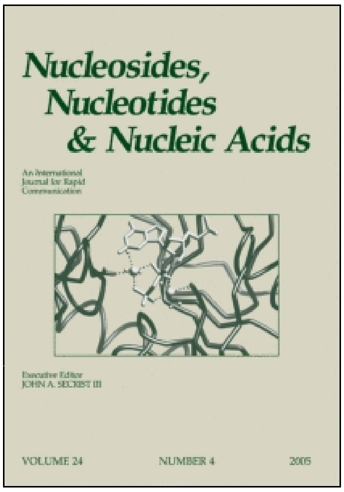

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Biological Evaluation of 9-(β-L-Arabinofuranosyl)Adenine

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To cite this Article Boudou, Valérie , Imbach, Jean-Louis and Gosselin, Grilles(1999) 'Synthesis and Biological Evaluation of 9-(β-L-Arabinofuranosyl)Adenine', Nucleosides, Nucleotides and Nucleic Acids, 18: 11, 2463 — 2473
To link to this Article: DOI: 10.1080/07328319908044620
URL: http://dx.doi.org/10.1080/07328319908044620

NUCLEOSIDES & NUCLEOTIDES, 18(11&12), 2463–2473 (1999)

SYNTHESIS AND BIOLOGICAL EVALUATION OF 9-(β-L-ARABINOFURANOSYL)ADENINE

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ABSTRACT: For the first time, the stereospecific synthesis of 9-(β-L-arabinofuranosyl) adenine was carried out. Unfortunately, and unlike its "natural" D-counterpart Vidarabine, this L-enantiomer did not show significant activity when evaluated against a broad range of viruses.

Introduction.

Non natural L-nucleoside enantiomers are known since 1964 when L-adenosine[1] and L-thymidine[2] were first synthesized. But it was only at the beginning of the 90s that some unnatural L-nucleoside analogues, modified either in the base and/or the sugar moiety, were considered as potential antiviral agents and evaluated as such.[3] In this regard, 2',3'-dideoxy-3'-thia-β-L-cytidine (β-L-(–)-SddC, 3TC)[4] has shown slightly more potent antiviral activity than its D-counterpart against either human immunodeficiency virus (HIV) or against human hepatitis B virus (HBV), and with less cytotoxic effects. As a result of its potent selectivity, the use of 3TC in combination with AZT was approved in November 1995 by the Food and Drug Administration for first-line treatment of HIV infection in adults and children. In December 1998, 3TC was also approved for treatment of adults with chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation.

