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A concise synthesis of 3′-α-fluoro-2′,3′-dideoxyguanosine (FddG) via 3′-α-selective fluorination of 8,2′-thioanhydronucleoside

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Abstract—The antiviral nucleoside 3′-α-fluoro-2′,3′-dideoxyguanosine (FddG) was synthesized via 3′-α-selective fluorination of 8,2′-thioanhydronucleoside as the key step. Desulfurization of 3′-α-fluoro-3′-deoxy-8,2′-thioanhydronucleoside could be achieved by the treatment with Raney Ni in toluene. This method provides a concise route to 3′-α-fluoro-2′,3′-dideoxynucleosides that avoids the use of explosive and expensive SF_4-related fluorinating reagents.

1. Introduction

3′-α-Fluoro-2′,3′-dideoxyguanosine (FddG) (**1**, Fig. 1) is being developed as a reverse transcriptase inhibitor of HIV for AIDS[1] as well as a potential treatment for hepatitis B virus infection.[2] We previously reported the synthesis of FddG (**1**) from guanosine by a 6-step sequence with bromine rearrangement during fluorination;[3] however, this method required the use of explosive and expensive SF_4-related fluorinating reagents. Although other methods for the synthesis of FddG (**1**) have been reported, they also required SF_4-related reagents for fluorination[1a,4,5] and/or rather lengthy reaction steps to be performed on an industrial scale.[6] Notably, conventional 3′-α-selective fluorination of 3′-β-hydroxy derivative via S_N2 inversion suffered from the generation of 3′,4′-didehydro-3′-deoxy by-products by trans-elimination, which reduced the yield of the desired product.[1a] We report here a concise synthesis of FddG (**1**) via 3′-α-selective fluorination of 8,2′-thioanhydronucleoside, which can be easily prepared from guanosine (**2**).

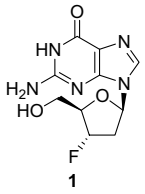

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Figure 1. Structure of FddG **1**.

2. Results and discussion

In contemplating the synthesis of FddG (**1**), we considered that 3′-α-selective fluorination of a 2′-substituted 2′-deoxyguanosine derivative could be achieved with the assistance of the neighboring effect of a hetero atom located at the 2′-β-position. We previously reported that the fluorination of both 3′-β-bromo-3′-deoxyadenosine (**3**) and 2′-β-bromo-2′-deoxyadenosine derivatives (**4**) with a SF_4-related fluorinating agent, which is crucial for the reaction, gave 3′-α-fluorinated compound (**5**) as a major product in a ratio of 7:1 (Scheme 1).[7] We concluded that selective fluorination of both regioisomers might proceed via a common bromonium ion intermediate which is attacked by the fluoride anion from the α-side of the 3′-position. However, the regioselectivity was not sufficient (2.8:1) in the case of guanine analogues.[3] These results prompted us to examine the fluorination of 8,2′-thioanhydronucleoside via a sulfonium ion intermediate, since we anticipated that retentive fluorination might proceed by means of sulfur

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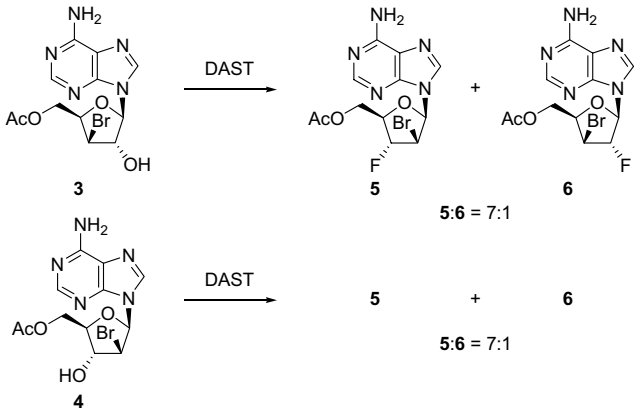
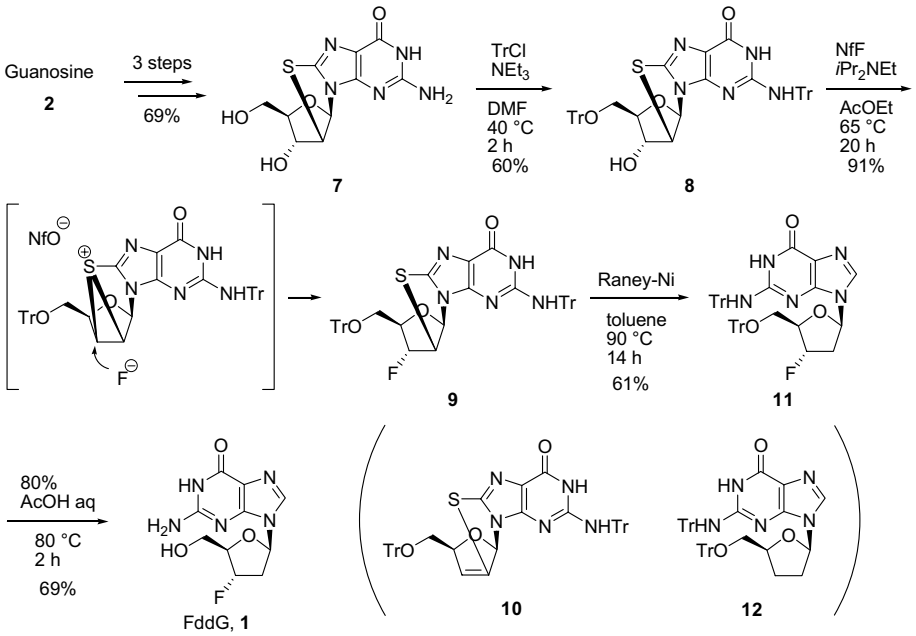


