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## A New Synthesis of 9-(2-Deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)guanine (araF-G)

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### ABSTRACT

Interesting and very promising antisense properties of 2'-deoxy-2'-fluoroarabino-nucleic acids ((a) Wilds, C.J.; Damha, M.J. 2'-Deoxy-2'-fluoroarabinonucleosides and oligonucleotides (2'F-ANA): synthesis and physicochemical studies. *Nucl. Acids Res.* **2000**, 28, 3625–3635; (b) Viazovkina, E.; Mangos, M.; Elzagheid, M.I.; Damha, M.J. *Current Protocols in Nucleic Acid Chemistry* **2002**, 4.15.1–4.15.21) (2'F-ANA) has encouraged our research group to optimize the synthetic procedures for 2'-deoxy-2'-fluoro- $\beta$ -D-arabinonucleosides (araF-N). The synthesis of araF-U, araF-T, araF-A and araF-C is straightforward, (Tann, C.H.; Brodfuehrer, P.R.; Brundidge, S.P.; Sapino, C., Jr. Howell H.G. Fluorocarbohydrates in synthesis. An efficient synthesis of 1-(2-deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)-5-iodouracil ( $\beta$ -FIAU) and 1-(2-deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)thymine ( $\beta$ -FMAU). *J. Org. Chem.* **1985**, 50, 3644–3647; Howell, H.G.; Brodfuehrer, P.R.; Brundidge, S.P.; Benigni, D.A.; Sapino, C., Jr. Antiviral nucleosides. A stereo-specific, total synthesis of 2'-fluoro-2'-deoxy- $\beta$ -D-arabinofuranosyl nucleosides. *J. Org. Chem.* 1988, 53, 85–88; Maruyama, T.; Takamatsu, S.; Kozai, S.; Satoh, Y.; Izana, K. Synthesis of 9-(2-deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)adenine

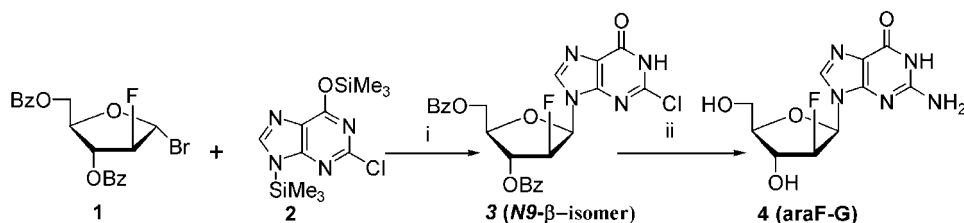
\*Correspondence: Masad J. Damha, Otto Maass Chemistry Building, McGill University, 801 Sherbrooke Street W., H3A 2K6 Montreal, Quebec, Canada; Fax: +1 514 398 3797; E-mail: masad.damha@mcgill.ca.



bearing a selectively removable protecting group. Chem. Pharm. Bull. 1999, 47, 966–970) however, the synthesis of the guanine analogue is more complicated and affords poor to moderate yields of araF-G (**4**) ((a) Elzagheid, M.I.; Viazovkina, E.; Masad, M.J. Synthesis of protected 2'-deoxy-2'-fluoro- $\beta$ -D-arabinonucleosides. Synthesis of 2'-fluoroarabino nucleoside phosphoramidites and their use in the synthesis of 2'-F-ANA. Current Protocols in Nucleic Acid Chemistry **2002**, 1.7.1–1.7.19; (b) Tennila, T.; Azhayeva, E.; Vepsalainen, J.; Laatikainen, R.; Azhayev, A.; Mikhailopulo, I. Oligonucleotides containing 9-(2-deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)-adenine and -guanine: synthesis, hybridization and antisense properties. Nucleosides, Nucleotides and Nucl. Acids **2000**, 19, 1861–1884). Here we describe an efficient synthesis of araF-G (**4**) that involves coupling of 2-deoxy-2-fluoro-3,5-di-*O*-benzoyl- $\alpha$ -D-arabinofuranosyl bromide (**1**) with 2-chlorohypoxanthine (**2**) to afford 2-chloro- $\beta$ -araF-I (**3**) in 52% yield. Nucleoside (**3**) was transformed into araF-G (**4**) by treatment with methanolic ammonia (150°C, 6 h) in 67% yield.

**Key Words:** Nucleoside synthesis; Guanine arabinonucleoside.

A very convenient method for the synthesis of araF-nucleosides (e.g., araF-T and C) involves direct coupling of 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro- $\alpha$ -D-arabinofuranosyl bromide with a silylated base.<sup>[1,3]</sup> This produces primarily the desired  $\beta$ -anomer with < 5% of the  $\alpha$ -stereoisomer which is removed by chromatography and/or crystallization. AraF-A can be prepared by the same procedure, except that a pre-silylation step is not required.<sup>[1b]</sup> A recently reported synthesis of araF-G required coupling of 2,6-dichloropurine to arabinoside **1**.<sup>[5b]</sup> This method produces a mixture of isomers ( $N^7$ - and  $N^9$ -regioisomers, as well as  $\alpha$  and  $\beta$  anomers) that can be separated by silica gel chromatography to afford the desired  $N^9$ - $\beta$ -anomer in 38% yield.<sup>[5a]</sup> Displacement of the chlorine atoms at positions 2 and 6 with lithium azide, followed by reduction with tin dichloride affords the araF-(2,6-diaminopurine) nucleoside. Removal of the sugar *O*-benzoyl protecting groups followed by regioselective deamination by treatment with adenosine deaminase affords araF-G in 20% overall yield (from **1**).<sup>[5a]</sup> To minimize the number of steps, we attempted coupling of arabinoside **1** with a variety of 'masked' guanines. Among these were 2-chloro-6-hydroxypurine (2-chlorohypoxanthine), 2-amino-6-chloropurine, 2,6-diaminopurine, 2-amino-6-(1,2,4-triazol-4-yl)-9-*H*-purine, guanine,  $N^2$ -acetyl- $O^6$ -diphenylcarbamoylguanine and  $O^6$ -diphenylcarbamoyl- $N^2$ -isobutyryl guanine. While



