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Synthesis of 2'-Deoxy-2'-fluoro-L-arabinofuranosyl Imidazole Derivatives

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A new series of imidazole nucleosides was synthesized via direct condensation and construction of heterocyclic moiety from glycosyl amine templates. The characterization of the compounds was accomplished by elemental analysis, ^{1}H-NMR, ^{13}C-NMR, IR, UV-VIS spectral data and optical rotation.

Introduction

The last few years have witnessed a revival of interest in analogues of nucleosides following the discoveries that several of such compounds exhibit powerful antiviral effects. Structural modifications of naturally occurring nucleosides often lead to the discovery of new agents displaying biological and chemotherapeutic activity. A greal deal of effort has been directed towards the modifications at the nucleobase[1–3].

An imidazole nucleoside, 5-amino imidazole-4-carboxamide riboside (AICA riboside), is known to be involved in the *de novo* biosynthesis of purine nucleotides[4]. It is also produced in histidine biosynthesis and is associated with the histamine metabolism. The naturally occurring nucleoside antibiotic, bredinin (Figure 1), has been isolated from the culture of *Eupenicillium brefeldianum* and shown to possess immunosuppressive properties as well as other biological activities[1,5].

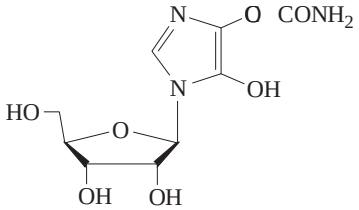


Figure 1. Bredinin

Recently, a number of studies about imidazole nucleosides have been published. These include 2'-deoxy-4'-thioimidazole nucleosides[6], imidazothiadiazine dioxides[7] and 5:7 fused, planar, aromatic imidazo [4,5-e] [1,3] diazepines[8]. Among these antiviral nucleosides, only the last group showed considerable activity. These limited studies concerning the heterocyclic nucleosides make further research in this area inevitable. In this study, we report on the design and synthesis of imidazole based arabinofuranosyl nucleosides.

Experimental

Melting points were determined on a Mel-temp II and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker 400 AMX spectrometer at 400 MHz, with $(CH_3)_4Si$ as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), bd (broad doublet), dd (di doublet), ddd (doublet doublet doublet) t (triplet), q (quartet), m (multiplet) or bs (broad singlet). Mass spectra were recorded on a Micromass Autospec high resolution mass spectrometer. IR spectra were measured on a Nicolet 510P FT-IR spectrometer. Optical rotations were determined on a Jasco DIP-370 Digital Polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either Silica Gel-60 (220-440 mesh) for flash chromatography or Silica Gel G (TLC grade, 440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranosyl azide (IVa) and 3,5-di-*O*- benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl azide (IVb)

To a solution of **II** (33.0 g, 67.6 mmol) in CH_2Cl_2 (100 mL) was added HBr/AcOH (20 mL, 45% w/v), and the mixture was stirred at rt overnight. After the usual work-up, **III** was obtained as a syrup, which was used directly for the next reaction without further purification.

To a stirred solution of **III** in anhydrous CH_3CN (100 mL) was added LiN_3 (8.2 g, 167.00 mmol), and the mixture was stirred at rt for 24 h followed by heating at 70°C for 1 h. The solvent was evaporated and the residue was extracted with ethyl acetate (2 x 100 mL), washed with water, and dried over $MgSO_4$. Removal of solvent gave a syrup, which was separated by silica gel column chromatography (10:1 Hexane-ethyl acetate). The fast moving spot was collected to give **IVa** as an oil (8.5 g, 34.0%), which upon standing became a wax-like solid: mp. 57-8°C; $[\alpha]_D^{25}$ -216.82° (*c* 0.3, $CHCl_3$); IR 2116, 1727, 1603, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.54-7.32 (m, 10H, benzoyl), 5.66 (bd, 1H, H-1', $J_{1',F}$= 12.5 Hz), 5.45 (dd, 1H, H-3', $J_{3',F}$= 20.5 Hz, $J_{3',4'}$= 8.9 Hz), 4.96 (bd, 1H, H-2', $J_{2',F}$= 49.0 Hz), 4.68-4.54 (m, 3H, H-4', H-5'a,b); ^{13}C-NMR ($CDCl_3$) 166.58, 165.90 (CO), 134.20, 133.55, 130.10, 129.93, 129.01, 128.88, 128.80 (Ar), 98.13 (d, J = 184.4 Hz, C-2'), 94.27 (d, J = 35.0 Hz, C-1'), 83.86 (C-4'), 77.45 (d, J = 30.7 Hz, C-3'), 64.11 (C-5').

