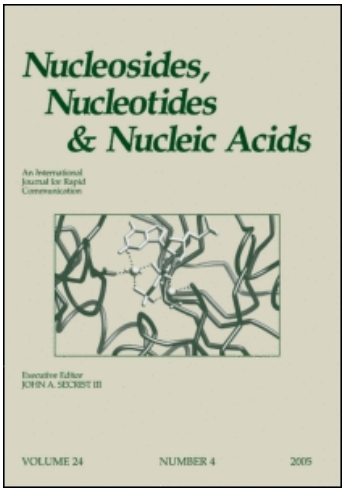

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Synthesis of 2,2'-Anhydro-2-Hydroxy- and 6,2'-Anhydro-6-Hydroxy-1-β-D-Arabindfuranosylnicotinamide as Conformationally Restricted Nicotinamide Nucleoside Analogs[1]

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SYNTHESIS OF 2,2'-ANHYDRO-2-HYDROXY- AND 6,2'-ANHYDRO-6-HYDROXY-1-β-D-ARABINOFURANOSYLNICOTINAMIDE AS CONFORMATIONALLY RESTRICTED NICOTINAMIDE NUCLEOSIDE ANALOGS.[1]

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Abstract: 1-(β-D-Ribofuranosyl)-2(1H)-pyridone-3-carboxamide (**6a**) and the 6(1H)-pyridone derivative (**6b**) were prepared by condensation of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (**3**) with 2- and 6-hydroxynicotinic acid, respectively, to **4a** and **4b**, followed by conversion of the carboxylic acid function of **4a,b** into their corresponding carboxamides **5**, and then deprotection of **5**. Both **6a** and **6b** were then treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane to give the corresponding 3',5'-O-TPDS derivatives, **7a** and **7b**. Mesylation of **7a,b** with mesyl chloride in pyridine afforded the stable, protected mesylates **8a,b**. Upon de-O-silylation of **8a,b** with Et_3NHF gave a mixture of unprotected mesylates **9a,b** and 2,2-anhydro- and 6,2'-anhydronucleosides, **1a** and **1b**. Upon storage of **9a,b** at room temperature, they are quantitatively converted into **1a,b**. Mild alkaline hydrolysis of **1a,b** afforded their corresponding arabino nucleosides **10a,b**.

The promising anticancer agent[2-8], 2-(β-D-ribofuranosyl)-thiazole-4-carboxamide, (Tiazofurin, TF, Figure **1**) is metabolically converted into the nicotinamide adenine dinucleotide (NAD) analogue, tiazofurin adenine dinucleotide (TAD)[9,10], which was found to be a potent inhibitor of IMP-dehydrogenase[11]. Since the replacement of nicotinamide riboside (NR) in NAD by tiazofurin has produced a dramatic effect on its biological activity, an interest in the synthesis of other NR and NAD analogues as potential anticancer agents has grown increasingly. The synthesis and enzymologic properties of nicotinamide arabinoside (NA)[12], carbacyclic

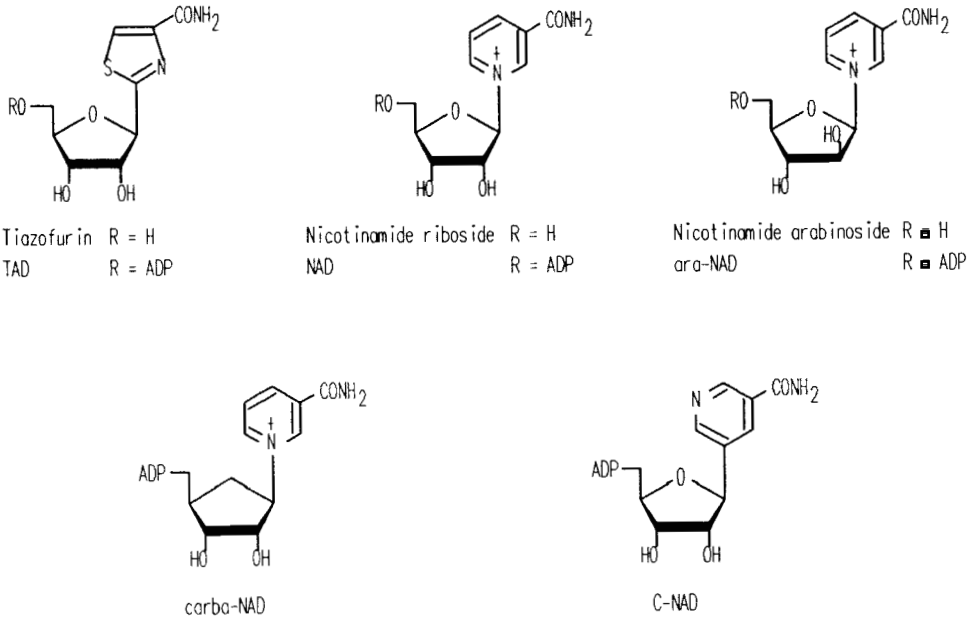
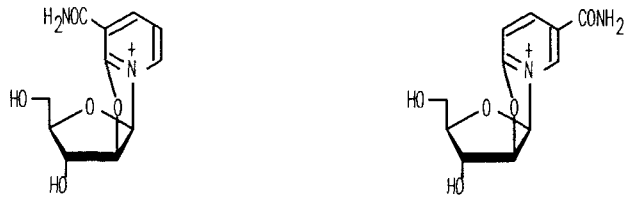