Scheme 1. Fluorination of **3** and **4**.

facilitating the attack of the fluoride ion[8] to the 3′α rather than the 2′α position due to possible steric requirements. In addition, with the assistance of the neighboring effect of the sulfur atom, elimination might be suppressed to allow the use of a non-SF_4-related reagent such as perfluorobutanesulfonyl fluoride (NfF) for fluorination in the presence of a base. If 3′-α-selective fluorination could be accomplished, the sulfur atom would be removed by treatment with Raney Ni. We report here a successful realization of this strategy.

First, we investigated the fluorination of N^2,$O^{5'}$-ditrityl-protected compound **8** (Scheme 2). Compound **8** could be obtained in 60% yield by treatment of 8,2′-anhydro-8-mercaptoguanosine (**7**), which can be easily prepared from guanosine (**2**) in 3 steps,[9] with trityl chloride in the presence of Et_3N. Although the reaction of **8** with DAST gave a complex mixture due to the unstable nature of the trityl groups under these reaction conditions, in the reaction with NfF/Et_3N, the desired 3′-α-fluorinated product **9** was obtained in 63% yield along with the elimination product **10**.[10] In this initial attempt, the ratio of **9**:**10** was 4:1 and no generation of 2′-α-fluorinated product was observed. After we optimized the reaction conditions, we eventually found that the yield could be improved to 91% by using an excess amount of NfF in the presence of *i*-Pr_2NEt as a base.[11]

Next, we investigated the reductive desulfurization of 3′-α-fluoro-3′-deoxy-8,2′-thioanhydronucleoside **9**. First, we attempted the desulfurization of 8,2′-anhydro-3′-α-fluoro-8-mercapto-3′-deoxyguanosine, which can be obtained by treatment of **9** with acetic acid; however, the reaction with Raney Ni in aq NaOH only gave 2′,3′-dideoxyguanosine (ddG). No generation of the desired FddG (**1**) was observed in the above reaction. We suspected that fluorine atom might be eliminated by the nucleophilic attack of the sulfur atom under these highly basic conditions to give the sulfonium ion again, which subsequently affords ddG by the reduction with Raney Ni. Accordingly, we tried to achieve desulfurization of compound **9** prior to deprotection with the acid. The reaction of **9** with Raney Ni in EtOH gave a small amount of the desired Tr_2–FddG (**11**)[12] along with Tr_2–ddG (**12**) as a major product in a ratio of 1:4. The reaction had to be performed in the presence of Et_3N to avoid the unfavorable removal of trityl groups under the above reaction conditions. To our delight, when we used toluene as a solvent in the presence of Et_3N, the preferential formation of Tr_2–FddG (**11**) versus Tr_2–ddG (**12**) was observed. Eventually, we discovered that the desulfurization of compound **9** with Raney Ni in toluene without any additives gave the best ratio of **11**:**12** (6:1). The use of aprotic solvent such as toluene may contribute to suppress the unfavorable removal of trityl groups even in the absence of a base. The desired



Scheme 2. Synthesis of FddG **1**.

product **11** could be isolated in 61% yield after column chromatography. Finally, the Tr_2–FddG (**11**) obtained was allowed to be deprotected under acidic conditions to give FddG (**1**)[13] in 69% yield.