Anal. For	$C_{19}H_{16}FN_3O_5$		
Calcd.	C:59.22	H:4.19	N:10.90
Found	C:59.10	H:4.27	N:10.34

The slow moving spot was collected and recrystallized from CH_3OH to give **IVb** as a white solid of 10.5 g (42.0%): mp. 86-8°C; $[\alpha]_D^{25}$ 52.94° (*c* 0.4, $CHCl_3$); IR 2124, 1725, 1603, 1586 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.90-7.30 (m, 10H, benzoyl), 5.57 (bd, 1H, H-1', $J_{1',F}$= 16.3 Hz), 5.21 (dd, 1H, H-3', $J_{3',F}$= 12.2 Hz, $J_{3',4'}$= 6.4 Hz), 5.12 (bd, 1H, H-2', $J_{2',F}$= 50.8 Hz), 4.57 (m, 2H, H-5'a,b), 4.32 (m, 1H, H-4'); ^{13}C-NMR ($CDCl_3$) 166.59, 165.68 (CO), 134.36, 133.64, 130.26, 130.20, 129.98, 128.89, 128.83 (Ar), 94.30 (d, J = 197.0 Hz, C-1'), 89.76 (d, J = 17.1 Hz, C-2'), 80.59 (C-4'), 76.54 (d, J = 27.4 Hz, C-3'), 64.35 (C-5').

Anal.	$C_{19}H_{16}FN_3O_5$		
Calcd.	C:59.22	H:4.19	N:10.90
Found	C:59.46	H:4.22	N:10.83

Ethyl 5-amino-1-(3',5'-di-*O*-benzoyl-2'-deoxy-2'-fluoro-α-L-arabinofuranosyl) imidazole-4-carboxylate (VIIa) and ethyl 5-amino-1-(3',5'-di-*O*-benzoyl-2'-deoxy-2'-fluoro-β-L-arabinofuranosyl) imidazole-4-carboxylate (VIIb)

A mixture of **IVa** (0.875 g, 2.24 mmol) and PtO_2 (0.12 g) in ethyl acetate (16 mL) was subjected to hydrogenation (1atm) at rt for 3 h and then filtered through a celite pad to a freshly prepared solution of **VI** in anhydrous CH_3CN. The mixture was then stirred at rt overnight. The solvent was evaporated and the residue was redissolved in CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$, and dried over $MgSO_4$. Removal of solvent gave a syrup, which was separated on a silica gel column (50:1 $CHCl_3$: CH_3OH). The fast moving spot was collected to give **VIIa** (0.257 g, 24.5%), which was recrystallized from EtOH to give a white solid: mp. 166-8°C; UV (CH_3OH) λ_{max} 231.5, 265.5 nm; $[\alpha]_D^{25}$ -45.70° (*c* 0.42, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.09, 7.44 (m, 11H, Ar-H), 6.06 (bd, 1H, H-1', $J_{1'-F}$= 15.8 Hz), 5.80 (bd, 1H, H-3', $J_{3'-F}$= 24.2 Hz), 5.77 (bd, 1H, H-2', $J_{2'-F}$ = 50.0 Hz), 5.23 (bs, 2H, NH_2,D_2O exchangeable), 4.72 (m, 3H, H-4', H-5'ab), 4.36 (q, 2H, O**C**$\mathbf{H}_2$$CH_3$), 1.39 (t, 3H, OCH_2**C**$\mathbf{H}_3$); ^{13}C-NMR ($CDCl_3$) 166.21, 165.35, 164.56 (CO), 144.90, 134.26, 133.50, 129.83, 129.80, 129.24, 128.90, 128.56, 128.30, 127.93, 112.98 (Ar), 96.60 (d, J = 188.0 Hz, C-2'), 88.23 (d, J = 36.2 Hz, C-1'), 86.60 (C-4'), 83.19 (C-3'), 63.11 (C-5'), 60.08 (O**C**H_2CH_3), 14.55 (OCH_2**C**H_3).

