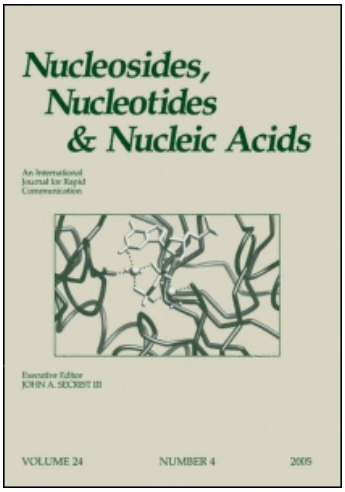

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A Novel PNA-Monomer for Recognition of Thymine in Triple-Helix Structures

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ABSTRACT

To expand the triplex recognition repertoire of Nucleic Acids, novel nucleobases that recognize thymine in a T-A base pair are still required. A novel conformationally constrained PNA-monomer **(II)** capable of binding T in a triplex motif was designed and synthesized in 7 steps starting from commercially available dimethyl 2-oxoglutarate.

Triplex targeting of double-stranded DNA is essentially limited to homopurine stretches. Therefore novel nucleobases that recognise C(-G) and especially T (-A) are required. The known E-base PNA-monomer (**I**)[1] synthesized some years ago is able to recognise T when incorporated into the Hoogsteen strand of a bis-PNA. But binding affinity is low which might be due to excessive flexibility and/or steric clash with the 5-methyl group of thymine. E-base PNAs bind somewhat stronger to uracil than thymine containing targets.[1] The new analogue (**II**) contains a double bond, thereby introducing restricted flexibility in the linker. The hope is to preorganise the mono-

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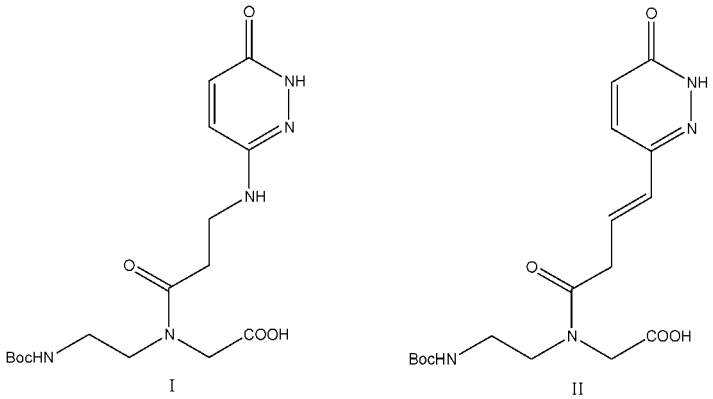

Figure 1. Structures of the known E-base PNA-monomer[1] (**I**) and the new analogue (**II**).

mer in a conformation more favourable for binding to thymine. The binding motif is the same for both monomers. The NH hydrogen functions as a donor and binds the 4-oxo group of thymine.

RESULTS AND DISCUSSION

In order to prepare the conformationally constrained PNA-monomer (**8**) commercially available dimethyl 2-oxoglutarate (**1**) was chosen as starting material. The first step was a ring closure to the known pyridazinone (**2**)[2] using hydrazine and acid catalysis in methanol. To improve hydrophobicity compound **2** was reacted with *p*-methoxybenzyl chloride and sodium hydride in DMF to obtain the PMB protected product (**3**). The ester functionality of **3** was subsequently reduced to the primary alcohol (**4**) using sodium borohydride in a refluxing mixture of THF and methanol.[3] Some cleavage of the ester was also observed due to the alkaline conditions, but to a much lesser extent than when pure hydroxylic solvent was used. Treatment of compound **4** with activated manganese(IV) oxide in refluxing toluene afforded a tandem reaction where the primary alcohol was first oxidised to the aldehyde and next an oxidative aromatisation took place to give compound **5**. The reduction-oxidation strategy to obtain the aldehyde was chosen since an earlier attempt with direct Dibal-H reduction of the ester was unsuccessful. The key step was a Wittig reaction between aldehyde (**5**) and 2-carboxyethyltriphenylphosphonium bromide.[4] The reaction took place in a 1:1 mixture of THF and DMSO using sodium hydride as base and afforded only the desired E-isomer (**6**) as expected.[5] Compound **6** was then condensed with methyl *N*-(2-Boc-aminoethyl)glycinate[6] using DCC and DHbtOH as coupling reagents. Basic hydrolysis of the resulting ester (**7**) gave the monomer **8**. Deprotection of *p*-methoxybenzyl is expected to take place under the acidic conditions required for cleavage of the other protecting groups when incorporated in PNA.

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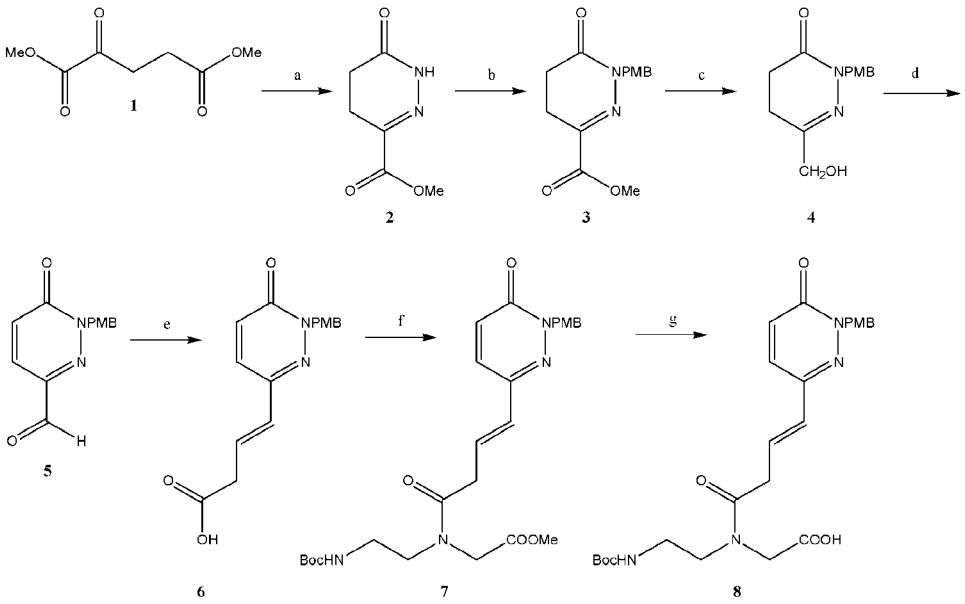

Scheme 1. Reagents, conditions and yields: **a**) NH_2NH_2, ACOH, MeOH, reflux (92%); **b**) *p*-methoxybenzylchloride, NaH, DMF, 0°C- > RT (84%); **c**) $NaBH_4$, THF, MeOH, reflux (58%); **d**) activated MnO_2, toluene, reflux (30%); **e**) $[P(Ph)_3(CH_2)_2COOH]^+Br^-$, NaH, THF/DMSO, 0°C- > RT (42%); **f**) methyl *N*-(2-Boc-aminoethyl)glycinate, DhbtOH, DCC, DMF, 0°C- > RT (50%); **g**) 2M NaOH, MeOH, 0°C (46%).

CONCLUSION

The synthesis of a novel PNA-monomer has been accomplished. The triplex recognition properties of this E-base analogue is currently under investigations.

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