Figure 1

analogue of NR[13], and their corresponding NAD analogs have been recently reported. Although, both ara-NAD and carba-NAD function as coenzymes for yeast and horse liver alcohol dehydrogenase, only carba-NAD is resistant to cleavage by NAD glycohydrolase[13,14] (owing to the known stability of the glycosyl bond of carbacyclic nucleosides).[15-17]

Recently, we have synthesized C-nucleoside analogues of NR[18-21] as well as 5-(ß-D-ribofuranosyl)nicotinamide adenine dinucleotide (C-NAD, Figure 1).[22] C-NAD was found to be an even better IMP-dehydrogenase inhibitor than TAD[23]. C-NAD is also an extremely potent inhibitor of alcohol dehydrogenase with a picomolar dissociation constant[23]. Since the C-C glycosyl bond in C-NAD is stable, we expect that this analogue should be also resistant to NAD glycohydrolase cleavage.

In this paper we report the synthesis of 2,2'-anhydro-2-hydroxy- and 6,2'-anhydro-6-hydroxy-1-(ß-D-arabinofuranosyl)nicotinamide (**1a** and **1b**, respectively, Figure 2), which, when converted into their corresponding NAD analogues may also be resistant to NAD glycohydrolase because of the



1a "syn" 1b "anti"

Figure 2

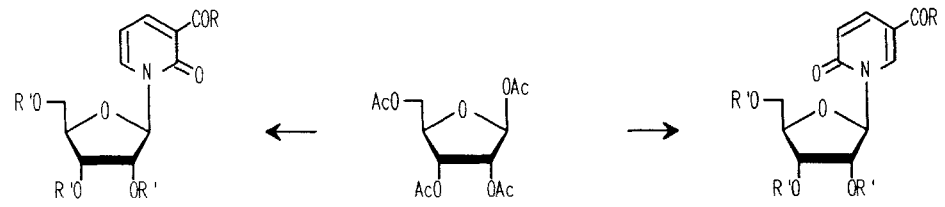
additional "built in" linkage between the nicotinamide aglycon and the sugar moiety.

Anhydro nucleosides **1a** and **1b** can, on the other hand, be considered as close analogues of nicotinamide arabinoside (NA) in which the conformation is restricted to **"syn"** and **"anti"**, respectively.

Oxidation-reductions by all known dehydrogenases are well established as stereospecific processes.[24] Some dehydrogenases transfer exclusively the pro-S hydrogen on the 4 position of the dihydropyridine ring in NADH, whereas others transfer pro-R hydrogen.[25] The X-ray structures of various dehydrogenase-NAD complexes revealed that those enzymes that bind NADH in the **"syn"** conformation transfer pro-R hydrogen.[26] It was recently found that unusually close intramolecular contact between the sulfur atom in the aglycon and oxygen in the sugar ring in the tiazofurin molecule would limit rotation about the C-glycosyl bond, resulting in the favorable conformation for binding to the enzyme(s) that converts tiazofurin to TAD, or for tight binding of TAD to IMP-dehydrogenase.[27] It was also reported recently that the **"anti"** form with C3'-endo conformation in the enzyme bound NAD is essential for activation of the L-lactate dehydrogenase of T. caldophilus.[28]

The importance of the conformational factors for inhibition of uridine phosphorylase was reported.[29] In these studies 2,2'-anhydro-5-ethyluridine was found to be the most potent inhibitor of this enzyme and its rigid **"syn"** conformation was shown to be responsible for its inhibitory activity.