Anal. For	$C_{25}H_{24}FN_3O_7.0.3\ H_2O$		
Calcd.	C:59.71	H:4.93	N:8.36
Found	C:59.43	H:4.90	N:8.11

The slow moving spot was collected and coevaporated with C_2H_5OH to give **VIIb** as a solid (0.256 g, 21.0%): mp. 174-6°C; UV (MeOH) λ_{max} 231.0, 267.0 nm; $[\alpha]_D^{25}$ 27.75 ° (*c* 0.36, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.08, 7.44 (m, 11H, Ar-H), 5.89 (dd, 1H, H-1', $J_{1'-2'}$= 2.6, $J_{1'-F}$= 22.5 Hz), 5.70 (dd, 1H, H-3', $J_{3'-F}$= 17.4 Hz), 5.38 (dd, 1H, H-2', $J_{1'-2'}$= 2.4, $J_{2'-F}$ = 53.5 Hz), 5.31 (bs, 2H, NH_2, D_2O exchangeable,), 4.79 (m, 2H, H-5'ab), 4.52 (m, 1H, H-4'), 4.33 (q, 2H, O**C**$\mathbf{H}_2$$CH_3$), 1.37 (t, 3H, OCH_2**C**$\mathbf{H}_3$); ^{13}C-NMR ($CDCl_3$) 166.20, 165.08, 164.64 (CO), 145.73, 134.22, 133.54, 129.89, 129.83, 129.74, 129.57, 129.18, 128.76, 128.61, 128.49, 128.12, 127.94, 112.04 (Ar), 93.26 (d,J = 194.3 Hz, C-2'), 85.04 (d, J = 17.7 Hz, C-1'), 80.95 (C-3'), 76.36 (C-4'), 63.12 (C-5'), 59.92 (O**C**H_2CH_3), 14.55 (OCH_2**C**H_3).

Anal. For	$C_{25}H_{24}FN_3O_7$		
Calcd.	C:60.36	H:4.86	N:8.45
Found	C:60.32	H:5.07	N:8.16

Ethyl 5-amino-1-(2'-deoxy-2'-fluoro-α-L-arabinofuranosyl) imidazole-4-carboxylate (VIIIa)

Compound **VIIa** (0.251 g, 0.50 mmol) was treated with saturated NH_3/CH_3OH at rt overnight. Removal of solvent followed by silica gel column chromatography (9:1 $CHCl_3$:CH_3OH) gave **VIIIa** as an amorphous solid (0.108 g, 73.9%): dec. 186°C; UV (H_2O) λ_{max} 266.0 (ε 6955) (pH 2), 268.0 (ε 7078) (pH 7), 268.5 nm (ε 6512) (pH 11); $[\alpha]_D^{25}$-55.23° (*c* 0.54, CH_3OH); ^{1}H-NMR (DMSO-d_6) δ 7.37 (s, 1H, H-2), 6.20 (bs, 2H, NH_2, D_2O exchangeable), 6.04 (t, 1H, 3'-OH, D_2O exchangeable), 6.02 (bd, 1H, H-1', $J_{1'-F}$= 19.7 Hz), 5.38 (bd, 1H, H-2', $J_{2'-F}$= 51.2 Hz), 4.98 (t, 1H, 5'-OH, D_2O exchangeable), 4.24 (d, 1H, H-3', $J_{3'-F}$= 21.0 Hz), 4.16 (q, 2H, O**C**$\mathbf{H}_2$$CH_3$), 4.02 (m, 1H, H-4'), 3.53 (m, 2H, H-5'a,b), 1.23 (t, 3H, OCH_2**C**$\mathbf{H}_3$); FABMS, m/z : 290 $(M+1)^+$.