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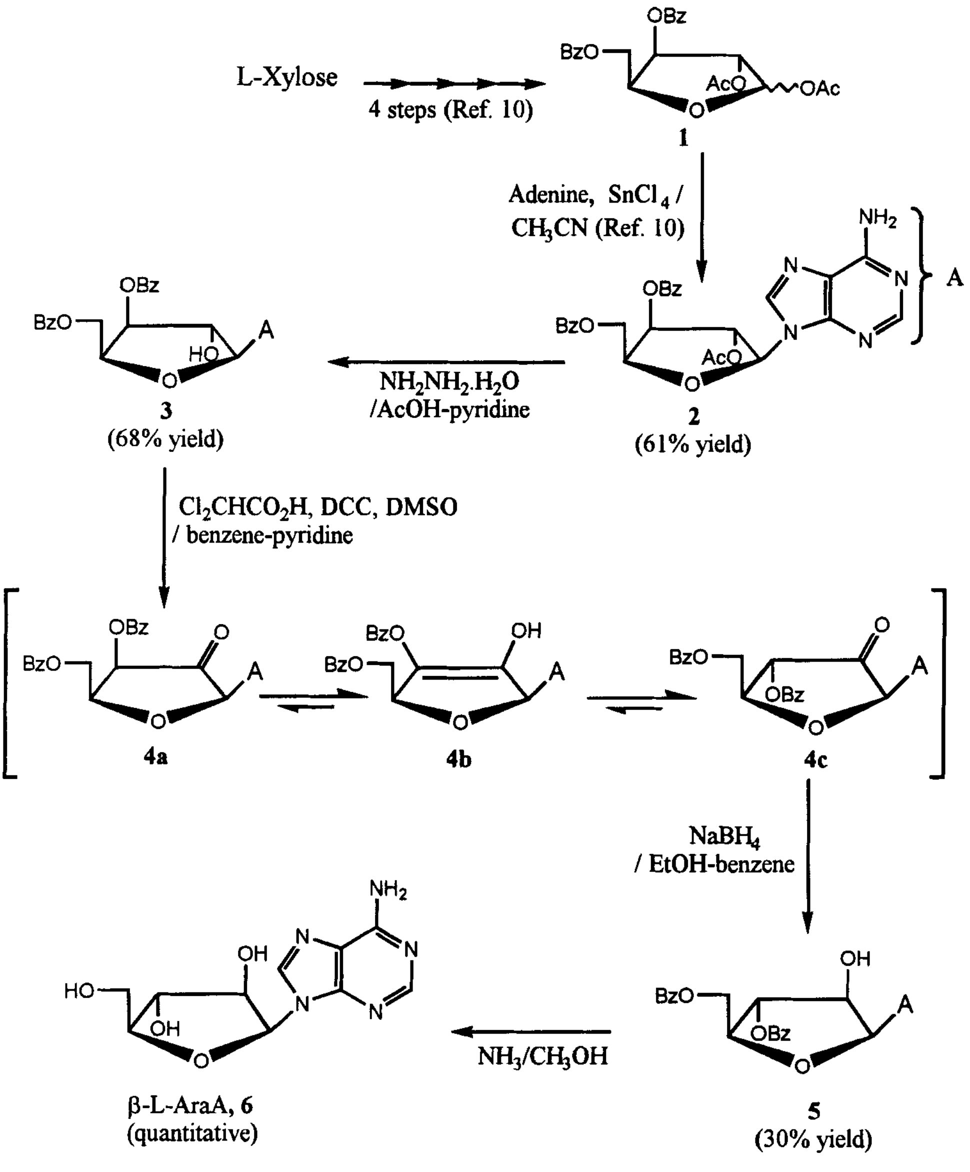
Over several years, our group has investigated to the chemistry and biological properties of L-nucleoside analogues, first dealing with the α-anomers,[5-9] and subsequently in synthesizing and studying β-anomers in the xylo-,[10-12] ribo-,[12-18] deoxyribo-[5,12-15,18-26] and dideoxyribofuranose[11,14,25-45] series.

Recently, we also decided to examine some β-L-arabinofuranosyl nucleosides. A thorough literature survey showed that in this series pyrimidine derivatives have been extensively studied,[46-48] notably those bearing a fluorine atom in the 2'-position.[49] On the other hand, purine β-L-arabinofuranosyl nucleosides have received less attention. For instance, 9-(β-L-arabinofuranosyl)guanine is hitherto unknown to the best of our knowledge, and there are only two mentions of 9-(β-L-arabinofuranosyl)adenine (β-L-araA) in the literature,[50,51] regarding its lack of substrate property for bacterial purine nucleoside phosphorylase and adenosine deaminase, respectively. Actually, no detailed synthesis and no full characterization were reported, the authors[50] just specifying that "*the α- and β-anomers of 9-(β-L-arabinofuranosyl)adenine were prepared from adenine and L-arabinose using polyphosphoric acid in triphenyl phosphate as described by Schramm*[52] *and purified by Dekker chromatography on Dowex 1 in 50% methanol*[53]" and that "*structural assignment of anomers was performed by means of CD spectra*". Since the β-D-enantiomer of araA (Vidarabine, *Vira*-A) is an important antiviral drug currently licensed for use in humans[54] and showing activity against herpes simplex virus-1 and -2 (HSV), cytomegalovirus (CMV), varicella-zoster virus (VZV) and HBV, we decided to carry out a stereospecific synthesis of β-L-araA and to evaluate its potential antiviral properties. We hoped that the L-counterpart of araA would retain the antiviral activity of the D-enantiomer, but with a reduction of host toxicity and of the rate of enzyme deamination which limit the clinical efficiency of the « natural » D-molecule.[55,56]

Results and Discussion.

Synthesis: The stereochemical synthesis β-L-araA, **6** is shown in Scheme 1. The starting material 9-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-xylofuranosyl)adenine **2** was prepared from per-acylated L-xylose following a procedure previously described by our group.[10]
Reaction of **2** with hydrazine hydrate in a mixture of acetic acid and pyridine gave the 2'-*O*-deacylated derivative **3**.


