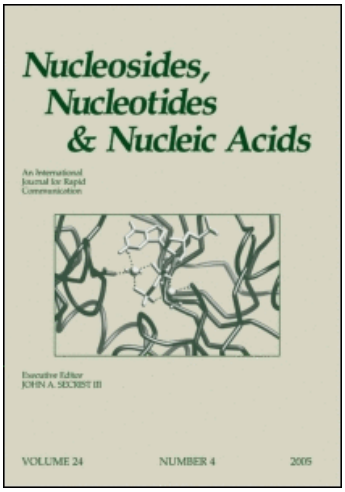


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

Grigorii G. Sivets[a]; Elena N. Kalinichenko[a]; Igor A. Mikhailopulo[ab]
[a] Institute of Bioorganic Chemistry, National Academy of Sciences, Minsk, Belarus [b] Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, Finland

To cite this Article Sivets, Grigorii G. , Kalinichenko, Elena N. and Mikhailopulo, Igor A.(2007) 'Synthesis of 9-(2,3-Dideoxy-2,3-Difluoro-β-D- Arabinofuranosyl)Adenine', Nucleosides, Nucleotides and Nucleic Acids, 26: 10, 1387 — 1389
To link to this Article: DOI: 10.1080/15257770701534063
URL: http://dx.doi.org/10.1080/15257770701534063

Nucleosides, Nucleotides, and Nucleic Acids, 26:1387–1389, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701534063

Taylor & Francis
Taylor & Francis Group

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*

□ *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

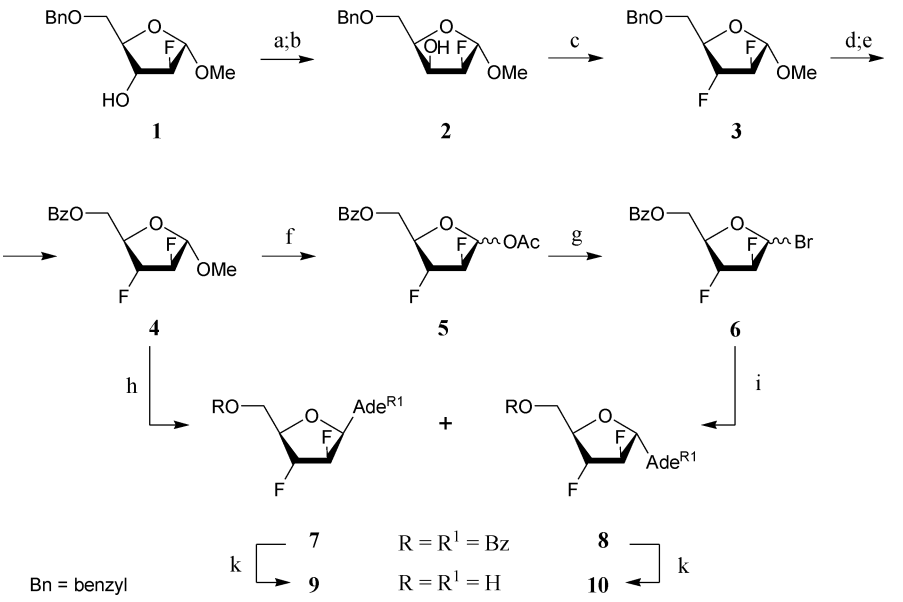
The replacement of the hydroxyl group in the sugar moiety of nucleosides with a fluorine atom results in nucleoside analogues which have interesting stereoelectronic properties and biological activities. Due to their broad chemotherapeutic potential, 2′-β-fluoro nucleosides have been extensively investigated 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

This work was supported from Belarus State Program of FOI "Physiological Active Compounds" (Grant 2.04).

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]; (Σ22%); 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, Σ90%); f) $AcOH/Ac_2O$/concn. H_2SO_4 (23:6:1, vol), 0°C, 30 minutes; 4°C, 18 hours (77%); g) TMS-Br/$CDCl_3$, 3 weeks, 15-16°C; hours) **4**/silylated N^{6Bz}Ade/$SnCl_4$/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 NH_3/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 $SnCl_4$ in acetonitrile resulted in a mixture of β- and α-nucleosides **7** and **8** (*ca.* 1:5 according to the ^{1}H 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 $SnCl_4$ 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 ^{1}H 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**.