Anal.	$C_{11}H_{16}FN_3O_5$		
Calcd.	C:45.67	H:5.58	N:14.53
Found	C:45.46	H:5.74	N:14.78

Ethyl 5-amino-1-(2'-deoxy-2'-fluoro-β-L-arabinofuranosyl) imidazole-4-carboxylate (VIIIb)

Compound **VIIb** (0.250 g, 0.50 mmol) was treated with saturated NH_3/CH_3OH at rt overnight. Removal of solvent followed by silica gel column chromatography (9:1 $CHCl_3$: CH_3OH) gave **VIIIb** as a hygroscopic solid (0.075 g, 51.4%): mp. 46°C; UV (H_2O) λ_{max} 266.5 (ε 9501) (pH 2), 268.0 (ε 7679) (pH 7), 268.0 nm (ε 9425) (pH 11); $[\alpha]_D^{25}$ -56.84° (*c* 0.48, CH_3OH); ^{1}H-NMR (DMSO-d_6) δ 7.28 (s, 1H, H-2), 6.17 (bs, 2H, NH_2, D_2O exchangeable), 5.97 (dd, 1H, H-1', $J_{1'-2'}$= 4.4, $J_{1'-F}$= 15.2 Hz), 5.92 (t, 1H, 3'-OH, D_2O exchangeable), 5.14 (t, 1H, 5'-OH, D_2O exchangeable), 5.08 (ddd, 1H, H-2', $J_{2'-F}$= 51.5 Hz, $J_{1'-2'}$= 11.7 Hz,$J_{2'-3'}$= 9.5 Hz), 4.31 (d, 1H, H-3', $J_{3'-F}$= 19.7 Hz), 4.15 (q, 2H, O**C**$\mathbf{H}_2$$CH_3$), 3.74 (m, 1H, H-4'), 3.52 (m, 2H, H-5'a,b), 1.23 (t, 3H, OCH_2**C**$\mathbf{H}_3$); FABMS m/z : 290 $(M+1)^+$.

Anal.	$C_{11}H_{16}FN_3O_5 \cdot 0.7H_2O$		
Calcd.	C:43.77	H:5.71	N:13.92
Found	C:43.30	H:5.36	N:14.11

Ethyl imidazole-4 (5)-carboxylate (IX)

Imidazole-4,5-dicarboxylic acid (24.0 g, 154.00 mmol) was refluxed in Ac_2O (800 mL) overnight and filtered while hot. The filtrate was evaporated to dryness, and to the residue was added water (300 mL) and the mixture was stirred at rt overnight during which time a white precipitate formed. It was heated at 90°C for 30 min, and C_2H_5OH (300 mL) and charcoal were added. The resulting mixture was heated for another 30 min and filtered hot. Cooling in a refrigerator followed by filtration gave a white solid 8.2 g of imidazole-4 (5)-carboxylic acid. The mother liquor was evaporated to dryness and recrystallized from C_2H_5OH/H_2O to give another batch of 1.7 g. Imidazole-4 (5)-carboxylic acid (8.0 g, 71.70 mmol) was stirred in C_2H_5OH (150 mL) with concentrated sulfuric acid (8 mL) at reflux overnight. It was cooled in an ice bath, and the pH was adjusted to 8 by concentrated NaOH solution. The suspension thus obtained was evaporated to dryness and the residue was recrystallized from water to give **IX** as a white solid (5.9 g, 59.0%): mp. 143°C; UV (MeOH) λ_{max} 233.0 nm; ^{1}H-NMR ($CDCl_3$) δ 7.77, 7.76 (2xs, 2H, H-2, H-5), 4.37 (q, 2H, O**C**$\mathbf{H}_2$$CH_3$), 1.37 (t, 3H, OCH_2**C**$\mathbf{H}_3$).

