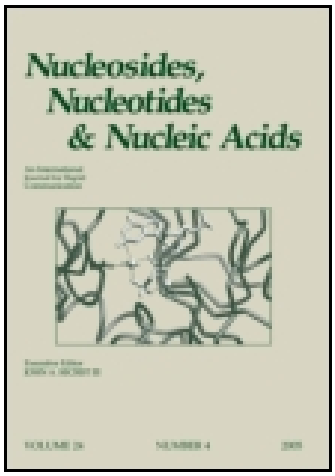

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METHYL 5-O-BENZOYL-2,3-OXAZOLE-D-RIBOFURANOSIDE: A USEFUL INTERMEDIATE FOR THE SYNTHESIS OF CONFORMATIONALLY RESTRAINED NUCLEOSIDES

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METHYL 5-*O*-BENZOYL-2,3-OXAZOLE-D-RIBOFURANOSIDE: A USEFUL INTERMEDIATE FOR THE SYNTHESIS OF CONFORMATIONALLY RESTRAINED NUCLEOSIDES

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ABSTRACT

The synthesis of methyl 5-*O*-benzoyl-2,3-oxazole-D-ribofuranoside, a tetrahydrofuro [3,4-*d*]oxazole is described. The key step involves the reaction of methyl 3-amino-3-deoxy-5-*O*-benzoyl-D-ribofuranoside with *N*,*N*-dimethylformamide dimethyl acetal with cyclisation to the 2,3-oxazole *via* a prototropic rearrangement-elimination reaction.

The conformation of nucleosides is important for optimal binding at a specified enzyme active site and can therefore have a profound impact on the biological activity. For example, conformational analysis of HIV-1 reverse transcriptase inhibitors has shown that the 3′-exo (and to a lesser extent 2′-endo) character of the sugar moiety with a trans (*ap*) C4′–C5′ conformation is the most favourable conformation with regards to biological activity (1). The introduction of either fused rings, *e.g.* benzofuran (2), in place of the sugar moiety or the introduction of cyclic moieties, *e.g.* cyclopropyl (3), in the sugar component, can result in the nucleoside being 'locked' in a specific conformation. The objective was to develop methodology for the synthesis of novel tetrahydrofuro[3,4-*d*]oxazoles (2,3-oxazole-D-ribofuranosides), which could be used for the synthesis of conformationally restrained nucleosides.

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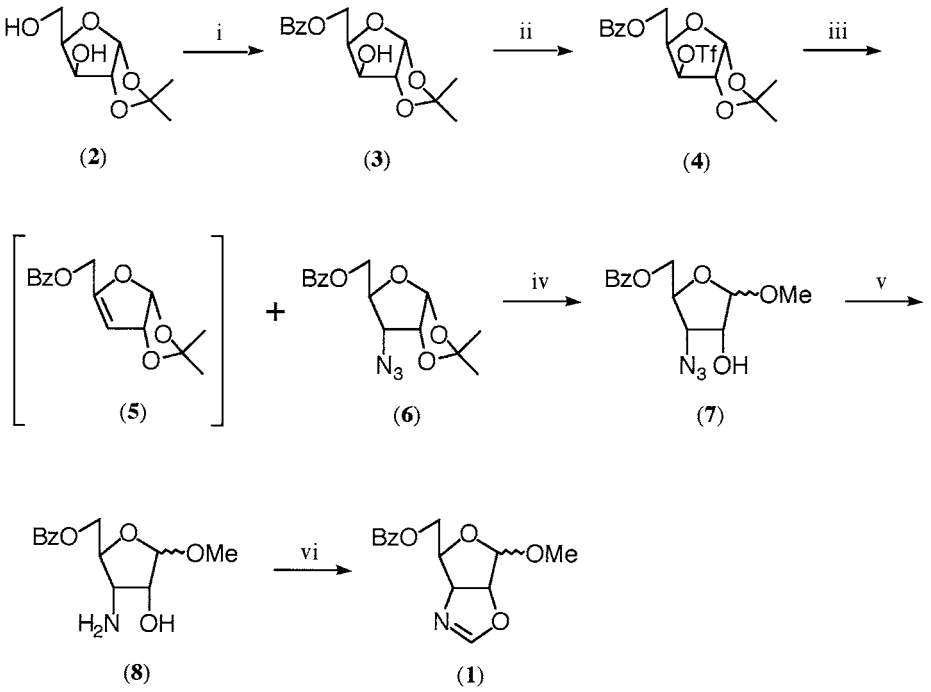
Initial studies involved the synthesis of methyl 2,3-oxazole-D-glucofuranoside, which was achieved in five steps from diacetone-D-glucose (4). The methodology established in this synthesis was then applied to the preparation of the required methyl 5-*O*-benzoyl-2,3-oxazole-D-ribofuranoside **1**, using 1,2-*O*-isopropylidene-D-xylofuranose **2** as the starting material.

After selective 5-*O*-benzoylation to give **3**, the 3-hydroxy was then converted to the triflate **4** in quantitative yield on reaction with triflic anhydride. Displacement of the triflate with azide anion gave the 3-azido-sugar **6** in only 26% yield owing to a competing base-induced elimination of TfOH from **4**, resulting in the formation of the 3,4-ene-sugar **5** in 44% yield (Scheme 1).

Removal of the 1,2-*O*-isopropylidene group of **6** with concommittant methylation at C-1 was achieved in a 1-pot reaction to give the methyl furanoside **7**, using methodology previously described by us (5), and reduction of the azido function with Ph_3P/H_2O gave the precursor methyl 3-amino-3-deoxy-5-*O*-benzoyl-D-ribofuranoside **8**. The resulting amino-sugar **8** was reacted with *N*,*N*-dimethylformamide dimethylacetal to give the cyclised product, methyl 5-*O*-benzoyl-2,3-oxazole-D-ribofuranoside **1**, *via* a prototropic rearrangement followed by ring closure with consecutive elimination of dimethylamine (5).



Scheme 1. *Reagents and conditions*: (i) BzCl, pyridine, CH_2Cl_2, −20 to −30°C, 10 min, 84% (ii) Tf_2O, pyridine, CH_2Cl_2, −20°C, 1.5 h, 97% (iii) NaN_3, DMF, 50°C, 2 h, 44% for **5** and 26% for **6** (iv) 0.5% wt/vol I_2 in MeOH, 80°C, 7 h then r.t. o/n, 80% (v) Ph_3P, THF, r.t. 1 h then H_2O, 60°C, 30 min, 86% (vi) *N*,*N*-dimethylformamide dimethylacetal, DMF, 20 h, 85%.

The methodology for the synthesis of novel tetrahydrofuro[3,4-*d*]oxazoles has been applied to the synthesis of a 2,3-oxazole-fused-ribose intermediate, which can be employed in the preparation of conformationally restrained nucleosides. Further work involving the preparation of conformationally restrained nucleosides using the tetrahydrofuro[3,4-*d*]oxazoles, as well as extension of the described methodology for the preparation of intermediates with modification in both the oxazole component and position of fusion, is currently underway.

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