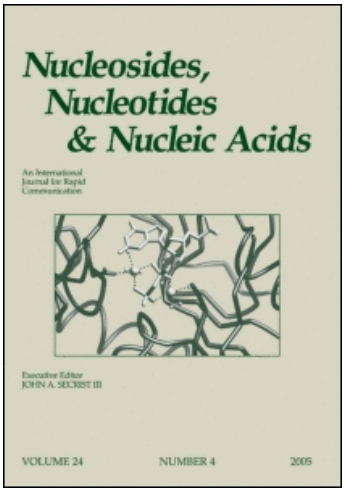

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INVESTIGATION OF 1,3-DIPOLAR CYCLOADDITION REACTIONS OF UNSATURATED NITRONES IN IONIC LIQUIDS

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□ *The effect of the media (achiral and chiral ionic liquids) on the stereochemistry of intramolecular 1,3-dipolar cycloaddition reactions of D-galactose-derived ω-unsaturated nitrones, leading to bicyclic isoxazolidines, has been investigated.*

Keywords 1,3-dipolar cycloaddition; Bicyclic isoxazolidines; Ionic liquids; Nitrone-alkene cycloaddition; PNA analogues

RESULTS AND DISCUSSION

The recent advancements in the synthesis of peptide nucleic acids (PNA)[1,2] indicate that conformationally rigid PNAs derived from pyrrolidine rings[3,4] have outstanding biological features among the newly synthesized analogues. This fact prompted us to investigate the synthetic routes leading to new PNA analogues with azetidine moieties (ANA-1 and ANA-2, Figure 1)

Our synthetic strategy was based on the preparation of carbohydrate-based bicyclic isoxazolidines that can further be elaborated into the target chiral azetidines. Herein we would like to report our preliminary results on intramolecular 1,3-dipolar cycloaddition reactions for the D-*galacto* series.

The reaction sequence shown in Scheme 1 was utilized since the simpler route, which involves iodination at the primary 6-hydroxyl group followed

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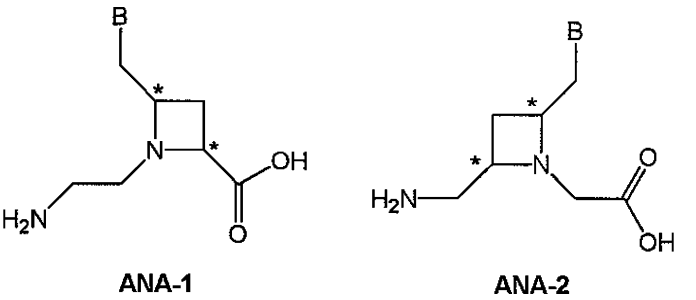
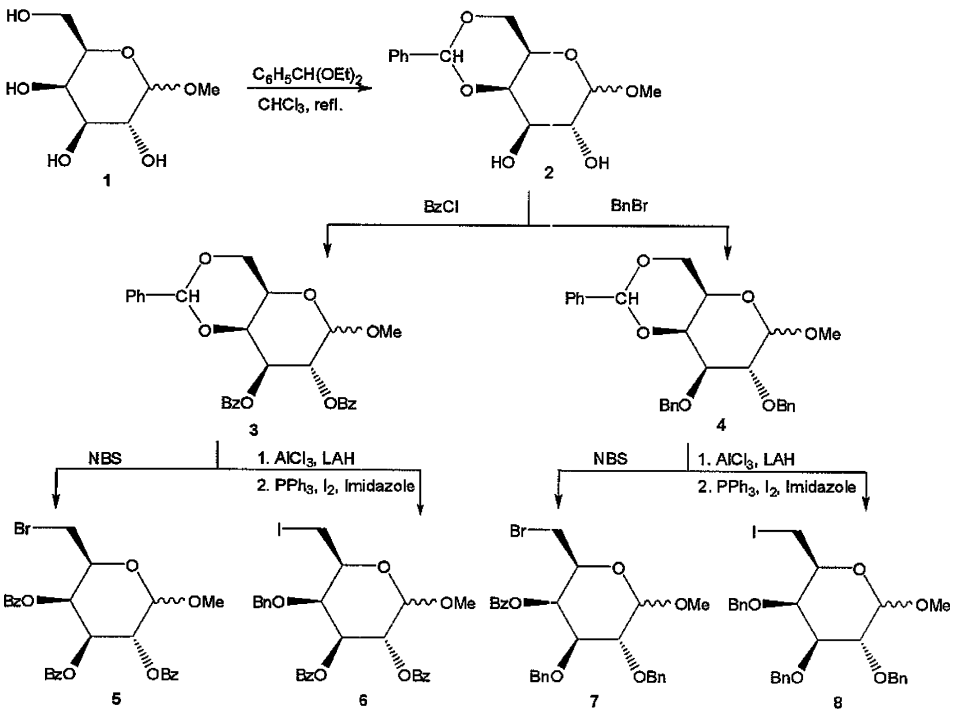
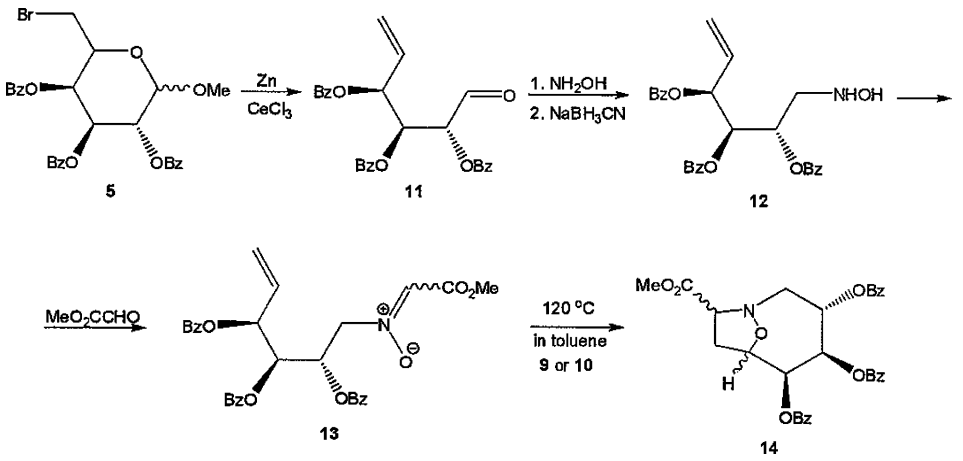


