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Synthesis of 9-(2,3-Dideoxy-2,3-Difluoro-β-D- Arabinofuranosyl)Adenine

Grigorii G. Sivets^a, Elena N. Kalinichenko^a & Igor A. Mikhailopulo^a

^a Institute of Bioorganic Chemistry, National Academy of Sciences , Minsk, Belarus

^b Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, Finland Published online: 05 Dec 2007.

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SYNTHESIS OF 9-(2,3-DIDEOXY-2,3-DIFLUORO- β -D-ARABINOFURANOSYL)ADENINE

Grigorii G. Sivets and Elena N. Kalinichenko *Institute of Bioorganic Chemistry, National Academy of Sciences, Minsk, Belarus*

Igor A. Mikhailopulo Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, Finland and Institute of Bioorganic Chemistry, National Academy of Sciences, Minsk, Belarus

 \Box Convergent synthesis of 9-(2, 3-dideoxy-2, 3-difluoro- β -D-arabinofuranosyl)adenine is described starting from methyl 5-O-benzyl-2-deoxy-2-fluoro- α -D-arabinofuranoside.

Keywords Dideoxydifluoro nucleosides; purine; convergent synthesis

INTRODUCTION

The replacement of the hydroxyl group in the sugar moiety of nucleosides with a fluorine atom results in nucleoside analogues which have interesting stereoelectronic properties and biological activities. Due to their broad chemotherapeutic potential, 2'- β -fluoro nucleosides have been extensively investigated in recent years.^[1] In continuation of our research on the synthesis of purine 2'-fluoroarabinonucleosides,^[2] we presently report the synthesis of the adenine nucleoside **9** containing two fluorine atoms in β -D-*arabino*-configuration by condensation of the nucleobase and sugar.

RESULTS AND DISCUSSION

We investigated a synthetic route to target nucleoside **9** from methyl 5-*O*-benzyl-2-deoxy-2-fluoro- α -D-arabinofuranoside (1) that was prepared by the known method starting from D-xylose.^[3] Oxidation of **1** followed by reduction of intermediate 3-keto derivative gave rise to lyxoside **2** in

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Address correspondence to G. G. Sivets, Laboratory of Nucleotides and Polynucleotides, Institute of Bioorganic Chemistry, National Academy of Sciences, 220141 Minsk, Acad. Kuprevicha 5/2, Belarus. E-mail: gsivets@yahoo.com



SCHEME 1 Reagents and conditions: a,b) Ref.^[4]; ($\Sigma 22\%$); c) DAST, toluene, rt, 20 hours (45%; 42% of starting **2** was recovered); d) [H]/10% Pd/C, EtOH, rt; e) BzCl/Py, rt (d + e, $\Sigma 90\%$); f) AcOH/Ac₂O/concn. H₂SO₄ (23:6:1, vol), 0°C, 30 minutes; 4°C, 18 hours (77%); g) TMS-Br/CDCl₃, 3 weeks, 15-16°C; hours) **4**/silylated N^{6Bz}Ade/SnCl₄/MeCN, reflux, 5 hours (**7**, 9%; **8**, 42%; calculated for consumed methyl glycoside **4**, 72% of which was recovered as a mixture of β - and α -anomers); i) **6**/Na-salt of N^{6Bz}Ade/THF, reflux, 5 hours (**7**, 22%; **8**, 3%); k) saturated NH₃/MeOH, rt (**9**, 88%; **10**, 81%).

22% isolated yield.^[4] Fluorination of the latter with DAST in toluene at room temperature afforded methyl 5-*O*-benzyl-2,3-dideoxy-2,3-difluoro- α -D-arabinofuranoside (3). Using two conventional steps, benzoate 4 was prepared from 3. The condensation of difluoride 4 with persilylated N^6 benzoyladenine in presence of SnCl₄ in acetonitrile resulted in a mixture of β - and α -nucleosides 7 and 8 (*ca.* 1:5 according to the ¹H NMR data) which was separated into individual anomers by column chromatography on silica gel (Scheme 1). It may be noted that α -methyl arabinoside 4 showed significantly lower reactivity *versus* the *ribo* isomer^[5] in the glycosylation reaction of persilylated N^6 -benzoyladenine and was mainly recovered from the reaction by column chromatography as a mixture of α - and β -methyl glycosides. Moreover, we have not detected by TLC the formation of N^7 -glycosides that may be explained by the use of excess SnCl₄ in the reaction in order to minimize their formation (*cf.*, refs.^[4,5] and refs. cited therein).

