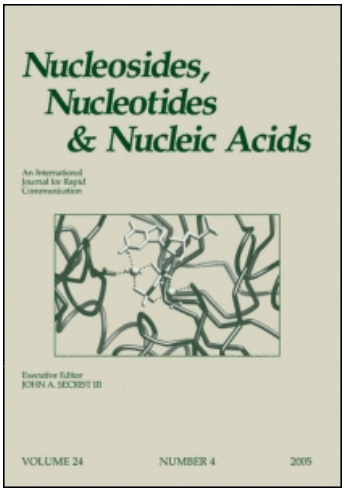

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PREPARATION OF 3′-*C*-BRANCHED URIDINE ANALOGUES, SUITABLE FOR CONVERSION INTO FUNCTIONALISED 3′-*C*-METHYLENE DERIVATIVES

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ABSTRACT

A novel method for preparation of 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-monomethoxytrityl-β-D-*ribo*-pentofuranosyl]uracil by hydroboration of corresponding 3′-deoxy-3′-*C*-methyleneuridine derivative has been developed. Further conversion of the hydroxyl function into different leaving groups was carried out to afford derivatives suitable for conversion into various 3′-*C*-branched uridine analogues through substitution.

INTRODUCTION

In the design of new potential antisense oligonucleotide analogues, resistance to nucleases and enhanced hybridisation affinity to the complementary RNA has to be considered. 3′-*C*-branched analogues containing internucleoside amide linkages (1,2,3,4,5) and methylene methylimino linkages (6,7) have shown promising properties. Most investigations so far concern oligodeoxynucleotide analogues, and to some extent 2′-*O*-alkyl derivatives (8,9,10), but only little has been done with oligonucleotide analogues having 2′-hydroxyl functions and 3′-*C*-branched internucleoside linkages (11,12). Further investigations in this field would be aided by

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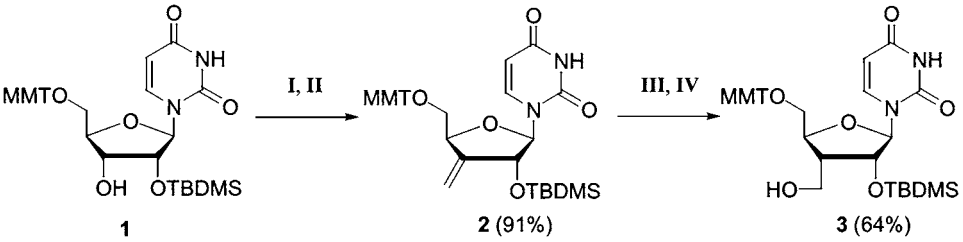
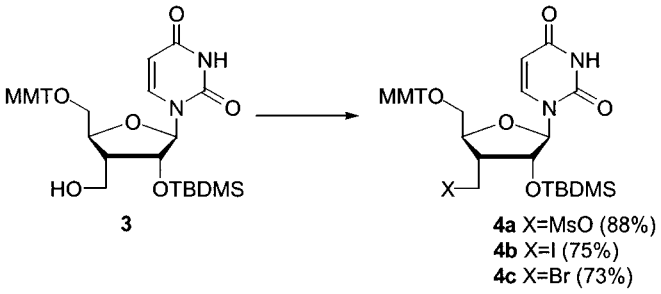


Reagents and conditions: I) CrO_3/pyridine/Acetic anhydride, CH_2Cl_2, 0°C, 1 h.; **II)** Methyltriphenylphosphonium bromide/*n*-butyl lithium, THF, rt., 20 h.; **III)** 9-BBN, hexane, rt., 20 h.; **IV)** $NaBO_3 \bullet 4H_2O$, THF-methanol-water (5:2:3), rt., 30 h.

a concise method for synthesis of 3′-*C*-branched nucleoside analogues, which can serve as precursors for the preparation of differently functionalised 3′-*C*-methylene derivatives. Synthesis of a uridine analogue having the 3′-hydroxyl function replaced by a hydroxymethyl group, and further conversion into the corresponding mesylate, iodo derivative and bromo derivative, is presented here.

RESULTS AND DISCUSSION

3′-*C*-branching of 2′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-monomethoxytrityluridine (13) (**1**) was achieved by oxidation/Wittig reactions followed by hydroboration. Oxidation of **1** was carried out using a mixture of CrO_3/acetic anhydride/pyridine in CH_2Cl_2 to give 1-[2-*O*-(tert-butyldimethylsilyl)-5-*O*-monomethoxytrityl-β-D-*erythro*-pentofuran-3-ulosyl]uracil (**2**). Wittig reaction of **2** using methyltriphenylphosphonium bromide and *n*-butyl lithium in THF afforded 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-methylene-5-*O*-monomethoxytrityl-β-D-*erythro*-pentofuranosyl]uracil (**3**). Subsequent hydroboration using 9-BBN in hexane, followed by oxidative treatment with $NaBO_3 \bullet 4H_2O$ resulted in



Reagents and conditions: Synthesis of **4a)** Methanesulfonyl chloride, acetonitrile-pyridine (9:1), rt., 20 h.; Synthesis of **4b)** Triphenylphosphine/I_2, acetonitrile-pyridine (95:5), rt., 40 h.; Synthesis of **4c)** Triphenylphosphine/CBr_4, acetonitrile-pyridine (95:5), rt., 40 h.

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two stereoisomers; 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-monomethoxytrityl-β-D-*ribo*-pentofuranosyl]uracil (**4**) and 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-monomethoxytrityl-β-D-*xylo*-pentofuranosyl]uracil. The *ribo*-isomer **4** was isolated from the mixture by silica gel column chromatography to give isomerically pure **4** in a yield of 64%.

Conversion of the hydroxyl function of **3** into a leaving group gives a derivative, which allow for further functionalisation through substitution. Such derivatives are valuable as intermediates in the synthesis of various 3′-*C*-branched uridine analogues. To cover the requirement of different leaving groups for the nucleophiles that might be used, mesylate **4a**, iodo derivative **4b**, and bromo derivative **4c**, were prepared.

CONCLUSIONS

We have developed a novel method for preparation of a 3′-deoxy-3′-*C*-hydroxymethyluridine derivative suitable for further conversion of the hydroxyl function into a leaving group. Since different nucleophiles can be used for substitution, mesylate **4a**, iodo derivative **4b** and bromo derivative **4c** are valuable intermediates in the synthesis of various 3′-*C*-branched uridine analogues. A detailed description on the synthesis of 1-[3-deoxy-3-*C*-hydroxymethyl-β-D-*ribo*-pentofuranosyl]uracil derivatives, and investigation of the influence of reagents and solvents on the stereoselectivity, will be published elsewhere. The use of the above methodology in the synthesis of some 3′-C-branched nucleoside analogues is now in progress.

ACKNOWLEDGMENTS

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