L-Xylose
4 steps (Ref. 10)
OBz
BzO
AcO
OAc
O
1
Adenine, SnCl4 /
CH3CN (Ref. 10)
NH2
N
A
2
(61% yield)
NH2NH2.H2O
/AcOH-pyridine
HO
3
(68% yield)
Cl2CHCO2H, DCC, DMSO
/ benzene-pyridine
OH
4a
4b
4c
NaBH4
/ EtOH-benzene
5
(30% yield)
NH3/CH3OH
HO
β-L-AraA, 6
(quantitative)

Scheme 1

In order to invert simultaneously the configuration of carbons C-2' and C-3' we applied an oxidation-reduction sequence approach like that we described fifteen years ago in the D-series.[57] In this approach, the C-2' and C-3' configuration inversions of 3',5'-di-*O*-benzoyl-β-xylofuranonucleosides were performed upon oxidation with dimethylsulfoxide/dicyclohexylcarbodiimide, subsequent reduction of the intermediate 2'-keto derivatives with sodium borohydride leading to the formation of the corresponding 3',5'-di-*O*-benzoyl-β-arabinofuranonucleosides. This oxidation-reduction sequence applied to **3** afforded only one compound, 9-(3,5-di-*O*-benzoyl-β-L-arabinofuranosyl)adenine (**5**). As in the series of methyl 3-deoxy-3-fluoro-α-D-pentofuranosides[58,59] and conveniently protected (3'-deoxy)ribonucleosides[60] no isomerization was observed at C-1'. Furthermore, we ascribe the stereoselectivity of the reduction step to the presence of bulky groups (benzoyl, adenine) on the β-face of the keto intermediate **4c,** forcing hydrogen attack at the less hindered α-face of the sugar ring. Treatment of compound **5** with methanolic ammonia afforded the desired β-L-araA **6**. Structural assignments for the isolated compounds **2**,**3**,**5** and **6** were based on elemental analysis and physical constants. Their melting point, UV, ^{1}H NMR and mass spectra were identical to those of their D-isomer and their optical rotation data agreed with their L-configuration.

Biological Evaluation: β-L-araA **6** was tested for its *in vitro* inhibitory effects on the replication of a number of DNA viruses [*viz* Human CMV, HSV-1 and -2, vaccinia virus, HBV], RNA viruses [*i.e.* parainfluenza virus, respiratory syncytial virus, sindbis virus, Coxsackie virus B3 and polio virus-1] and retroviruses [HIV-1 Lai and IIIB] in different cell systems (MRC-5, Vero, KB cells, Hep-G2 cells, MT-4 and CEM cells). But, it did not show marked antiviral effects or detectable alteration of host cell morphology at the highest concentration tested (generally 100 μM).

Conclusion.

From the present work, it appears that the inversion of the enantiomeric configuration (L *versus* D) leads to the loss of the anti-herpes activity observed for β-D-araA. Moreover, this modification does not induce new antiviral properties, especially against the HIV replication. Among the several hypotheses that could explain the lack of activity of β-L-araA, the inability of this enantiomer to enter cells, to serve as a substrate for the enzymes catalyzing phosphorylations, or to inhibit enzymes involved in the metabolism of nucleic acids can be proposed. Further research is needed to test these hypotheses, and in this regard we have recently shown that both enantiomers of β-araA are average substrates of recombinant human deoxycytidine kinase compared to deoxyadenosine.[18] Other work related to this topic is currently in progress in our laboratory.

Experimental

Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. The ^1H NMR spectra were recorded in dimethylsulfoxide-d_6 on a Brüker 250 AC spectrometer. Chemical shifts are given in δ (ppm) values, $(CD_3)(CD_2H)SO$ being set at δ 2.49 as a reference. Mass spectra were recorded using the fast atom bombardment (FAB) ionization method, in the positive and negative-ion mode, on a JEOL JMS DX 300 mass spectrometer. The matrices used were either glycerol/thioglycerol [50/50, v/v, (G/T)] or 3-nitrobenzyl alcohol (NBA). UV spectra were obtained on a Kontron Uvikon 810 spectrophotometer. Specific rotations were measured on a Perkin-Elmer Model 241 spectropolarimeter adjusted on the sodium D line. Elemental analyses were performed by Service de Microanalyses de C.N.R.S., Division de Vernaison, France. The silica gel (0.040-0.063 mm, 60H, Art. 9385) used for column chromatography was purchased from Merck. TLC analyses were performed on precoated aluminum sheets of silica gel $60F_{254}$ (Merck, Art. 5554). Visualization of products was accomplished by UV absorbance at 254 nm followed by charring with 5% ethanolic sulfuric acid and heating. In the particular case of the keto intermediate **4**, a solution of ortho-dianisidine in glacial acetic acid was used.

