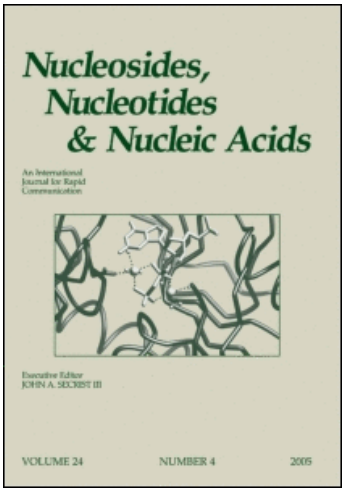

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Buchini, Sabrina and Leumann, Christian J.(2003) 'New Nucleoside Analogues for the Recognition of Pyrimidine-Purine Inversion Sites', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1199 — 1201
To link to this Article: DOI: 10.1081/NCN-120022835
URL: http://dx.doi.org/10.1081/NCN-120022835

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1199–1201, 2003

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).[1,2] 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**).[3] Nonetheless the stability of the resulting triple helix is quite

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DOI: 10.1081/NCN-120022835
1525-7770 (Print); 1532-2335 (Online)

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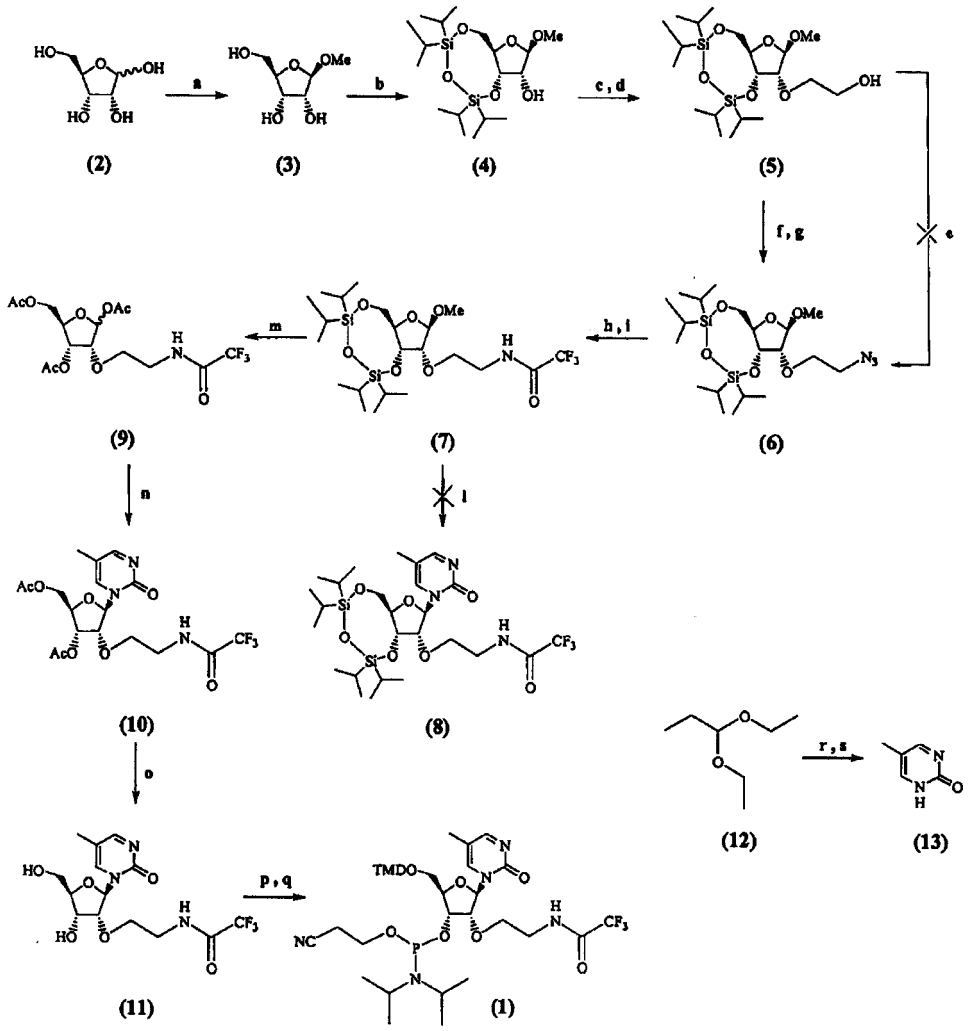

Figure 1. a) HCl (2% w/w), MeOH, 3.5 h, R.T., 63%. b) TIPS-Cl (1.2 eq.), pyridine, 1 h, R.T., 83%. c) $BrCH_2CO_2Me$ (5 eq.), NaH (2.2 eq.), DMF, 10 h, −10°C-R.T., 77%. d) $LiBH_4$ (4 eq.), THF/MeOH (4/1), 1 h, 0°C, 94%. e) Ph_3P (1.4 eq.), LiN_3 (4 eq.), CBr_4 (1.4 eq.), DMF, 9 h, 0°C-R.T. f) TsCl (2 eq.), NEt_3 (2.1 eq.), DMAP (0.1 eq.), CH_2Cl_2, overnight, R.T., 93%. g) LiN_3 (2 eq.), DMF, 1.5 h, 90°C, 96%. h) Lindlar catalyst (50% w/w), H_2, THF, overnight, R.T., quantitative. i) Et_3N (1 eq.), CF_3CO_2Et, 4 h, R.T., 89%. l) **(13)** (1.05 eq.), HMDS (0.5 eq.), TCS (0.5 eq.), CH_3CN, 13 h, R.T. m) $Ac_2O/AcOH/H_2SO_4$, 14 h, R.T., 91%. n) **(13)** (1.05 eq.), BSA (2.6 eq.), $SnCl_4$ (1 eq.), CH_3CN, 2 h, 0°C, 55%. r) i. $POCl_3$ (2.2 eq.), DMF (2.4 eq.), 2 h, 70°C, 83%. ii. H_2O, overnight, K_2CO_3, 30%. s) i. Na (2.3 eq.), Urea (1.2 eq.), EtOH, 2d, reflux. ii. HCl 25% (pH = 2), 1d, reflux, 50%. o) Na_2CO_3 an. (10% w/w), MeOH, 30 min., R.T., 90%. p) DMT-Cl (2 eq.), pyridine, 5 h, R.T., 75%. q) iPr_2NEt (3 eq.), $[(iPr_2N)(NCCH_2CH_2O)P]Cl$ (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.[4] 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 over-reduction of the base. In the second strategy, the base **13** was synthesised in two steps starting from propionaldehyde diethylacetal[5,6] 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 β-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 (→ **9**) in order to facilitate the nucleosidation step.[7] 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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