In summary, a concise synthesis of FddG (**1**) using the 3′-α-selective fluorination of 8,2′-thioanhydronucleoside **8** has been achieved. This synthetic method using retentive fluorination at the C3′ position has the advantage of providing FddG (**1**) in high yields with a safer fluorination agent, NfF. Further studies are now in progress.

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10. The ^{1}H NMR spectrum of **9** shows a C3′ proton at δ 5.29 with a large geminal coupling constant ($J_{3'\text{-F}} = 52.1$ Hz), indicating that a fluorine atom is attached to C3′, not C2′. This is also supported by vicinal coupling constants of H2′-F ($J_{2'\text{-F}} = 20.4$ Hz) and H4′-F ($J_{4'\text{-F}} = 22.9$ Hz). Since the vicinal coupling constants for $J_{2'-3'}$ and $J_{3'-4'}$ are almost 0 Hz, the C3′ proton should be in the β configuration, and, therefore the fluorine atom at the C3′ position should be in the α configuration.
11. Experimental procedure and characterization data: To a solution of **8** (78.2 mg, 0.1 mmol) in AcOEt (2 mL) was added NfF (0.224 mL, 1.2 mmol) and *i*-Pr_2NEt (0.216 mL, 1.2 mmol), and the mixture was stirred for 20 h at 65 °C. After the mixture was cooled to room temperature, AcOEt (5 mL) and H_2O (2 mL) were added and the mixture was separated. The organic layer was dried over $MgSO_4$. After the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (32:1 CH_2Cl_2–CH_3OH) to give **9** (71.8 mg, 91%) as colorless crystals. Mp 201–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03–3.09 (1H, m, H-5′), 3.18–3.23 (1H, m, H-5′), 4.60 (1H, dt, $J = 22.9$, 6.9 Hz, H-4′), 4.83 (1H, dd, $J = 20.4$, 6.5 Hz, H-2′), 5.29 (1H, d, $J = 52.1$ Hz, H-3′), 6.34 (1H, d, $J = 6.5$ Hz, H-1′), 6.43 (1H, br, NH), 7.05–7.40 (31H, m, aromatic and NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.7 ($J = 24$ Hz), 62.4 ($J = 10$ Hz), 71.0, 73.3, 85.8 ($J = 24$ Hz), 87.0, 97.7 ($J = 187$ Hz), 123.0, 127.3, 127.9, 128.3, 128.4, 128.5, 128.6, 143.0, 143.2, 143.6, 146.8, 150.0, 151.4; HRMS (FAB+) calcd for $C_{48}H_{39}FN_5O_3S$ (MH^+), 784.2758, found 784.2765.
12. Compound **11**: mp 167–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00–2.30 (2H, m, H-2′), 3.20–3.30 (2H, m, H-5′), 4.25 (1H, dm, $J = 26.6$ Hz, H-4′), 5.03 (1H, dm, $J = 54.7$ Hz, H-3′), 5.57–5.62 (1H, m, H-1′), 7.15–7.45 (33H, m, aromatic, H-8 and NH × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.7 ($J = 30$ Hz), 63.3 ($J = 9$ Hz), 71.1, 81.8, 83.7 ($J = 18$ Hz), 87.1, 94.1 ($J = 177$ Hz), 125.1, 127.4, 127.9, 128.0, 128.5, 128.6, 128.9, 135.0, 135.5, 143.3, 143.6, 144.1, 151.2; HRMS (FAB+) calcd for $C_{48}H_{41}FN_5O_3$ (MH^+), 754.3193, found 754.3221.
13. Compound **1**: mp 255 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50–2.67 (1H, m, H-2′), 2.70–2.90 (1H, m, H-2′), 3.50–3.60 (2H, m, H-5′), 4.16 (1H, dt, $J = 27.0$, 4.9 Hz, H-4′), 5.15 (1H, d, $J = 5.4$ Hz, OH), 5.38 (1H, dd, $J = 53.6$, 4.3 Hz, H-3′), 6.15 (1H, dd, $J = 9.4$, 5.6 Hz, H-1′), 6.49 (2H, br, NH_2), 7.94 (1H, s, H-8), 10.54 (1H, br, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 37.2 ($J = 20$ Hz), 61.3 ($J = 11$ Hz), 83.0, 85.5 ($J = 22$ Hz), 95.3 ($J = 172$ Hz), 117.1, 135.7, 151.4, 154.1, 157.0; HRMS (FAB+) calcd for $C_{10}H_{13}FN_5O_3$ (MH^+), 270.1002, found 270.1011.