The synthesis of **1a** and **1b** was achieved by preparation of the pyridine nucleosides containing an oxygen function in the aglycon which was subsequently used for nucleophilic displacement of the leaving group



4a R = OH, R' = Ac
5a R = OMe, R' = Ac
6a R = NH_2, R' = H

3

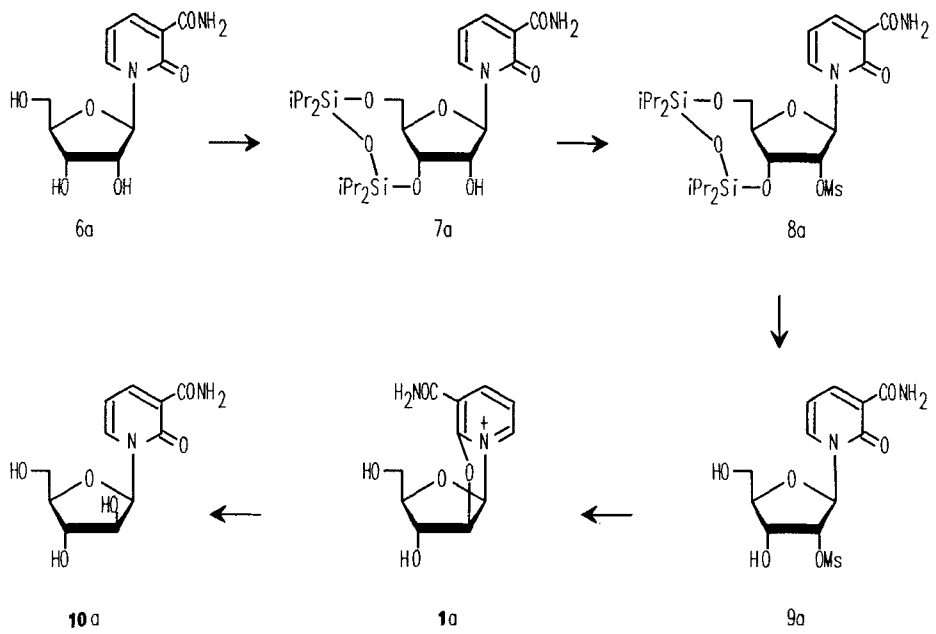
4b R = OH, R' = Ac
5b R = OMe, R' = Ac
6b R = NH_2, R' = H

Scheme 1

on C-2' in the sugar moiety. Thus, condensation of 2-hydroxynicotinic acid with 1,2,3,5-tetra-O-acetyl-ß-D-ribofuranose (**3**, Scheme **1**) according to Niedballa and Vorbrüggen[30] afforded exclusively ß-nucleoside **4a** in almost quantitative yield. Esterification of **4a** followed by $MeOH/NH_3$ treatment gave 1-(ß-D-ribofuranosyl)-2(1H)-pyridone-3-carboxamide (**6a**) in high yield. Similarly, condensation of **3** with 6-hydroxynicotinic acid gave a good yield of nucleoside **4b**, which in the same manner was converted further into the corresponding 6(1H)-pyridone derivative **6b** (Scheme **1**). Carboxamide **6b** was earlier synthesized by Schlimme at al.[31] by an alternative method.

Pyridone nucleoside **6a** was treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane to give the 3',5'-O-TPDS protected derivative **7a** (Scheme **2**), which, by treatment with mesyl chloride, afforded the mesylate **8a**. All our attempts at displacement of the mesyl group in **8a** were unsuccessful. Desilylation of **8a** with Et_3NHF, however, gave a mixture of the unprotected mesylate **9a** and the desired 2,2'-anhydro arabino derivative **1a** (pyridinium mesylate). During storage of at room temperature (as a foam) or in solution (Me_2SO-d_6, pyridine or EtOH), **9a** was completely converted into **1a**.