FIGURE 1 The structure of azetidine nucleic acid monomers ANA-1 and ANA-2.

by protection of the remaining secondary hydroxyl groups, failed. After selective protection of 4- and 6-hydroxyl groups of **1** as an acetal, the remaining free hydroxyl groups of compound **2** were protected either with benzoyl or benzyl protecting groups (**3** and **4**). The selective opening of the 4,6-*O*-benzylidene ring with *N*-bromosuccinimide[5] or with the $LiAlH_4$-$AlCl_3$ reagent[6] provided a series of 6-deoxy-6-halo derivatives with different protecting group patterns (**5–8**). The oximes so obtained serve as building blocks for the synthesis of our target ANA derivatives (Scheme 2).



SCHEME 1



SCHEME 2

Starting from *N*-methyl-imidazole and L-alanine, ionic liquids **9**[7] and **10**[8] were prepared (Figure 2) to investigate the effect of media on the stereochemical outcome of cycloaddition reaction.

Starting from the bromine derivative **5**, nitrone **13** was synthesized in four steps as depicted in Scheme 2. Nitrone **13** was heated in toluene in the presence of **9** and **10**. The reactions carried out in toluene and in **9** furnished two isomers **14** out of the possible four diastereomers in ratios of ca. 3:1 and 8:1. In the presence of **10** only one isomer (the main product of the former two reacions) could be detected. Additionally, the conversion after 24 h at reflux was about 70% in toluene alone, whereas in the ionic liquids the starting nitrone **13** completely disappeared (TLC). The detailed NMR experiments to identify the absolute stereochemistry of the products formed are in progress.

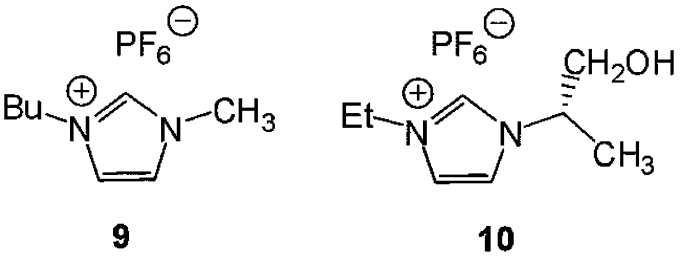


FIGURE 2 The structure of ionic liquids **9** and **10**.

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