The low yield of desired nucleoside 7 prompted us to study another approach (Scheme 1). Acetolysis of 4 gave a mixture of acetates 5 after chromatography on silica gel. Bromination of 5 under mild conditions $(TMSiBr/CDCl_3)^{[6]}$ generated intermediate glycosyl bromide 6 that was reacted with the sodium salt of N^6 -benzoyladenine in tetrahydrofuran^[7] to

afford a mixture of β - and α -nucleosides **7** and **8** (*ca.* 7:1 according to the ¹H NMR data), the β -nucleoside **7** being the main product which was isolated by chromatography in moderate yield (22%). TLC of the reaction mixture displays some additional spots of lower intensity compared to that of nucleosides **7** and **8** but the corresponding compounds have not been isolated (*cf.* ref.^[7]).

Standard deprotection of individual blocked nucleosides **7** and **8** with methanolic ammonia gave pure amorphous 9-(2,3-dideoxy-2,3-difluoro- β -D-arabinofuranosyl)adenine (**9**) and its α -anomer **10**, respectively. Thus, we have complemented a set of known 2',3'-dideoxy-2',3'-difluoro- β -D-arabinofuranosyl pyrimidine nucleosides^[8] with the first purine nucleoside of this class.

The structure of all compounds was verified by ${}^{1}H^{[9]}$ and ${}^{13}C$ NMR spectroscopy, and by UV and mass spectroscopy in the case of nucleosides **9** and **10**.

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- 9. ¹H NMR (CD₃OD; δ_{TMS} , ppm; *J*, Hz); compound **9**–8.30 (d, 1H, $J_{8,2'F} = 2.3$; H-8); 8.21 (s, 1H; H-2); 6.53 (ddd, 1H, $J_{1',2'} = 3.97$; $J_{1',2'F} = 17.67$; ⁴ $J_{1',3'F} = 1.86$; H-1'); 5.50 (dddd, 1H, $J_{2',3'} = 2.17$; $J_{2',3'F} = 12.82$; $g^{\text{em}}J_{2',2'F} = 50.52$; H-2'); 5.46 (dddd, 1H, $J_{3',4'} = 3.76$; $J_{3',2'F} = 15.29$; $g^{\text{em}}J_{3',3'F} = 51.24$; H-3'); 4.30 (dm, 1H, $J_{4',5'} = 4.27$; $J_{4',5''} = 4.85$; $J_{4',3'F} = 24.80$; H-4'); 3.89 (ddd, 1H, $g^{\text{em}}J_{5',5''} = 12.80$; $J_{5',3'F}(2'F) \approx 1.0$; H-5'); 3.85 (m, 1H; H-5''). Compound **10**: 8.40 & 8.39 (2s, 2H; H-8 & H-2); 6.53 (dd, 1H, $J_{1',2'} = 2.42$; $J_{1',2'F} = 15.90$; H-1'); 6.04 (ddt, 1H, $J_{2',3'} = 2.74$; $J_{2',3'F} = 14.00$; $g^{\text{em}}J_{3',2'F} = 49.70$; H-2'); 5.47 (dddd, 1H, $J_{3',4'} = 3.90$; $J_{3',2'F} = 15.90$; $g^{\text{em}}J_{3',3'F} = 51.70$; H-3'); 4.81 (ddt 1H, $J_{4',5'} = 5.04$; $J_{4',5''} = 4.98$; $J_{4',3',F} = 21.16$; H-4'); 3.83 (dd, 1H, $g^{\text{em}}J_{5',5''} = 12.85$; H-5'); 3.79 (ddd, 1H; $J_{5',3'F} = 1.15$; H-5'').