Ethyl 1-(3',5'-di-*O*-benzoyl-2'-deoxy-2'-fluoro-β-L-arabinofuranosyl) imidazole-4-carboxylate (X)

To a stirred suspension of **IX** (0.190 g, 1.36 mmol) in CH_3CN (7 mL) was added NaH (0.045 g, 1.81 mmol, 95% in mineral oil) and the mixture was stirred at rt for 20 min and then cooled in an ice bath. To this was added a solution of **III** (0.407 g, 0.90 mmol) in acetonitrile. The mixture was stirred at rt for 3 h, filtered and washed with ethyl acetate. The combined filtrate was evaporated to dryness and the residue was purified on a silica gel column (3:1 to 1:1 hexane-ethylacetate) to give a thick syrup (0.167 g, 76.9%): UV (CH_3OH) λ_{max} 229.0 nm; $[\alpha]_D^{25}$ 26.51° (*c* 1.26, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.11, 7.44 (m, 10H, Ar-H), 8.04 (d, 1H, J_{5-2}= 1.3 Hz, H-2), 7.84 (d, 1H, J_{2-5}= 1.3 Hz, H-5), 6.09 (dd, 1H, $J_{1'-2'}$= 2.6, $J_{1'-F}$= 21.0 Hz, H-1'), 5.70 (dd, 1H, $J_{3'-F}$= 16.3 Hz, H-3'), 5.25 (dd, 1H, $J_{2'-1'}$= 2.6, $J_{2'-F}$= 50.0 Hz, H-2'), 4.76 (m, 2H, H-5'ab), 4.55 (m, 1H, H-4'), 4.36 (q, 2H, O**C**$\mathbf{H}_2$$CH_3$), 1.37 (t, 3H, OCH_2**C**$\mathbf{H}_3$); ^{13}C-NMR ($CDCl_3$) 166.23, 165.12, 162.61 (CO), 137.74, 134.10, 133.91, 133.41, 129.85, 129.71, 129.34, 128.68, 128.53, 128.23, 124.69

(Ar), 92.91 (d, J = 193.7 Hz, C-2'), 86.52 (d, J = 16.8 Hz, C-1'), 80.77 (C-4'), 76.65 (d, J = 30.5 Hz, C-3'), 63.33 (C-5'), 60.52 ($O\mathbf{C}H_2CH_3$), 14.28 ($OCH_2\mathbf{C}H_3$).

Anal.	$C_{25}H_{23}FN_2O_7 \cdot 0.33H_2O \cdot 0.08C_6H_6$		
Calcd.	C:61.87	H:4.92	N:5.66
Found	C:62.10	H:5.52	N:5.45

1-(2'-Deoxy-2'-fluoro-β-L-arabinofuranosyl) imidazole-4-carboxamide (XI)

