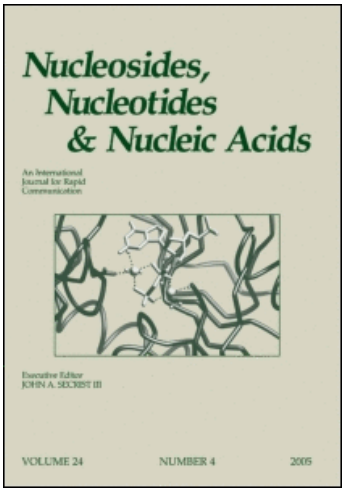

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Synthesis of 2-Deoxy-4-thio-D-ribofuranose and Its 3-Azido Analogue from L-Arabinose; Intermediates in the Synthesis of 4'-Thiodeoxynucleosides

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SYNTHESIS OF 2-DEOXY-4-THIO-D-RIBOFURANOSE AND ITS 3-AZIDO ANALOGUE FROM L-ARABINOSE; INTERMEDIATES IN THE SYNTHESIS OF 4'-THIODEOXYNUCLEOSIDES

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ABSTRACT

1-*O*-Acetyl-3,5-di-*O*-benzoyl-2-deoxy-4-thio-α,β-D-ribofuranose and its 3-azido analogue have been prepared by an efficient route starting from L-arabinose. A key intermediate in this route is 2-deoxy-4,5-*O*-isopropylidene-L-*erythro*-pentose dibenzyl dithioacetal which is readily substituted in the 3-position thus offering extensive scope for the synthesis of 3-substituted 2-deoxy-4-thio-α,β-D-ribofuranoses and subsequent nucleoside derivatives.

INTRODUCTION

Modified nucleosides have occupied a central role in medicinal chemistry research with the recognition of their ability to intervene in DNA replication. A number of 2'-deoxy and 2',3'-dideoxynucleosides have been shown to exhibit antiviral activity.[1-5] Furthermore, 4'-thionucleosides analogues have been of interest in this area since it is known that replacing a furanose ring oxygen by sulfur increases their metabolic stability towards phosphorylase enzymes.[6] Consequently, 2'-deoxy-4'-thionucleosides could be especially advantageous to an antiviral strategy when incorporated into a DNA matrix.[7] Some work on analogous oligoribonucleotides has been reported by Imbach and coworkers.[8] We have been interested in synthesis various 4-thiosugars and using them in the synthesis of nucleosides with potential antiviral activity.[9,10]

Published routes to 2-deoxy-4-thioribofuranose are costly and inconvenient for the preparation of the relatively large amount of material required for the large scale synthesis of nucleosides and extensive biological evaluations or applications. The initial pioneering work was undertaken by Nayak and Whistler,[11] who synthesised methyl 2-deoxy-4-thio-α,β-D-*erythro*-pentofuranoside from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in 14 steps with an overall

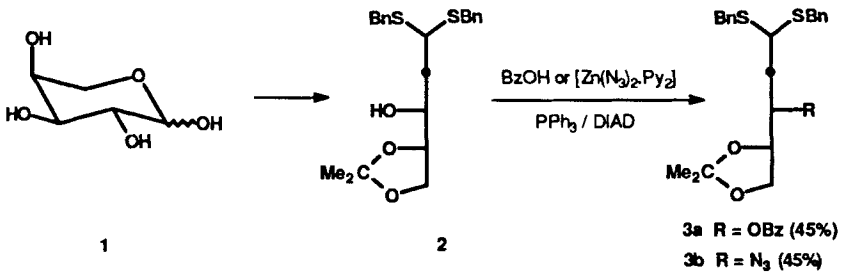
yield of 11%. An alternative strategy was described by Fu and Bobek[12] starting from L-arabinose which was also composed of 14 steps but returned a lower overall yield (ca. 4%). Recently a shorter synthesis was reported by Walker[13] in which benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-α,β-D-*erythro*-pentofuranoside was synthesised in 7 steps from 2-deoxy-D-ribose in 11% overall yield.

