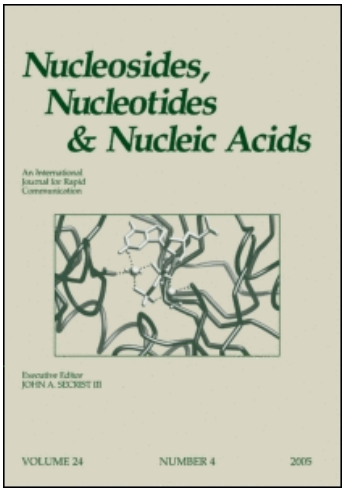

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SYNTHESIS STUDY OF 3′-α-FLUORO-2′,3′-DIDEOXYGUANOSINE

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▫ *A synthetic method was established for 3′-α-fluoro-2′,3′-dideoxyguanosine* ***1*** *from guanosine* ***2*** *in 27% overall yield and 6 steps. A byproduct* ***6a*** *of fluorination was identified by NMR studies, its presence strongly supporting our supposition that the fluorination itself proceeded via a bromonium cation.*

Keywords 3′-α-Fluoro-2′,3′-dideoxyguanosine

INTRODUCTION

3′-α-Fluoro-2′,3′-dideoxyguanosine **1** is now being developed as a reverse transcriptase inhibitor for HIV as well as a potential treatment for hepatitis B virus.[1,2] There have only been a few reports describing the preparation of **1**,[3–6] (notably that by Herdewijn's group) probably because guanosine derivatives are normally difficult to synthesize and also because of the necessity of introducing a fluorine atom with appropriate stereo- and regioselectivity. Previously, we reported a synthetic method for a 3′-α-fluorinated 2′,3′-dideoxyadenosine derivative involving a novel rearrangement.[7,8] We wish to disclose herein that the same method can be applied to the synthesis of **1**.

RESULTS AND DISCUSSION

*N*2,5′-*O*-Diacetyl-3′-β-bromo-3′-deoxyguanosine **4a** was synthesized by the selective 2′-*O* deacetylation of *N*2,2′,5′-*O*-triacetyl-3′-β-bromo-3′-deoxyguanosine **3** in 77% yield—this was easily prepared from guanosine.[9,10] The 3′-α-fluorinated compound **5a** was successfully obtained by treating **4a** with DAST* in 59% yield. The reaction proceeded *via* a rearrangement of the bromine atom from the 3′-β to

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*A similar result was obtained when MOST was used as the fluorinating reagent. The yield of **5a** was 58%, the ratio of **5a**/**6a** was 2.7.

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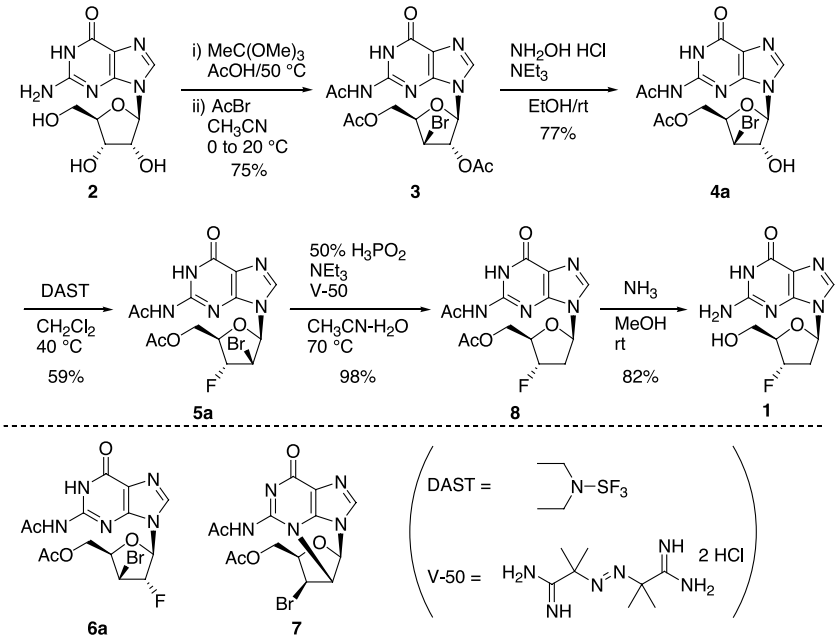


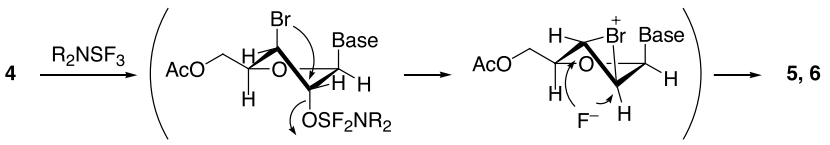
SCHEME 1 Synthesis of 3′-α-fluoro-2′,3′-dideoxyguanosine **1**.

the 2′-β position, 3′-α fluorination taking place simultaneously.[7,8] In this reaction, the 2′-α fluorinated compounds **6a** and **7** were also obtained as byproducts, although these were not observed in the case of adenosine. The ratio of **5a**/**6a** was 2.8.