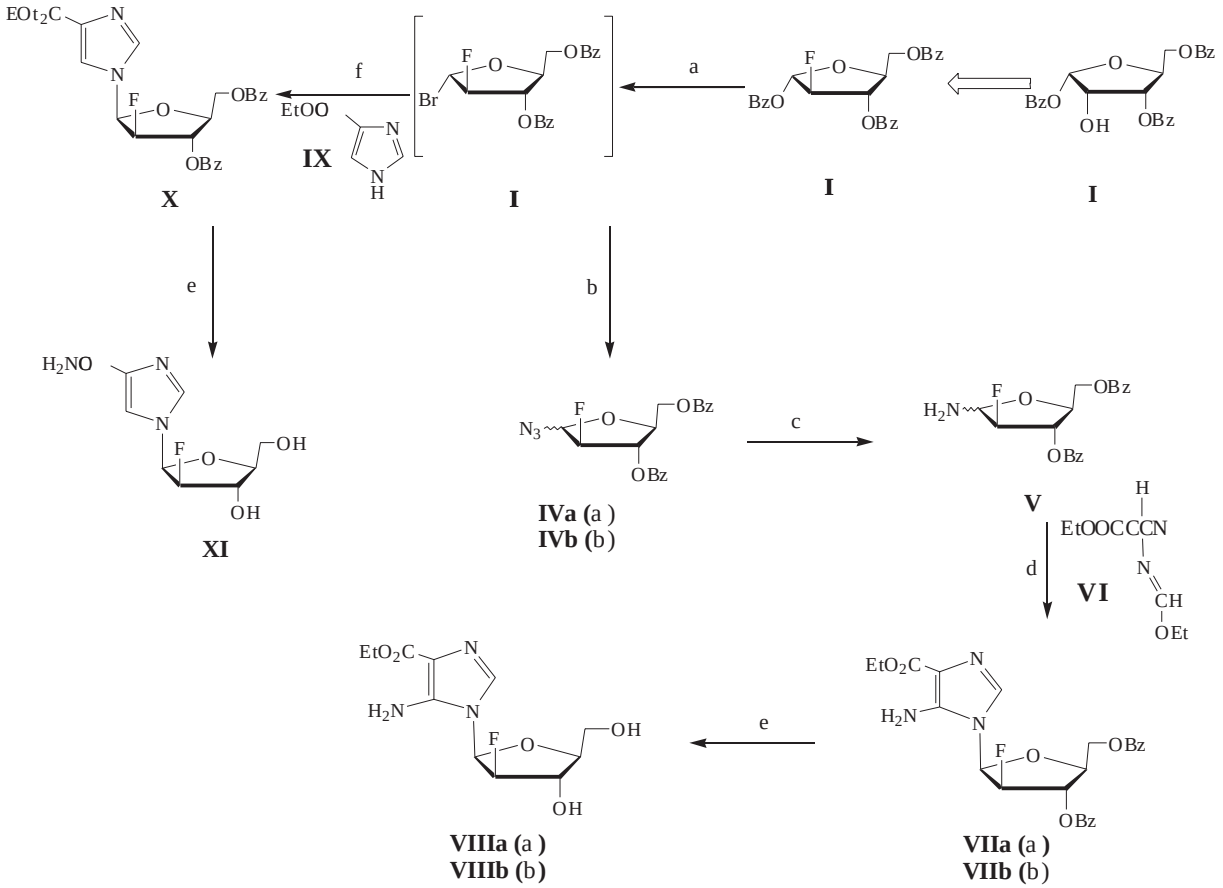
A suspension of **X** (0.167 g, 0.34 mmol) in concentrated NH_4OH was stirred in a sealed bomb at 80°C for 18 h. Removal of solvent followed by silica gel column chromatography gave a thick syrup (0.071 g, 83.3%), which upon standing became a white solid: mp 139-40°C; UV (H_2O) λ_{max} 212.5 (ε 14022) (pH 2), 232.5 (ε 9499) (pH 7), 232.0 nm (ε 11099) (pH 11); $[\alpha]_D^{25}$ -32.51° (c 0.7, MeOH); ^{1}H-NMR (DMSO-d_6) δ 7.86, 7.76 (2 x s, 2H, H-2 and H-5), 7.33, 7.12 (2 x s, 2H, NH_2, D_2O exchangeable), 6.15 (dd, 1H, H-1', $J_{1'-2'}$= 4.3, $J_{1'-F}$= 14.6 Hz), 5.98 (t, 1H, 3'-OH, D_2O exchangeable), 5.08 (ddd, 1H, H-2', $J_{2'-F}$= 52.4 Hz, $J_{1'-2'}$= 12.4 Hz,$J_{2'-3'}$= 6.7 Hz), 5.06 (t, 1H, 5'-OH, D_2O exchangeable), 4.32 (d, 1H, H-3', $J_{3'-F}$= 18.4 Hz), 3.78 (m, 1H, H-4'), 3.46 (m, 2H, H-5'a,b); FABMS, m/z : 246 $(M+1)^+$.