A similar difficulty in an intramolecular displacement of the 2'-"down" mesyl group of the 3',5'-O-TPDS protected nucleoside versus unprotected 2'-mesylate of ψ-uridine was noticed previously.[32] This may be explained on the basis of the conformational influence of TPDS protection. The sugar moiety of such protected nucleosides was proved[33] to be in C3'-endo conformation in which the oxygen of the aglycon and C-2'



Scheme 2

are held far enough apart to prevent anhydro bond formation. The mesylate **8b** was obtained from **6b** in a similar manner as **8a** and was desilylated to give a mixture of mesylate **9b** and anhydronucleoside **1b**. This mixture when kept in MeOH for 5 days afforded **1b** as pyridinium mesylate. Both pyridinium mesylates **1a** and **1b** were converted into their corresponding pyridinium chlorides by passing a water solution of pyridinium mesylates **1** through a column of Dowex 1X-8 (chloride form).

Attempted separation of **9a** and **9b** from **1** on a silica gel column was not successful. Instead of expected nucleosides **9** and **1**, the 1-(β-D-arabinofuranosyl)pyridone-3-caboxamides **10a** and **10b** were eluted from the column in good yield. Apparently the conversion of **9** into **1** took place first, followed by hydrolysis of the anhydro linkage on the silica gel giving rise to the arabino derivatives **10**. Nucleosides **10a** and **10b** were also prepared from **1** in high yield by treatment with 0.1 N KOH.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX

90Q spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), brs (broad singlet). Exchangeable signals are reported as those, which disappear upon exchange with D_2O. Values given for coupling constants are first order. TLC was performed on Uniplates (Analtech Co., Newark, DE) and column chromatography on Woelm silica gel (70-230 mesh). Microanalyses were performed by Galbraith Laboratories, Inc., or by M.H.W. Laboratories.

1-(2,3,5-Tri-O-acetyl-ß-D-ribofuranosyl)-2(1H)-pyridone-3-carboxylic Acid (4a). To a suspension of 2-hydroxynicotinic acid (4.5 g, 32.3 mmol) in CH_3CN (110 mL) was added bis(trimethylsilyl)trifluoroacetamide (20 mL, 78 mmol), and the mixture was stirred at room temperature under an argon atmosphere for 1 h, then excess silylating agent was removed in vacuo. The residue was dissolved in a solution of 1,2,3,4-tetra-O-acetyl-ß-D-ribofuranose (**3**, 11.6 g, 35.5 mmol) in CH_3CN (57 mL). A 1M solution of $SnCl_4$ in CH_2Cl_2 (112 mL) was added. The mixture was stirred at room temperature overnight, and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL), washed with saturated $NaHCO_3$, dried over $MgSO_4$, and then concentrated in vacuo. The residue was chromatographed on a column of silica gel using $CHCl_3$/MeOH (9:1, v/v) as the eluent to give **4a** (12.3 g, 96%) as a foam. ^1H NMR (Me_2SO-d_6) δ 2.05-2.09 (9H, m, 3Ac), 4.30-4.38 (3H, m, H-4', 5', 5''), 5.36-5.56 (2H, m, H-2', 3'), 6.22 (1H, d, H-1', $J_{1',2'}$ = 3.3 Hz), 6.77 (1H, t, H-5, $J_{4,5} = J_{5,6}$ = 7.0 Hz), 8.23 (1H, dd, H-4, $J_{4,6}$ = 1.9 Hz), 8.38 (1H, dd, H-6). Anal. Calcd for $C_{17}H_{19}NO_{10}$: C, 51.39; H, 4.82; N, 3.52. Found: C, 51.18; H, 4.96; N, 3.41.

