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# New Nucleoside Analogues for the Recognition of Pyrimidine-Purine Inversion Sites

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## New Nucleoside Analogues for the Recognition of Pyrimidine-Purine Inversion Sites

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### ABSTRACT

A new nucleoside designed to enhance triplex stability has been synthesised in 15 steps starting from sugar 2. This pathway contains the sugar derivative 9 which is a useful intermediate for the introduction of other natural and unnatural bases into the 2'-aminoethoxy nucleoside containing scaffold.

Strong and sequence specific triple helix formation of oligonucleotides with a DNA target duplex can selectively interfere with gene expression on the level of transcription (antigene strategy).<sup>[1,2]</sup> Despite considerable efforts directed to the removal of the homopurine/homopyrimidine sequence requirement for stable DNA triple helix formation by third strand oligonucleotides, a general recognition motif by third strands for any given DNA sequence is still elusive. We recently reported that selective recognition of a cytosine-guanine base pair within the parallel DNA triple helical binding motif can be achieved by a DNA third strand containing 5-methyl-pyrimidin-2-(1*H*)-one ( $^{4H}$ T).<sup>[3]</sup> Nonetheless the stability of the resulting triple helix is quite

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*Figure 1.* a) HCl (2% w/w), MeOH, 3.5 h, R.T., 63%. b) TIPS-Cl (1.2 eq.), pyridine, 1 h, R.T., 83%. c) BrCH<sub>2</sub>CO<sub>2</sub>Me (5 eq.), NaH (2.2 eq.), DMF, 10 h,  $-10^{\circ}$ C-R.T., 77%. d) LiBH<sub>4</sub> (4 eq.), THF/MeOH (4/1), 1 h, 0°C, 94%. e) Ph<sub>3</sub>P (1.4 eq.), LiN<sub>3</sub> (4 eq.), CBr<sub>4</sub> (1.4 eq.), DMF, 9 h, 0°C-R.T. f) TsCl (2 eq.), NEt<sub>3</sub> (2.1 eq.), DMAP (0.1 eq.), CH<sub>2</sub>Cl<sub>2</sub>, overnight, R.T., 93%. g) LiN<sub>3</sub> (2 eq.), DMF, 1.5 h, 90°C, 96%. h) Lindlar catalyst (50% w/w), H<sub>2</sub>, THF, overnight, R.T., quantitative. i) Et<sub>3</sub>N (1 eq.), CF<sub>3</sub>CO<sub>2</sub>Et, 4 h, R.T., 89%. l) (13) (1.05 eq.), HMDS (0.5 eq.), TCS (0.5 eq.), CH<sub>3</sub>CN, 13 h, R.T. m) Ac<sub>2</sub>O/AcOH/H<sub>2</sub>SO<sub>4</sub>, 14 h, R.T., 91%. n) (13) (1.05 eq.), BSA (2.6 eq.), SnCl<sub>4</sub> (1 eq.), CH<sub>3</sub>CN, 2 h, 0°C, 55%. r) i. POCl<sub>3</sub> (2.2 eq.), DMF (2.4 eq.), 2 h, 70°C, 83%. ii. H<sub>2</sub>O, overnight, K<sub>2</sub>CO<sub>3</sub>, 30%. s) i. Na (2.3 eq.), Urea (1.2 eq.), EtOH, 2d, reflux. ii. HCl 25% (pH = 2), 1d, reflux, 50%. o) Na<sub>2</sub>CO<sub>3</sub> an. (10% w/w), MeOH, 30 min., R.T., 90%. p) DMT-Cl (2 eq.), pyridine, 5 h, R.T., 75%. q) iPr<sub>2</sub>NEt (3 eq.), [(iPr<sub>2</sub>N) (NCCH<sub>2</sub>CH<sub>2</sub>O)P]Cl (1.5 eq.), THF, 2 h, R.T., 75%.

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low. It has also been described that the presence of a 2'-aminoethoxy function enhances the affinity of the triplex forming oligonucleotide for its complementary DNA double strand.<sup>[4]</sup> By combining those two elements, we synthesised the new nucleoside analogue 1 which is expected to improve the stability of the triple helices at pyrimidine-purine inversion sites. Three different approaches for the synthesis of 1 were investigated. First, we tried to modify the base starting from ribothymidine, via sulphur-oxygen exchange at C4, followed by reduction with Raney-Ni. Unfortunately this route revealed to be more problematic than expected, mainly due to overreduction of the base. In the second strategy, the base 13 was synthesised in two steps starting from propionaldehyde diethylacetal<sup>[5,6]</sup> and then coupled to the sugar. Here we encountered problems with the introduction of the 2'-O-aminoethyl chain due to the instability of the base during the necessary transformations. Finally, we found a promising synthetic pathway (Fig. 1) which includes compound 9, a potentially useful intermediate for the introduction of various bases into the 2'O-aminoethyl nucleoside scaffold at a late stage.

Methyl  $\beta$ -D-ribofuranoside **3** was synthesised starting from ribose and then protected with dichloro-1,1,3,3-tetraisopropyldisiloxane. Alkylation of the protected sugar 4 with methyl bromoacetate followed by reduction of the methyl ester, tosylation and replacement of the tosyloxy group by azide yielded the azidoethyl derivative 6. After reduction of the azide and protection of the resulting amine, the sugar was acetylated ( $\rightarrow$  9) in order to facilitate the nucleosidation step.<sup>[7]</sup> Phosphoramidite 1 was successfully obtained by standard procedures. Compound 1 will be incorporated into oligonucleotides and its binding/pairing properties will be studied.

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