Anal.	$C_9H_{12}FN_3O_4$		
Calcd.	C:44.08	H:4.93	N:17.14
Found	C:44.21	H:4.95	N:17.21

Results and Discussion

The glycosyl bromide **III** was synthesized starting from commercially available 2-hydroxy-1, 3, 5-tri-O-benzoyl-α-L-ribofuranose **I** by adapting the method of Ma *et al.*[9] and then converted to the glycosyl azide **IVa,b** by using LiN_3in a 1 : 1.2 ratio. The glycosyl azide was subjected to hydrogenation in the presence of PtO_2 to give the glycosylamine **V**, which was immediately treated with freshly prepared ethyl N-[(cyano)(ethoxycarbonyl)methyl] formimidate[10] **VI** to give an anomeric mixture in 43.5% yield (Scheme). Upon silica gel column chromatography, the α and β-isomers were isolated in a 1 : 1 ratio **VIIa**: **VIIb**. Treatment of the protected nucleosides with either saturated methanolic ammonia or concentrated ammonia gave the 4-carboxylate derivatives **VIIIa** or **VIIIb**. The anomeric configurations of these nucleosides were assigned similarly by using ^{1}H, ^{13}C and NOESY NMR spectroscopy.

The synthesis of the imidazole derivative **XI** was achieved by direct coupling of the heterocyclic base with the glycosyl bromide **III** (Scheme). Theoretically, this can result in an anomeric mixture. However, several examples have been reported in the literature in which only β-isomers are obtained by using the sodium salt method[11,12]. Thus, ethyl imidazole-4 (5)-carboxylate[13] **IX**, prepared from imidazole-4 (5)-dicarboxylic acid, was treated with NaH in anhydrous acetonitrile and coupled with the glycosyl bromide **III** at rt for 3 h. After silica gel column chromatography, **X** was isolated in 76.9% yield as the only product. The anomeric configuration was assigned as β since the ^{13}C-NMR spectrum showed a $J_{C1'-F}$ of 17.7 Hz. This was supported by the NOESY spectrum for the final product **XI**, in which the correlation of H-1' and H-4' was clearly observed. The interactions of the 5'-OH and H-3' with H-2 and H-5 on the heterocyclic ring also supported this assignment (Figure 2).



Reagents: (a) HBr, AcOH, CH_2Cl_2, rt; (b) LiN_3, CH_3CN, rt to 70°C; (C) PtO_2, H_2, EtOAc, rt; (d) CH_3CN, rt; (e) NH_3, MeOH; (f) NaH, CH_3CN, rt.

Scheme. Synthesis of 2'-Deoxy-2'-fluoro-L-arabinofuranosyl Imidazole Derivatives

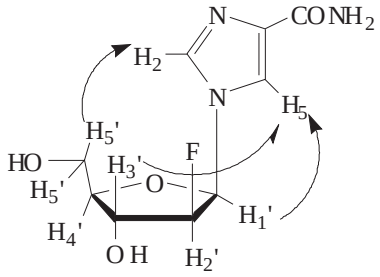


Figure 2. NOE correlations from NOESY Spectra of **XI**β.

The regio-chemistry was assigned as reported by Matthews and Rapoport[14], where a cross-ring coupling constant J_{2-5}= 1.3 Hz was observed for **X**, although the ^{1}H-NMR of **XI** showed two singlets for H-2 and H-5. Additionally, the λ_{max} of **XI** exhibited a pH-dependent pattern similar to the ribosyl derivative reported by Srivastava *et al.*[15] This regio-assignment has also been confirmed based on the presence of cross peaks between H-1' and H-5 in the NOESY spectrum observed.

In addition to NMR spectroscopy, the products have also been characterized by microanalysis, mass spectroscopy, IR, UV and optical rotation.

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