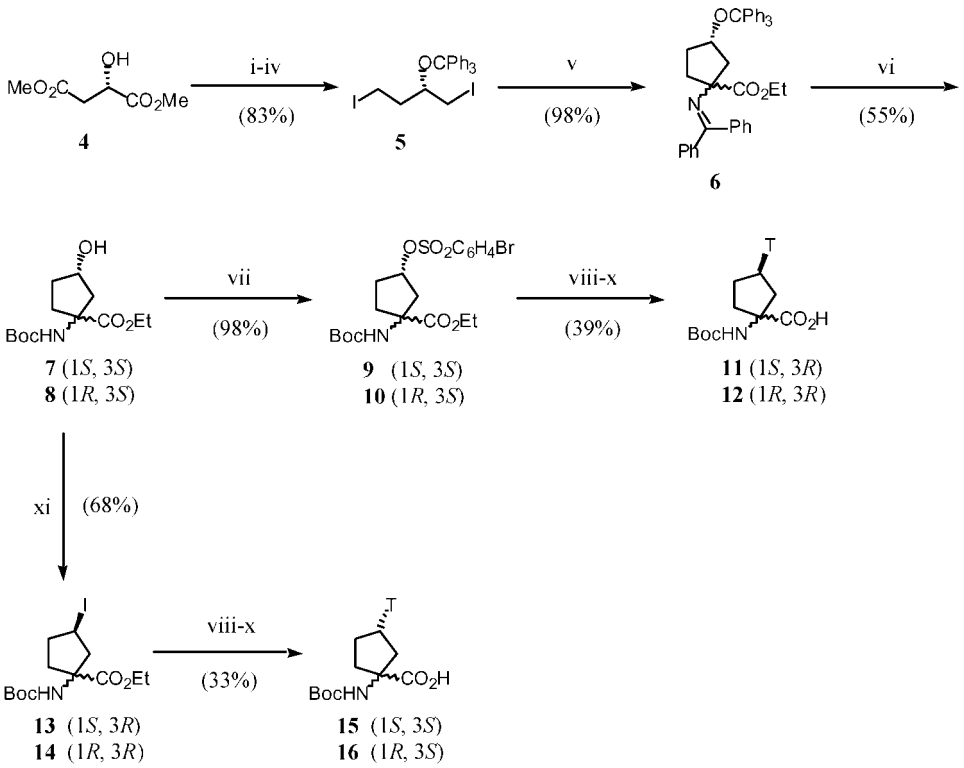
L-α-PNA oligomers fail to hybridise to single-stranded target DNAs. We believe that this is due to flexibility in the side chain linking the bases to the backbone and so we are currently exploring side chain restricted analogues. One of the proposed oligomers for study is α-cycloPNA (**3**).



1 **2** **3**

Synthetic routes to all four diastereoisomers of the thymine monomer required for construction of the α-cycloPNA oligomers have now been developed starting from commercially available (*S*)-dimethyl L-malate (**4**) as outlined below.



4 **5** **6**

7 (1*S*, 3*S*)
8 (1*R*, 3*S*)

9 (1*S*, 3*S*)
10 (1*R*, 3*S*)

11 (1*S*, 3*R*)
12 (1*R*, 3*R*)

13 (1*S*, 3*R*)
14 (1*R*, 3*R*)

15 (1*S*, 3*S*)
16 (1*R*, 3*S*)

Reagents: i. Ph_3CCl, DBU, DCM; ii. $LiBH_4$, B-methoxy-9-BBN, THF; iii. MsCl, Et_3N, DCM; iv. NaI, acetone; v. $Ph_2CNCH_2CO_2Et$, LiHMDS, THF; vi. (a) 2M(aq) HCl (b) $(Boc)_2O$, Na_2CO_3; vii. $BrC_6H_4SO_2Cl$, DMAP, Et_3N, $CHCl_3$; viii. *N*3-benzoylthymine, NaH, DMF; ix. NaOEt, EtOH; x. 2/3M(aq) NaOH, dioxane; xi. PPh_3, DIAD, MeI, THF.

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Finally, monomer **12** has been successfully incorporated into an α-cycloPNA oligomer using our established manual solid phase protocol.[2]

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