REFERENCES

1. Pankiewicz, K.W. Fluorinated nucleosides. *Carbohydr. Res.* **2000**, 327, 87–105.
2. Sivets, G.G.; Kalinichenko, E.N.; Mikhailopulo, I.A. Synthesis of C2′-β-fluoro-substituted adenine nucleosides *via* pivaloyl derivatives of adenosine and 3′-deoxyadenosine. *Letters Org. Chem.* **2006**, 5, 402–408.
3. Wright, J.A.; Taylor, N.F.; Fox, J.J. Nucleosides. LX. Fluorocarbohydrates. XXII. Synthesis of 2-deoxy-2-fluoro-D-arabinose and 9-(2-deoxy-2-fluoro-α- and β-arabinofuranosyl)adenines. *J. Org. Chem.* **1969**, 34, 2632–2636.
4. Mikhailopulo, I.A.; Sivets, G.G.; Poopeiko, N.E.; Khripach, N.B. Oxidation-reduction sequence for the synthesis of peracylated fluorodeoxy pentofuranosides. *Carbohydr. Res.* **1995**, 278, 71–89.
5. Mikhailopulo, I.A.; Pricota, T.I.; Sivets, G.G.; Altona, C. 2′-Chloro-2′,3′-dideoxy-3′-fluoro-D-ribofuranosides: Synthesis, stereospecificity, some chemical transformations, and conformational analysis. *J. Org. Chem.* **2003**, 68, 5897–5908.
6. Gillard, J.W.; Israel, M. Trimethylsilyl bromide as a mild, stereoselective anomeric brominating agent. *Tetrahedron Lett.* **1981**, 22, 513–516.
7. Jin, F.; Wang, D.; Confalone, P.N.; Pierce, M.E.; Wang, Z.; Xu, G.; Choudhury, A.; Nguyen, D. (2*R*,3*S*,5*S*)-2-Acetoxy-3-fluoro-5-(*p*-toluoyloxymethyl)tetrahydrofuran: A key intermediate for the practical synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranofuranosyl)adenine (FddA). *Tetrahedron Lett.* **2001**, 42, 4787–4789.
8. Martin, J.A.; Busnell, D.J.; Duncan, I.B.; Dunsdon, S.J.; Hall, M.J.; Machin, P.J.; Merret, J.H.; Parkes, K.E.B.; Roberts, N.A.; Thomas, G.J.; Galpin, S.A.; Kinchington, D. Synthesis and antiviral activity of monofluoro and difluoro analogues of pyrimidine deoxyribonucleosides against human immunodeficiency virus (HIV-1). *J. Med. Chem.* **1990**, 33, 2137–2145.
9. ^{1}H NMR (CD_3OD; 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, $J_{1',2'} = 3.97$; $J_{1',2'F} = 17.67$; $^4J_{1',3'F} = 1.86$; H-1'); 5.50 (dddd, 1H, $J_{2',3'} = 2.17$; $J_{2',3'F} = 12.82$; $^{gem}J_{2',2'F} = 50.52$; H-2'); 5.46 (dddd, 1H, $J_{3',4'} = 3.76$; $J_{3',2'F} = 15.29$; $^{gem}J_{3',3'F} = 51.24$; 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, $^{gem}J_{5',5''} = 12.80$; $J_{5',3'F(2'F)} \approx 1.0$; 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, $J_{2',3'} = 2.74$; $J_{2',3'F} = 14.00$; $^{gem}J_{2',2'F} = 49.70$; H-2'); 5.47 (dddd, 1H, $J_{3',4'} = 3.90$; $J_{3',2'F} = 15.90$; $^{gem}J_{3',3'F} = 51.70$; 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, $^{gem}J_{5',5''} = 12.85$; H-5'); 3.79 (ddd, 1H; $J_{5',3'F} = 1.15$; H-5").