9-(3,5-Di-*O*-benzoyl-β-L-xylofuranosyl)adenine (3). To a solution of 9-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-xylofuranosyl) adenine **2**[10] (11.0 g, 21.3 mmoles) in a mixture of pyridine/acetic acid (4/1, v/v, 225 ml) was added hydrazine monohydrate 98% (3.1 ml, 63.9 mmoles). After one day under stirring at room temperature, the reaction was quenched by adding acetone (54 ml) and the mixture was stirred for 1 h. The resultant solution was partially evaporated *in vacuo* and extracted from water (300 ml) into chloroform (2×200 ml). The combined organic layers were washed several times with aq. saturated $NaHCO_3$ (100 ml) then with water (100 ml), dried over anhydrous Na_2SO_4, evaporated to dryness and coevaporated (toluene, then methanol). The residue was purified on a silica gel column using a stepwise gradient of methanol (0–5%) in methylene chloride as eluent to give **3** as a white foam which was precipitated from a mixture of methylene chloride and diisopropyl ether (6.85 g, 68%); mp: decomposition at 107–168°C (lit.[61], mp 94–165°C, decomposition for the D enantiomer); UV (95% ethanol): λ max 257 nm (ε 16,400), 230 nm (ε 29,300); λ min 246 nm (ε 14,800); ^1H NMR (dimethylsulfoxide-d_6): δ 4.5–4.9 (m, 4H, H-', H-4', H-5' and H-5"), 5.64 (t, 1H, $J_{2',3'} = J_{3',4'} = 3.5$ Hz, H-3'), 6.30 (br s, 1H, D_2O-exchangeable, OH-2'), 6.45 (d, 1H, $J_{1',2'} = 4.6$ Hz, H-1'), 7.31 (br s, 2H, D_2O-exchangeable, NH_2-6), 7.4-7.9 (m, 10H, $2{\times}C_6H_5C{=}O$), 8.07 and 8.34 (2s, 2H, H-2 and H-8); ms: matrix G/T, (FAB>0) m/z 476 $[M+H]^+$, 136 $[BH_2]^+$, 105 $[C_6H_5C{\equiv}O]^+$, (FAB<0) m/z 474 $[M-H]^-$, 134 $[B]^-$, 121 $[C_6H_5CO_2]^-$; $[\alpha]_D^{20}$ -64 (*c* 1.07, $CHCl_3$) (lit.[61] +54 (*c* 1.0, $CHCl_3$) for the D enantiomer).

Anal. Calcd. for $C_{24}H_{21}N_5O_6$: C, 60.63; H,4.45; N, 14.73. Found : C, 60.41; H, 4.68; N, 14.27.

9-(3,5-Di-*O*-benzoyl-β-L-arabinofuranosyl)adenine (5). To a solution of **3** (1.0 g, 2.10 mmoles) in an anhydrous mixture of benzene/dimethylsulfoxide (6/4, v/v, 24 ml) was added successively dry pyridine (0.160 ml), dicyclohexylcarbodiimide (1.36 g, 6.30 mmoles) and dichloroacetic acid (0.089 ml). The mixture was stirred for 24 h at room temperature with exclusion of moisture; then ethyl acetate (100 ml) and oxalic acid (0.570 g, 6.33 mmol) in methanol (2 ml) were added to precipitate dicyclohexylurea. The resultant white solid was removed by filtration and the filtrates were washed with brine (3×200 ml), 3% aqueous $NaHCO_3$ (3×200 ml) and water (3×200 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford crude **4c** as a solid residue.

