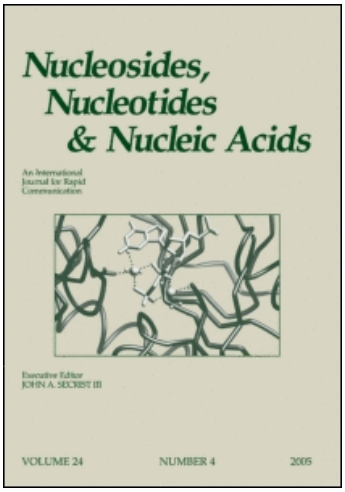

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Synthesis of New Pseudonucleosides Containing Chiral *Cyclosulfamides* as Agycone

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Synthesis of New Pseudonucleosides Containing Chiral *Cyclosulfamides* as Agycone

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ABSTRACT

A series of chiral *cyclosufamides* have been synthesized in four steps, starting from N-benzoylaminoacids. Regioselective glycosylation of these pseudopyrimidic heterocycles was carried out after deprotection. Best glycosylation results were obtained by preliminary silylation of *cyclosulfamides*, and their condensation with a tetraacetylribofuranose and pentaacetylglucopyranose is described, which yielded the *pseudonucleosides* in a β-anomeric configuration.

Key Words: Chlorosulfonyle isocyanate; Aminoacids; Cyclosulfamide; Glycosylation; Regiospecific; Pseudonucleoside.

INTRODUCTION

Nucleosides and analogues such as pseudonucleosides have attracted a wide interest in view of the importance of their biological activities. Many of them, natural or synthetic, are well known for their potent antiviral and antitumor activities. The modification of the heterocyclic aglycone is important for the synthesis of new nucleosidic analogues with potential antiviral and/or antitumoral activity.[1] In order

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to interfere with biological processes, it must be able to inhibit nucleoside biogenesis enzymes, or to selectivily hybridise with natural nucleotides. In our previous works, we reported the synthesis of new pseudonucleosides containing chiral sulfa-hydantoïns.[2,3]

Recently, we have reported the synthesis of new chiral 1,2,5 thiadiazolidines 1,1-dioxides and their natural amino acids derivatives.[4–5]

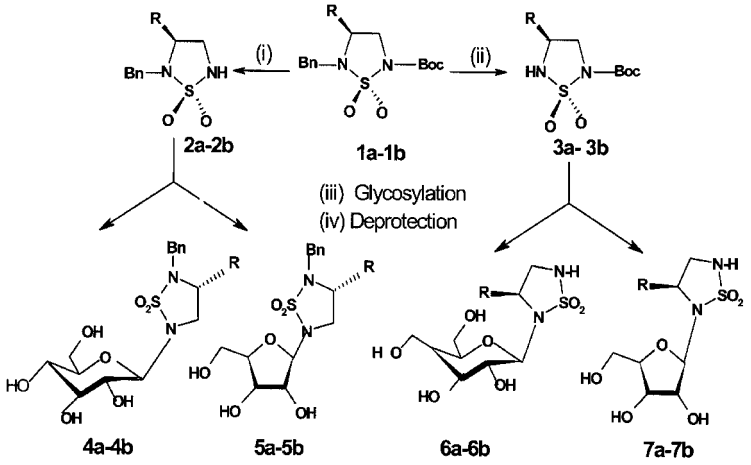
We describe here the synthesis of a series of pseudonucleosides containing chiral *cyclosulfamides* as aglycone.

SYNTHESIS

The new Chiral *cyclosulfamides*[5] **1a–1b** (sulfa-analogues of cyclic ureas) have been synthesized starting from N-benzoylaminoacids (Val, Leu) and chlorosulfonyl isocyanate (CSI), for these compounds the N[5] position was protected with a benzyl group, removable by hydrogenolysis. Orthogonal protecting groups can be independently removed in appropriate conditions (40% trifluoroacetic in dichloromethane for the BOC group; Pd-C and ammonium formate for the benzyl group).

The regiospecific glycosylation of these pseudopyrimidic heterocycles was carried out after silylation. The Vorbrüggen method[5] of glycosylation was applied. This route requires preliminary silylation of the aglycone by BSA or HMDS. The heterocycles **2a–2b**, **3a–3b** were first treated by hexamethyldisilasane (HMDS) or bis-trimethylsilylacetamide (BSA) containing catalytic quantities of ammonium sulphate.

The condensation with 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranosyl and 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose was carried out in acetonitril, in presence of tin tetrachloride. Finaly the ester groups were removed by treatment with methanolic-ammonia affording the corresponding pseudonucleosides.



Scheme 1. (i): TFA, CH_2Cl_2 0°C; (ii): NH_4^+ $HCOO^-$ (iii): HMDS, $(NH_4)_2$ SO_4, $SnCl_4$, AcCN, 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose/1,2,3,4,6-penta-O-acetyl-β-D-glucopyranosyl; (iv): $MeOH/NH_3$.

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The structure of the products was confirmed by usual spectroscopic methods: IR, $_1$H and $_{13}$C, NMR, mass spectrometry and elemental analysis. The β anomeric configuration of the pseudonucleosides was confirmed by NMR studies ($J'_1 - J'_2 = 7.8$ Hz).

CONCLUSION

We describe here the preparation of new pseudonucleosides containing chiral *cyclosulfamides*. The structure of all the compounds were unambiguously confirmed by spectroscopic methods. The biological evaluation of the resulting compounds and their incorporation in biomolecules are currently in progress.

ACKNOWLEDGMENTS

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