1-ß-D-Ribofuranosyl-2(1H)-pyridone-3-carboxamide and 1-ß-D-ribofuranosyl-6(1H)-pyridone-3-carboxamide (6a and 6b). A solution of **4a** (3.7 g, 9 mmol) in MeOH (40 mL) was cooled to 0 °C, and then treated with an ethereal solution of CH_2N_2 (50 mL, prepared from 1-methyl-3-nitro-1-nitrosoguanidine)[34] for 15 min. Excess of CH_2N_2 was decomposed by addition of AcOH (1 mL) and the mixture was concentrated in vacuo to give crude **5a** (3.0 g). An analytical sample of this compound was obtained by chromatographic purification on a silica gel column ($CHCl_3$/MeOH, 40:1, v/v). ^1H NMR (Me_2SO-d_6) δ 2.05-2.08 (9H, m, 3Ac), 3.75 (3H, s, Me), 4.17-4.45 (3H, m, H-4',5',5"), 5.36-5.53 (2H, m, H-2',3'), 6.07 (1H, d, H-1', $J_{1',2'}$ = 3.0 Hz),

6.44 (1H, t, H-5, $J_{4,5} = J_{5,6} = 6.9$Hz), 7.96-8.14 (2H, dt, H-4,6, $J_{4,6} = 2.2$ Hz). Anal. Calcd for $C_{18}H_{21}NO_{10}$: C, 52.55; H, 5.15; N, 3.40. Found: C, 52.46; H, 5.22, N, 3.39.

Crude **5a** (2.5 g) was treated with MeOH/NH_3 (60 mL) overnight. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel ($CHCl_3$-MeOH, 5:1, v/v) to give crystalline **6a** (1.6 g,98 %), m.p. 176-178 °C (EtOH). ^{1}H NMR (Me_2SO-d_6), δ 3.71-3.76 (2H, m, H-5',5"), 3.93-3.99 (3H, m, H-2',3',4'), 5.07 (1H, d, OH exchg.), 5.21 (1H, t, OH exchg.), 5.53 (1H, d, OH exchg.), 6.09 (1H, d, H-1', $J_{1',2'} = 1.9$ Hz), 5.54 (1H, t, H-5, $J_{4,5} = J_{5,6} = 6.9$ Hz), 7.63 (1H, d, NH exchg.), 8.32 (1H, dd, H-4, $J_{4,6} = 2.2$ Hz, 8.42 (1H, dd, H-6), 8.95 (1H, d, NH exchg.). Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.36. Found: C, 49.07; H, 5.37; N, 10.51.

Similarly, **4b** (7.07 g, 18 mmol) was converted into **5b** (7.2 g, 99 %). Analytical sample was obtained as above. ^{1}H NMR (Me_2SO-d_6) δ 2.07-2.10 (9H, m, 3 Ac), 3.80 (3H, s, CH_3), 4.34-4.45 (3H, m, H-4',5',5"), 5.32-5.53 (2H, m, H-2',3'), 6.18 (1H, d, H-1', $J_{1',2'} = 3.5$ Hz), 6.46 (1H, d, H-5, $J_{4,5} = 9.6$ Hz), 7.84 (1H, dd, H-4, $J_{2,4} = 2.5$ Hz), 8.49 (1H, d, H-2). Anal. Calcd for $C_{18}H_{21}NO_{10}$: C, 52.55; H, 5.15; N, 3.41. Found: C, 52.85; H, 5.28; N, 3.15.

Crude **5b** (7.0 g) was treated with MeOH/NH_3 (200 mL) at 100 °C in a sealed steel cylinder for 2 days[35], then the mixture was treated with activated charcoal, filtered and concentrated in vacuo to give crystalline **6b** (3.1 g, 65%), m.p. 212-214 °C (EtOH). ^{1}H NMR spectrum of **6b** was identical with that of authentic sample.[31]

1-(3,5-O-Tetraisopropyldisiloxan-1,3-di-yl-ß-D-ribofuranosyl)-2(1H)-pyridone-3-carboxamide and -6(1H)-pyridone-3-carboxamide (7a and 7b). Nucleoside **6a** (4.0 g, 14.8 mmol) was dissolved in pyridine (30 mL) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (5.0 g, 15.8 mmol) was added. The mixture was stirred at room temperature overnight, and then concentrated in vacuo. The residue was partitioned between $CHCl_3$ (400 mL) and water (100 mL). The organic layer was separated, washed with water (3 x 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give **7a** (6.6 g, 87%) as a foam. The analytical sample was prepared by purification on a silica gel column ($CHCl_3$-EtOAc, 5:1, v/v). ^{1}H NMR (Me_2SO-d_6) δ 0.93-1.08 (28H, m, iPr), 4.04-4.14 (5H, m, H-2',3',4',5',5"), 5.80-5.85 (2H, m, H-1',OH, collapsed to a singlet upon addition of D_2O), 6.51 (1H, t, H-5, $J_{4,5} = J_{5,6}$

