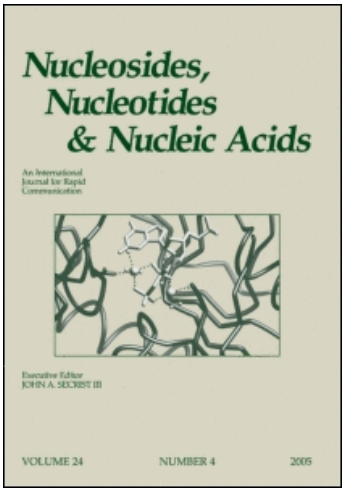

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METHYL 5-*O*-BENZOYL-2,3-OXAZOLE-D-RIBOFURANOSIDE: A USEFUL INTERMEDIATE FOR THE SYNTHESIS OF CONFORMATIONALLY RESTRAINED NUCLEOSIDES

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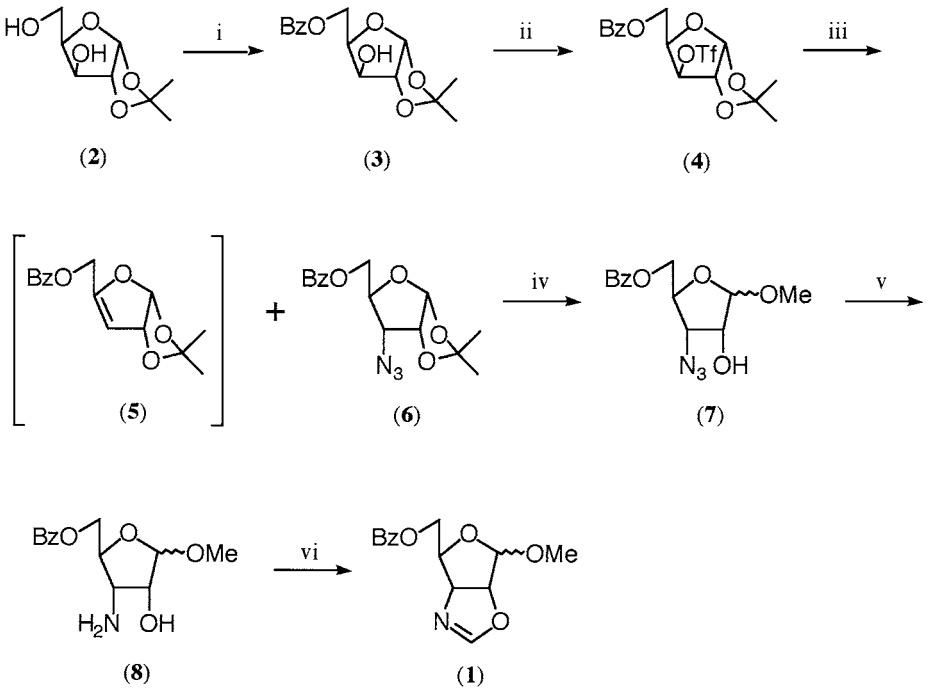
Initial studies involved the synthesis of methyl 2,3-oxazole-D-glucofuranoside, which was achieved in five steps from diacetone-D-glucose (4). The methodology established in this synthesis was then applied to the preparation of the required methyl 5-*O*-benzoyl-2,3-oxazole-D-ribofuranoside **1**, using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

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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.

REFERENCES

1. Van Roey, P.; Taylor, E.W.; Chu, C.K.; Schinazi, R.F. *Ann. N.Y. Acad. Sci*., **1990**, *616*, 29–39.
2. Ewing, D.F.; Fahmi, N-E.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P.; Shaw, G. *Nucleosides & Nucleotides*, **1999**, *18*, 2613–2630.
3. Marquez, V.E.; Siddiqui, M.A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R.W.; Matteucci, M.D. *J. Med. Chem*., **1996**, *39*, 3739–3747.
4. Molina, J.; Simons, C. *J. Carbohydr. Res*., **1999**, *18*, 535–544.
5. Molina, J.; Simons, C. *J. Carbohydr. Res*., **2000**, *19*, 991–996.

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