The synthesis of 3'-azido-3'-deoxy-4'-thiothymidine, which is the 4'-thio analogue of AZT (3'-azido-3'-deoxythymidine), has been reported previously.[14,15] The azido group was introduced through the inversion of a 2,3'-anhydronucleoside intermediate thus restricting the procedure to pyrimidine bases and to β nucleosides. More recently, we have reported an efficient route to 4'-thio-AZT and its analogues starting from D-xylose.[16]

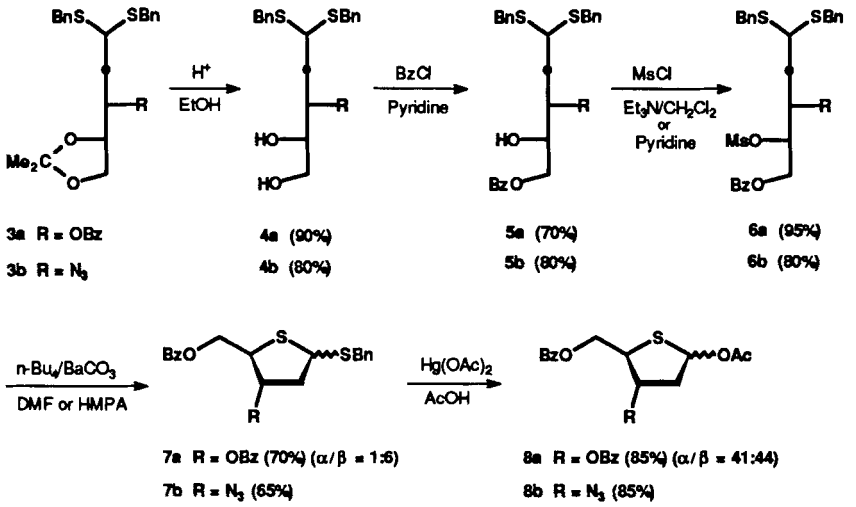
Alternative strategies to 2'-deoxy-4'-thionucleosides have employed non-glycosidic starting materials. Uenishi[17] reported the synthesis of 2'-deoxy-4'-thiouridine from an allylic alcohol and Secrist[15] the synthesis of a series of 2',3'-dideoxynucleosides from L-glutamic acid.

RESULTS

In the present work we report the relatively simple synthesis of 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-4-thio-α,β-D-*erythro*-pentofuranose **8a** and its 3-azido analogue **8b** starting from L-arabinose **1**, a relatively inexpensive sugar. A particular feature of the strategy employed is its convenient adaptability in permitting regioselective and stereoselective choice of a range of functional groups on C-3 of the 2-deoxy-4-thio-D-*erythro*-pentofuranose nucleus. In addition, such derivatized 4-thiosugars are potential intermediates for a wide variety of 3'-substituted 4'-thionucleosides possessing different heterocyclic bases.



A key intermediate in this methodology is 2-deoxy-4,5-*O*-isopropylidene-L-*erythro*-pentose dibenzyl dithioacetal **2**, prepared in four steps (60% overall yield) from L-arabinose according to a procedure developed by Wong and Gray.[18] This intermediate possesses only one free hydroxyl group and provides extensive scope for derivatization. Such was exemplified in this preliminary study in which SN_2 type reactions involving Mitsunobu's reagents[19] and either BzOH or the [$Zn(N_3)_2$.2Pyr] complex gave, respectively, **3a** and **3b**. Such derivatizations are



effected at an economical stage in the synthesis and are both stereoselective and regioselective.

Selective deprotection of the 4,5-*O*-isopropylidene group and subsequent selective benzoylation of the 5-OH group gave the intermediates **5a** and **5b** in preparation for the respective cyclisation steps. The use of L-arabinose in this strategy allows this step to be effected in a single inversion which is advantageous over either 2-deoxy-D-ribose as used by Walker[13] or D-xylose as used in our earlier work[16], which both require a double inversion. Mesylation of **5a** and **5b** using MsCl in either pyridine or TEA and CH_2Cl_2 gave the products **6a** and **6b** which were each purified by silica gel chromatography. Cyclisation was effected using $(n\text{-Bu})_4NI$ and $BaCO_3$ to give **7a** and **7b** respectively, in good yields (65 - 70%). The solvents, DMF and HMPA respectively, used in these reactions were chosen for their ability to solvate cations.

The anomeric thiobenzyl group was replaced by an *O*-acetyl group to give **8a** and **8b**, respectively, in good yields (85%) using mercuric acetate in acetic acid.[20] This last step gives intermediates which are more useful precursors of nucleosides which might involve a variety of different heterocyclic bases.

CONCLUSION

The strategy presented herein provides convenient and efficient access to protected 2-deoxy-4-thio-α,β-D-ribofuranose and its 3-azido analogue in good overall yields (17 and 15%, respectively) in 10 steps starting from L-arabinose. The protection strategy permits regio- and stereoselective changes in functional groups to be efficiently effected at position 3 of the thiosugar. Also the intermediates prepared are potential precursors for the synthesis of a wide variety of 2'-deoxy-4'-thionucleosides and nucleotides.

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