= 6.9 Hz), 7.63 (1H, d, NH exchg.), 8.12 (1H, dd, H-4, $J_{4,6}$ = 2.2 Hz), 8.35 (1H, dd, H-6), 8.88 (1H, d, NH exchg.). Anal. Calcd for $C_{23}H_{40}N_2O_7Si_2$: C, 53.87; H, 7.86; N, 5.46. Found: C, 53.97; H, 7.87; N, 5.36.

In the same manner **6b** (540 mg, 2 mmol) was converted into **7b** (650 mg, 63%) and purified on silica gel with $CHCl_3$-Me_2CO (3:1, v/v). ^1H NMR (Me_2SO-d_6) δ 0.96-1.06 (28H, m, iPr), 3.85-4.11 (5H, m, H-2',3',4',5',5"), 5.61 (1H, brs, OH exchg.), 5.73 (1H, s, H-1'), 6.40 (1H, d, H-5, $J_{4,5}$ = 9.3 Hz), 7.10 (1H, brs, NH exchg.), 7.61 (1H, brs, NH exchg.), 7.86 (1H, dd, H-4, $J_{2,4}$= 2.5 Hz), 8.35 (1H, d, H-2). Anal. Calcd for $C_{23}H_{40}N_2O_7Si_2$. Found: C, 53.70; H, 7.73; N, 5.30.

1-(2-O-Mesyl-3,5-O-tetraisopropyldisiloxan-1,3-di-yl-ß-D-ribofuranosyl)-2(1H)-pyridone-3-carboxamide and -6(1H)-pyridone-3-carboxamide (8a and 8b). A mixture of **7a** (3.1 g, 6.05 mmol) and MsCl (0.92 mL, 12 mmol) in pyridine (50 mL) was stirred at room temperature for 3 days, and quenched with EtOH (100 mL). The mixture was concentrated in vacuo and the residue was chromatographed on silica gel ($CHCl_3$-EtOAc, 1:1, v/v) to give **8a** (2.5 g, 70%) as a foam. ^1H NMR (Me_2SO-d_6) δ 0.97-1.07 (28H, m, iPr), 3.44 (3H, s, Ms), 4.03-4.32 (4H, m, H-3',4',5',5"), 5.27 (1H, d, H-2', $J_{2',3'}$ = 4.1 Hz), 6.09 (1H, s, H-1'), 6.56 (1H, t, H-5, $J_{4,5}$ = $J_{5,6}$ = 6.9 Hz), 7.05 (1H, d, NH exchg.), 8.08 (1H, dd, H-4', $J_{4,6}$ = 2.2 Hz), 8.37 (1H, dd, H-6), 8.90 (1H, d, NH exchg.). Anal. Calcd for $C_{24}H_{42}N_2O_9SSi_2$: C, 48.79; H, 7.16; N, 4.74. Found: C, 48.59; H, 7.13; N, 4.56.

A mixture of **7b** (512 mg, 1 mmol), DMAP (122 mg, 1 mmol), and MsCl (154 uL, 2 mmol) in CH_2Cl_2 (10 mL) containing Et_3N (202 mg, 2 mmol) was stirred overnight. The reaction was quenched by addition of EtOH (5 mL). The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel ($CHCl_3$-EtOH, 33:1, v/v) to give **8b** (350 mg, 60%) as a foam. ^1H NMR (Me_2SO-d_6) δ 0.98-1.10 (28H, m, iPr), 4.00-4.35 (4H, m, H-3',4',5',5"), 5.18 (1H, d, H-2', $J_{2',3'}$ = 4.8 Hz), 5.96 (1H, s, H-1'), 6.50 (1H, d, H-5, $J_{4,5}$ = 9.6 Hz), 7.32 (1H, brs, NH exchg.), 7.68 (1H, brs, NH exchg.), 7.93 (1H, dd, H-4, $J_{2,4}$ = 2.2 Hz), 8.36 (1H, d, H-2). Anal. Calcd for $C_{24}H_{42}N_2O_9SSi_2$. C, 48.79; H, 7.16; N, 4.74. Found: C, 48.72; H, 7.18; N, 4.52.