To a stirred and cooled (0°C) solution of crude **4c** in ethanol/benzene (2/1, v/v, 17 ml) was added sodium borohydride (0.120 g, 3.17 mmoles) and the reaction mixture was allowed to stand at 0°C for 1 hour. After dilution with ethyl acetate (110 ml), the mixture was filtered and the solid residue washed several times with ethyl acetate. The combined filtrates were washed with brine (3×150 ml) and water (3×150 ml). The organic layer was dried over $NaSO_4$, filtered and evaporated to dryness. Chromatography on a silica gel column [eluent: stepwise gradient of methanol (0-7%) in methylene chloride] gave the pure compound **5** (0.3 g, 30%) which was crystallized from methylene chloride; mp 225-226°C (lit.[57], mp 225-226°C for the D enantiomer); UV (95% ethanol): λ max 256 nm (ε 16,800), 230 nm (ε 29,600); λ min 247 nm (ε 15,100); ^1H NMR (dimethylsulfoxide-d_6): δ 4.55 (q, 1H, H-4', $J = 3.5$ Hz), 4.6-4.7 (m, 1H, H-2'), 4.7-4.8 (m, 2H, H-5' and H-5"), 5.45 (pt, 1H, H-3'), 6.2 (br s, 1H, D_2O-exchangeable, OH-2'), 6.35 (d, 1H, $J_{1',2'} = 1.6$ Hz, H-1'), 7.3 (br s, 2H, D_2O-exchangeable, NH_2-6), 7.4-8.1 (m, 10H, $2\times C_6H_5C{=}O$), 8.15 and 8.21 (2s, 2H, H-2 and H-8); ms: matrix G/T, (FAB>0) m/z 476 $[M+H]^+$, 136 $[BH_2]^+$, 105 $[C_6H_5C{\equiv}O]^+$, (FAB<0) m/z 474 $[M-H]^-$, 134 $[B]^-$, 121 $[C_6H_5CO_2]^-$; $[\alpha]_D^{20}$ +48 (*c* 1.07, DMSO).

Anal. Calcd. for $C_{24}H_{21}N_5O_6$: C, 60.63; H, 4.45; N, 14.73. Found : C, 60.35; H, 4.52; N, 14.85.

9-(β-L-Arabinofuranosyl)adenine (6). Compound **5** (0.140 g, 0.29 mmole) was deacylated by treatment with 10 ml methanolic ammonia (previously saturated at –10°C and tightly stoppered) in a sealed flask over night at room temperature. The solution was evaporated to dryness under reduced pressure and the residue was coevaporated several times with methanol. The crude material was dissolved in water (40 ml), washed with chloroform (5×40 ml) and ethyl ether (2×40 ml). The aqueous layer was evaporated to dryness and coevaporated with absolute ethanol. Crystallization at room temperature from methanol afforded pure **6** (78 mg, quantitative yield), mp 261–262°C (lit. for the D enantiomer : mp 257–258°C[28,60], 258–260°C[62], 260°C[63]); UV (95% ethanol): λ max 257 nm (ε 13,200), λ min 226 nm (ε 2,600); ^1H NMR (dimethylsulfoxide-d_6): δ 3.6-3.7 (m, 2H, H-5' and H-5'), 3.7–3.8 (m, 1H, H-4'), 4.12 (s, 2H, H-2' and H-3'), 5.1 (br s, 1H, D_2O-exchangeable, OH-5'), 5.52 and 5.62 (br s and d, 2H, D_2O-exchangeable, OH-2' and OH-3', oxide-), 6.23 (d, 1H, $J_{1',2'} = 4.1$ Hz, H-1'), 7.2 (br s, 2H, D_2O-exchangeable, NH_2-6), 8.11 and 8.17 (2s, 2H, H-2 and H-8); ms: matrix G/T, (FAB>0) m/z 268 $[M+H]^+$, 136 $[BH_2]^+$, (FAB<0) m/z 266 $[M-H]^-$; $[\alpha]_D^{20}$

+6 (c 1.13, DMSO) ($[\alpha]_D^{20}$ −7 (*c* 1.05, DMSO) for a β-D-araA commercial sample). Anal. Calcd. for $C_{10}H_{13}N_5O_4$, 1/4 CH_3OH : C, 44.72; H, 5.13; N, 25.45. Found : C, 44.78; H, 4.90; N, 25.51.

Acknowledgments.

The investigations were supported by Grants from the Agence Nationale de Recherche sur le SIDA (ANRS, France). Valérie Boudou was a recipient of the Ministère de la Recherche et de la Technologie (France). We gratefully acknowledge Dr. A.-M. Aubertin and the late Prof. G. Obert (Université de Strasbourg, France), as well as Prof. J.-P. Sommadossi (University of Alabama, Birmingham, Alabama, USA) for the antiviral evaluations. The assistance of Mrs. M.-C. Bergogne in typing this manuscript is also greatly appreciated.

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Received 2/28/99

Accepted 6/1/99