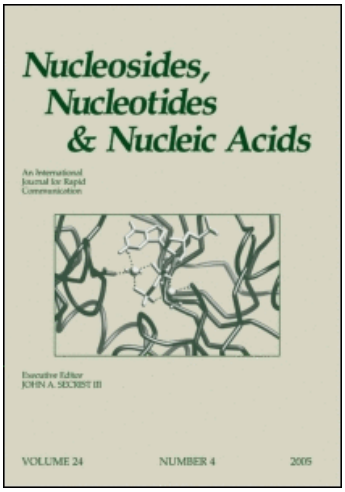

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Mohamed I. Elzagheid[a]; Ekaterina Viazovkina[a]; Masad J. Damha[ab]
[a] Department of Chemistry, McGill University, Montreal, QC, Canada [b] Otto Maass Chemistry Building, McGill University, Montreal, Quebec, Canada

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A New Synthesis of 9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)guanine (araF-G)

Mohamed I. Elzagheid, Ekaterina Viazovkina, and Masad J. Damha*

Department of Chemistry, McGill University, Montreal, QC, Canada

ABSTRACT

Interesting and very promising antisense properties of 2′-deoxy-2′-fluoroarabinonucleic 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-β-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-β-D-arabinofuranosyl)-5-iodouracil (β-FIAU) and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (β-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 stereospecific, total synthesis of 2′-fluoro-2′-deoxy-β-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-β-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.

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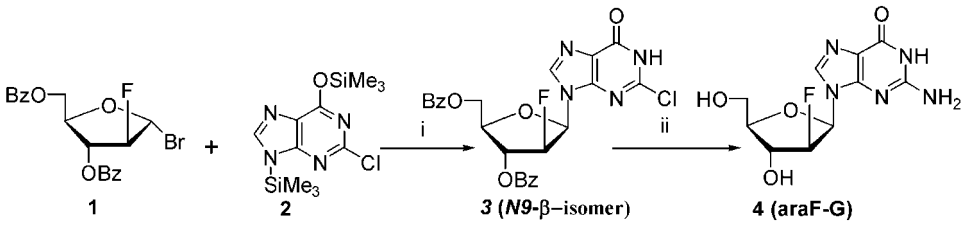
bearing a selectively removable protecting group. Chem. Pharm. Bull. 1999, *47*, 966–970) however, the synthesis of the guanine analogue is more complicated and affords poor to moderate yields of araF-G (**4**) ((a) Elzagheid, M.I.; Viazovkina, E.; Masad, M.J. Synthesis of protected 2′-deoxy-2′-fluoro-β-D-arabinonucleosides. 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-β-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-α-D-arabinofuranosyl bromide (**1**) with 2-chlorohypoxanthine (**2**) to afford 2-chloro-β-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-α-D-arabinofuranosyl bromide with a silylated base.[1,3] This produces primarily the desired β-anomer with $< 5\%$ of the α-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.[1b] A recently reported synthesis of araF-G required coupling of 2,6-dichloropurine to arabinoside **1**.[5b] This method produces a mixture of isomers (N^7- and N^9-regioisomers, as well as α and β anomers) that can be separated by silica gel chromatography to afford the desired N^9-β–anomer in 38% yield.[5a] 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**).[5a] 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) CCl_4, 77°C, 3 days, 52%; ii) saturated methanolic ammonia, steel bomb, 150°C, 6 h, 67%.

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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-β-anomers in 50–60% yield. Displacement of the chloro function in 9-(2-deoxy-2-β-D-fluoroarabinofuranosyl)-2-amino-6-chloropurine with 0.1–2 M hydrochloric acid[6,7] or 2 N sodium hydroxide in dioxane[8] or a mixture of sodium methoxide/ mercaptoethanol/ water[9,10] were not successful and gave only modified starting material (not isolated). Treatment of the same nucleoside, 9-(2-deoxy-2-β-D-fluoroarabinofuranosyl)-2-amino-6-chloropurine, with trimethylamine gave the trimethylammonium salt of the nucleoside.[11,12] 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**[a] with methanolic ammonia (150°C, 6 h) afforded araF-G (**4**)[b] in 67% yield (35% overall, from **1**) (Sch. 1).

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[a]N^9-β-isomer **3**: TLC (9:1 [v/v] methylene chloride/methanol) 0.42; ^{1}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″); ^{13}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 ($M + H^+$), 535 ($M + Na^+$).

[b]AraF-G **4**: ^{1}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_2), 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″); ^{19}F-NMR (300 MHz, DMSO-d_6, 99% [v/v] trifluoroacetic acid as external reference): −120.14 (ddd): FAB-MS (NBA-matrix): 286 [$M + H^+$].

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