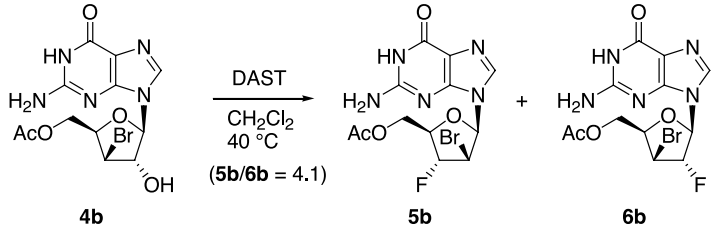
We identified the structure of byproduct **6a** by NMR-study.† The ^{1}H-NMR spectrum of **6a** shows a C2′ proton at $\delta = 5.56$ with a large geminal coupling constant ($J_{2'\text{-F}} = 50.3$ Hz), indicating that a fluorine atom is attached to C2′. This is also supported by a vicinal coupling constant of H1′-F ($J_{1'\text{-F}} = 21.3$ Hz). Since the ^{1}H-NMR spectrum does not show long-range coupling between H-8 and the C2′ fluorine, the fluorine should be in the α configuration.[11] The generation of **6a** as a result of the fluorination of **4a** strongly supported our supposition that the fluorination itself proceeded *via* a bromonium cation[7,8] and fluoride attack at C3′ or C2′ from the α side.

In the case of **4b**, which is the *N*-deacetylated compound of **4a**, the ratio of fluorination at C3′/C2′ was improved from 2.8 to 4.1. Variations in C3′/C2′ ratio were nucleic base dependent between *N*-acetylguanine, guanine, and adenine. Although the reason for this is not clear, we may speculate it is related to the electronic properties of each respective base.

†H NMR (400 MHz, DMSO-*d6*) of **6a**: δ 11.79 (1H, s), 8.15 (1H, s, H-8), 6.04 (1H, d, $J = 21.3$ Hz, H-1′), 5.56 (1H, d, $J = 50.3$ Hz, H-2′), 4.64–4.45 (4H, m, H-3′, 4′, 5′), 2.20 (3H, s, NAc), 2.08 (3H, s, OAc).



SCHEME 2 Putative fluorination mechanism.



SCHEME 3 Fluorination of **4b**.

The structure of byproduct **7** was identified by NMR-study[‡] as an N3-C2′ cyclized compound. The yield of **7** was less than 10%. Similar cyclizations have already been reported by several groups,[11,12] one, in particular, describing an N3 attack of the aglycon on the C2′ of an adenosine derivative.[13] We considered that **7** was formed in a similar manner to that reported by Herdewijn et al.[11] We note with interest, however, that no such cyclized product was observed in the case of the adenosine derivative.[7,8]

5a was isolated by chromatography. The debromination of **5a** proceeded by means of radical reduction, using hypophosphorus acid and triethylamine,[14,15] to give *N*2,5′-*O*-diacetyl-3′-α-fluoro-2′,3′-dideoxyguanosine **8** in 98% yield. Acetyl groups were deprotected using ammonia-methanol to obtain the target nucleoside **1** in 82% yield. Structural confirmation was obtained by a comparison with analytical data.[3–6]

In conclusion, we established a synthetic method for **1** from **2** in 27% overall yield in 6 steps. To the best of our knowledge, this is the highest overall yield of **1** starting from guanosine that has yet been reported.

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[‡]H NMR (400 MHz, DMSO-*d6*) of **7**: δ 8.13 (1H, s, H-8), 6.56 (1H, d, *J* = 3.9 Hz, H-1′), 5.68 (1H, t, *J* = 3.6 Hz, H-3′), 5.41 (1H, t, *J* = 3.8 Hz, H-2′), 4.79 (1H, m, H-4′), 4.31 (1H, d–d, *J* = 12.5, 5.3 Hz, H-5′a), 3.97 (1H, d-d, *J* = 12.5, 4.8 Hz, H-5′b), 2.15 (3H, s, NAc), 1.76 (3H, s, OAc).

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