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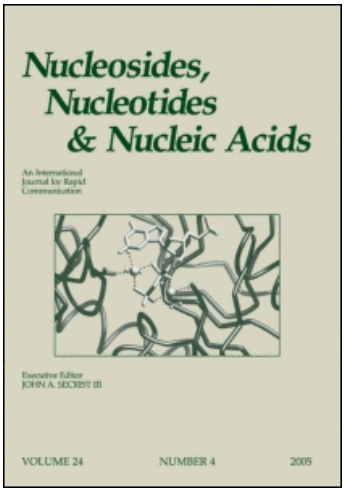

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Synthesis and Properties of Halogenated 7-Deaza-2'-deoxyxanthosine and Protected Derivatives for Oligonucleotide Synthesis

F. Seela[ab]; K. Shaikh[a]; T. Wiglenda[a]
[a] Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Osnabrück, Germany [b] Organische Chemie und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Osnabrück, Germany

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Synthesis and Properties of Halogenated 7-Deaza-2′-deoxyxanthosine and Protected Derivatives for Oligonucleotide Synthesis

F. Seela,* K. Shaikh, and T. Wiglenda

Laboratorium für Organische und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Osnabrück, Germany

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ABSTRACT

The 7-bromo- (**4a**) and 7-iodo- (**4b**) derivatives of 7-deaza-2′-deoxyxanthosine (**5**) are prepared. Furthermore, the building blocks **6**–**8** of 7-deaza-2′-deoxyxanthosine (**5**) are synthesized and tested for their usage in oligonucleotide synthesis.

Key Words: 7-Deaza-2′-deoxyxanthosine; Oligonucleotides; Halogen derivatives.

7-Deaza-2′-deoxyxanthosine (**5**) was first prepared by Seela et al. in 1985.[1] Now, the synthesis of the 7-bromo- (**4a**) and 7-iodo- (**4b**) derivatives are disclosed as versatile synthons for further derivatization. For this purpose the halogenated compounds **1a,b**[2] are first deprotected to the halogenated 7-deaza-2′-deoxyspongosines **2a**,**b**. Deamination of **2a,b**[3] with $NaNO_2$/HOAc gave compounds **3a,b** and a significant amount of a by-product which might be the corresponding 7-halogeno-8-nitro derivative. While the demethylation of **3b** [$(CH_3)_3SiCl$/NaI, MeCN, 0.5 h, r.t.] afforded **4b**, partial Br → I exchange occured during demethylation of **3a**. Therefore,

*Correspondence: F. Seela, Organische Chemie und Bioorganische Chemie, Institut für Chemie, Universität Osnabrück, Barbarastrasse 7, D-49069 Osnabrück, Germany; Fax: +49 541 969 2370; E-mail: frank.seela@uni-osnabrueck.de.

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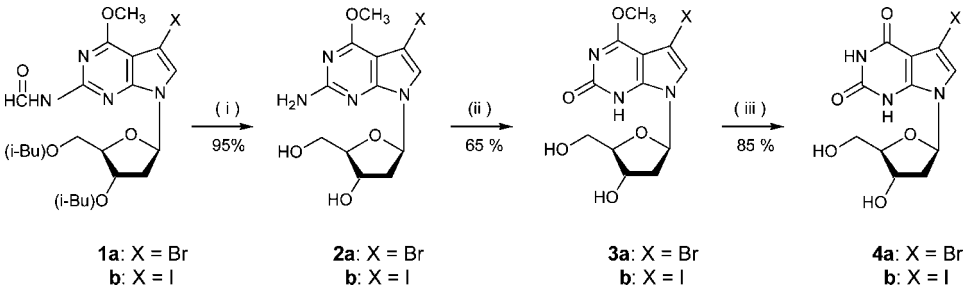
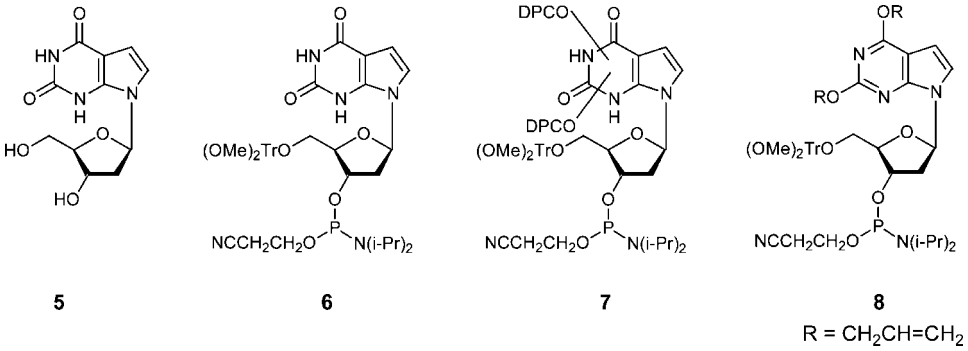


Scheme 1. (i) 0.5 N NaOMe/MeOH, overnight; (ii) $NaNO_2$, 10%aq. AcOH; (iii) 2 N NaOH, reflux, 3 days.



Scheme 2.

this reaction was carried out for both compounds with 2N NaOH which gave **4a** and **b** in a clean reaction.

2′-Deoxyxanthosine possesses a labile N-glycosylic bond which prevented until now the incorporation of this compound into oligonucleotides to become routine. On the other hand, 7-deaza-2′-deoxyxanthosine (**5**) is stable.[1] The synthesis of oligonucleotides containing **5** has yet been reported only by applying phosphonate chemistry.[3] The limited application of this method prompted us to prepare corresponding phosphoramidites. For that, the building block **6** - without base protecting groups - and **7** - carrying two diphenylcarbamoyl (DPC) residues - were synthesized.

Solid-phase oligonucleotide synthesis, however, turned out to be problematic in both cases. Applying **6** for the preparation of 5′-d(TAGG**5**CAA**5**ACT) for example, gave only moderate (80%) coupling yields. Using the DPC-protected phosphoramidite **7** improved the yields (85–98%) when the coupling time was set to 500 s, but later the DPC groups were difficult to remove. To overcome these problems, the allyloxy group which had already successfully been applied for a pyranosyl derivative of xanthosine was now chosen for the synthesis of **8**.[4]

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