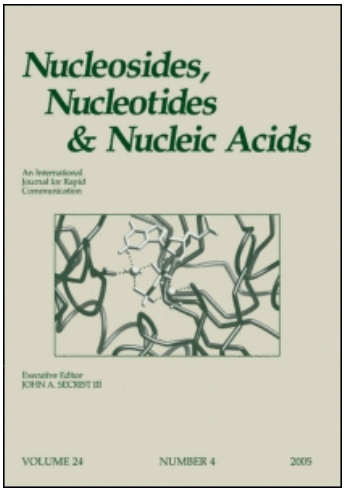

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Kovács, Lajos , Hornyák, Miklós and Howarth, Nicola M.(2003) 'Conformationally Restricted Chiral Peptide Nucleic Acids Derived from Azetidines', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1363 — 1365
To link to this Article: DOI: 10.1081/NCN-120022966
URL: http://dx.doi.org/10.1081/NCN-120022966

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1363–1365, 2003

Conformationally Restricted Chiral Peptide Nucleic Acids Derived from Azetidines

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ABSTRACT

The initial experiments towards the chemical synthesis of conformationally rigid peptide nucleic acid analogues with azetidine moieties have been described.

Key Words: Peptide nucleic acid analogues; Conformational restriction; Azetidines.

The recent success of peptide nucleic acids (PNA)[1,2] is shadowed by their poor cellular uptake, ability to form aggregates and limited water solubility. The advent of conformationally rigid PNA analogues derived from pyrrolidine rings[3,4] prompted us to embark upon the synthesis of new PNA analogues with azetidine moieties (Sch. 1). This structural unit should have similar characteristics as the pyrrolidines and has the added advantage of being cationic due to the slightly basic azetidine ring which should enhance cellular uptake.

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DOI: 10.1081/NCN-120022966
1525-7770 (Print); 1532-2335 (Online)

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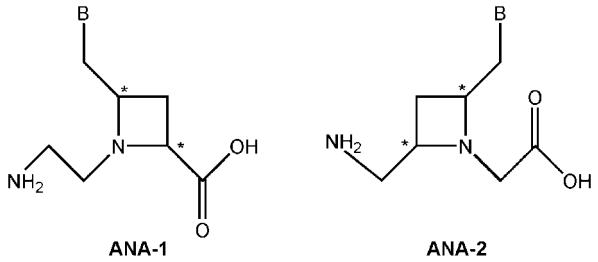
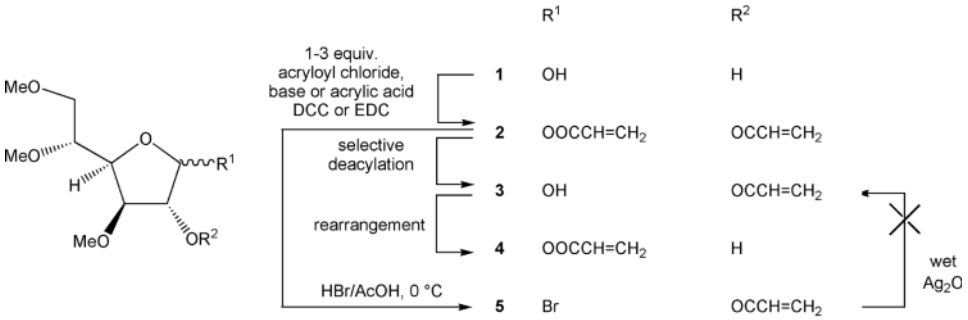


Scheme 1.

The aims of this work were as follows: 1. to synthesize azetidine nucleic acid (ANA) monomers (ANA-1, ANA-2) based on 1,3-dipolar cycloaddition reaction of the appropriate nitrones and alkenes followed by ring transformations of isoxazoles into the corresponding azetidines; 2. to reduce the formation of isomers by employing chiral auxiliaries (e.g., 3,5,6-tri-*O*-methyl-D-glucofuranose and 2,3 : 5,6-di-*O*-isopropylidene-α-D-mannofuranose, respectively) and/or conduct the reactions intramolecularly.

The synthesis of ANA-1 monomer was undertaken using the chiral auxiliary **1**[5] available from D-glucose in simple steps (Sch. 2). The acryloylation of this latter substance yielded different proportions of mono- and bis-acylated derivatives **2**–**4**, depending on the amount of acylating agent applied. The transformation of the 1,2-bis-*O*-acryloylated derivative **2** into the desired 2-*O*-acryloyl compound **3** was attempted under a variety of conditions [$(Bu_3Sn)_2O$, toluene, Δ; Bu_3SnOMe, $ClCH_2CH_2Cl$, Δ; $(NH_4)_2CO_3$/DMF; montmorillonite K10, wet acetonitrile, Δ; BF_3OEt_2, wet acetonitrile, 0°C] but exclusively the 1-*O*-acryloyl derivative **4** was obtained indicating an unwanted acyl migration of the acrylate group from position 2 to 1. The glycosyl halide **5**, easily available from compound **2**, was surprisingly stable and it did not afford the 2-*O*-acryloyl derivative **3** with wet silver oxide. Direct oxime formation with hydroxylamine hydrochloride was not successful.

The rationale behind the synthesis of compound **3** was its transformation into the corresponding oxime which, in turn, with nucleobase-substituted acetaldehydes



Scheme 2.

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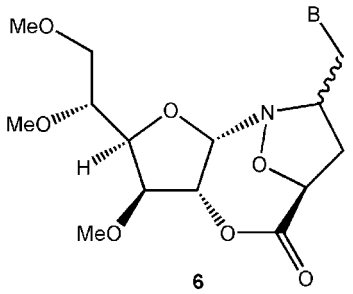

Scheme 3.

should give a nitrone, the intramolecular 1,3-dipolar cycloaddition of which would result in the formation of the desired isoxazole **6** (Sch. 3).

ACKNOWLEDGMENT

The financial support of The Wellcome Trust (grant no. 063879/Z/01/Z) is gratefully acknowledged.

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