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## Nucleosides, Nucleotides and Nucleic Acids

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

Anna Winqvist<sup>a</sup>; Roger Strömberg<sup>b</sup>

<sup>a</sup> Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden

<sup>b</sup> Division of Organic and Bioorganic Chemistry, MBB, Scheele Laboratory, Karolinska Institutet, Stockholm, Sweden

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

Anna Winqvist<sup>1,2</sup> and Roger Strömberg<sup>2,\*</sup>

<sup>1</sup>Department of Organic Chemistry, Arrhenius Laboratory,  
Stockholm University, SE-106 91 Stockholm, Sweden

<sup>2</sup>Division of Organic and Bioorganic Chemistry, MBB, Scheele  
Laboratory, Karolinska Institutet, SE-171 77 Stockholm, Sweden

### ABSTRACT

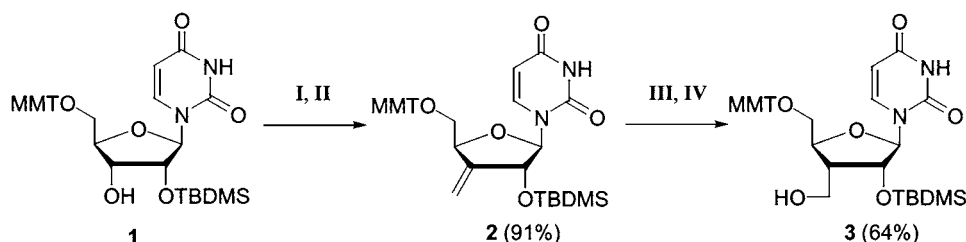
A novel method for preparation of 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-monomethoxytrityl- $\beta$ -D-ribo-pentofuranosyl]uracil by hydroboration of corresponding 3'-deoxy-3'-*C*-methyleneuridine derivative has been developed. Further conversion of the hydroxyl function 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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\*Corresponding author.

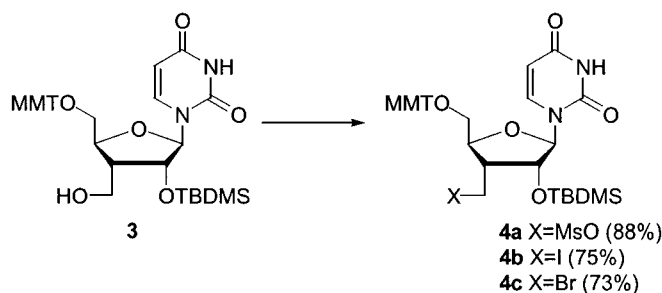


**Reagents and conditions:** I)  $\text{CrO}_3$ /pyridine/Acetic anhydride,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 1 h.; II) Methyltriphenylphosphonium bromide/*n*-butyl lithium, THF, rt., 20 h.; III) 9-BBN, hexane, rt., 20 h.; IV)  $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ , THF-methanol-water (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  $\text{CrO}_3$ /acetic anhydride/pyridine in  $\text{CH}_2\text{Cl}_2$  to give 1-[2-*O*-(*tert*-butyldimethylsilyl)-5-*O*-monomethoxytrityl- $\beta$ -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- $\beta$ -D-*erythro*-pentofuranosyl]uracil (**3**). Subsequent hydroboration using 9-BBN in hexane, followed by oxidative treatment with  $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$  resulted in



**Reagents and conditions:** Synthesis of **4a**) Methanesulfonyl chloride, acetonitrile-pyridine (9:1), rt., 20 h.; Synthesis of **4b**) Triphenylphosphine/ $\text{I}_2$ , acetonitrile-pyridine (95:5), rt., 40 h.; Synthesis of **4c**) Triphenylphosphine/ $\text{CBr}_4$ , acetonitrile-pyridine (95:5), rt., 40 h.



two stereoisomers; 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-monomethoxytrityl- $\beta$ -D-*ribo*-pentofuranosyl]uracil (**4**) and 1-[2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-hydroxymethyl-5-*O*-monomethoxytrityl- $\beta$ -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- $\beta$ -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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