**Scheme 1.** i)  $\text{CCl}_4$ , 77°C, 3 days, 52%; ii) saturated methanolic ammonia, steel bomb, 150°C, 6 h, 67%.

coupling of guanine (and its derivatives) and 2,6-diaminopurine (and its derivatives) to arabinoside **1** were not successful and gave non nucleosidic products, coupling of 2-chloro-6-hydroxypurine and 2-amino-6-chloro-purine to the same arabinoside gave the anticipated  $N^9$ - $\beta$ -anomers in 50–60% yield. Displacement of the chloro function in 9-(2-deoxy-2- $\beta$ -D-fluoroarabinofuranosyl)-2-amino-6-chloropurine with 0.1–2 M hydrochloric acid<sup>[6,7]</sup> or 2 N sodium hydroxide in dioxane<sup>[8]</sup> or a mixture of sodium methoxide/ mercaptoethanol/ water<sup>[9,10]</sup> were not successful and gave only modified starting material (not isolated). Treatment of the same nucleoside, 9-(2-deoxy-2- $\beta$ -D-fluoroarabinofuranosyl)-2-amino-6-chloropurine, with trimethylamine gave the trimethylammonium salt of the nucleoside.<sup>[11,12]</sup> When the latter intermediate was treated with 1 N sodium hydroxide, at room temperature, it resulted in the formation of araF-G in less than 5% yield. In contrast, the treatment of  $N^9$ -glycoside **3**<sup>a</sup> with methanolic ammonia (150°C, 6 h) afforded araF-G (**4**)<sup>b</sup> in 67% yield (35% overall, from **1**) (Sch. 1).

### ACKNOWLEDGMENTS

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<sup>a</sup> $N^9$ - $\beta$ -isomer **3**: TLC (9:1 [v/v] methylene chloride/methanol) 0.42; <sup>1</sup>H-NMR (400 MHz DMSO- $d_6$ ): 8.10–7.46 (10H, m, Bz), 8.15 (1H, d,  $J_{8,F}$  = 2.8 Hz, H-8), 6.50 (1H, dd,  $J_{1',2'} = 4.4$  Hz,  $J_{1',F} = 18$  Hz, H-1'), 5.85 (1H, 2 dd,  $J_{3',F} = 19.2$  Hz, H-3'), 5.70 (1H, 2dd,  $J_{2',F} = 50$  Hz, H-2'), 4.80–4.65 (3H, m, H-4', H-5', 5''); <sup>13</sup>C-NMR (100.61 MHz, DMSO- $d_6$ ): 166 (C-6), 165 (C-4), 148.49 (C-2), 139.92 (d,  $J_{C8,F} = 5.3$  Hz, C-8), 134.54–129.14 (Bz), 123.09 (C-5), 92.70 (d,  $J_{C2',F} = 189.7$  Hz, C-2'), 83.19 (d,  $J_{C1',F} = 16.7$  Hz, C-1'), 79.26 (d,  $J_{C4',F} = 3$  Hz, C-4'), 77.21 (d,  $J_{C3',F} = 29$  Hz, C-3'), 64.48 (C-5'); APCI-MS: 512.9 (M + H<sup>+</sup>), 535 (M + Na<sup>+</sup>).

<sup>b</sup>AraF-G **4**: <sup>1</sup>H-NMR (400 MHz, DMSO- $d_6$ ): 10.62 (1H, s, N-H), 7.77 (1H, d,  $J_{8,F} = 2.8$ , H-8), 6.51 (2H, br, s, NH<sub>2</sub>), 6.11 (1H, dd,  $J_{1',2'} = 4.4$  Hz,  $J_{1',F} = 15.80$  Hz, H-1'), 5.91 (1H, d,  $J_{OH,2'} = 4.8$  Hz, HO-C2'), 5.00 and 5.15 (1H, dt or ddd,  $J_{2',F} = 32.80$  Hz,  $J_{2',3'} = 3.60$  Hz, H-2'), 5.05 (1H, t, HO-C5'), 4.32 (1H, m,  $J_{3',F} = 14$  Hz, H-3'), 3.77 (1H, m, H-4'), 3.57 (2H, m, H-5' and H-5''); <sup>19</sup>F-NMR (300 MHz, DMSO- $d_6$ , 99% [v/v] trifluoroacetic acid as external reference): –120.14 (ddd); FAB-MS (NBA-matrix): 286 [M + H<sup>+</sup>].



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