2,2'-Anhydro-2-hydroxy-1-(ß-D-arabinofuranosyl)nicotinamide (1a) and 6,2'-anhydro-6-hydroxy-1-(ß-D-arabinofuranosyl)nicotinamide (1b). To a

solution of **8a** (590 mg, 1 mmol) in THF (5 mL) was added a 1 M solution of Et_3NHF in THF (2.5 mL, 2.5 equiv.). The mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was chromatographed on a silica gel with $CHCl_3$-EtOH (5:1, v/v) to give **9a** (287 mg, 82%) as a foam. This compound, when dissolved in Me_2SO-d_6 in NMR tube, was converted immediately into an approximately 1:1 mixture of **9a** and **1a**. ^1H NMR (Me_2SO-d_6) δ 2.30 (3H, s, Ms-**1a**), 3.32 (3H, s, Ms-**9a**), 3.32-4.40 (7H, m, H-3',4',5',5"-**9a** and H-4',5',5"-**1a**), 4.77 (1H, d, H-3'-**1a**, become a singlet upon exchange), 5.05 (1H, t, OH-**1a** exchg.), 5.10 (1H, dd, H-2'-**9a**, $J_{1',2'}$ = 1.9 Hz, $J_{2',3'}$ = 4.9 Hz), 5.36 (1H, t, OH-**9a**), 5.64 (1H, d, H-2'-**1a**, $J_{1',2'}$ = 6.0 Hz), 5.77 (1H, d, OH-**9a** exchg.), 6.14 (1H, d, H-1'-**9a**), 6.25 (1H, d, H-1'-**9a**), 6.58 (1H, t, H-5-**9a**, $J_{4,5} = J_{5,6}$ = 7.1 Hz, 7.07 (1H, d, H-1'-**1a**), 7.16-7.22 (2H, m, NH, H-5-**1a**), 8.29-8.48 (3H, m, NH, H-4,6-**9a**), 8.72-8.97 (2H, m, H-4,6-**1a**).

The same sample, when recorded after 8 h, gave a spectrum for pure **1a**. ^1H NMR δ 2.37 (3H, s, Ms), 3.23 (1H, dd, H-5", $J_{5',5"}$ = 12.6, $J_{4',5"}$ = 2.5 Hz), 3.44 (1H, dd, H-5', $J_{4',5'}$ = 1.9 Hz), 4.35 (1H, d, H-4'), 4.67 (1H, d, H-3', a singlet upon exchange), 4.85 (1H, t, OH exchg.), 5.65 (1H, d, H-2', $J_{1',2'}$ = 6.1 Hz), 6.14 (1H, d, OH exchg.), 7.07 (1H, d, H-1'), 7.62-7.77 (2H, dd on brs, NH, H-5, $J_{4,5} = J_{5,6}$ = 6.0 Hz), 8.18 (1H, brs, NH exchg.), 8.76 (1H, dd, H-4, $J_{4,6}$= 1.5 Hz), 8.93 (1H, dd, H-6).

After being kept at room temperature for 4 days, compound **9a** (190 mg, foam) was completely converted into **1a** as judged by ^1H NMR (CD_3Cl) analysis. Anal. Calcd for $C_{12}H_{16}N_2O_8S$: C, 41.38; H, 4.63; N, 8.04. Found: C, 41.40; H, 4.71; N, 7.97.

Compound **8b** (590 mg, 1 mmol) was treated with a 1 M solution of Et_3NHF in THF as above. Approximately 1:1 mixture of **9b** and **1b** (296 mg, 87%) was obtained as a foam. This mixture, when kept in MeOH (3 mL) for 5 days, afforded **1b**. ^1H NMR (CD_3OD) δ 2.68 (3H, s, Ms), 3.47 (1H, dd, H-5', $J_{4',5'}$ = 2.0, $J_{5',5"}$ = 11.0 Hz), 3.60 (1H, dd, H-5", $J_{4',5"}$ = 2.0 Hz), 4.47 (1H, m, H-4'), 4.70 (1H, d, H-3', $J_{3',4'}$ = 1.0 Hz), 5.73 (1H, d, H-2', $J_{1',2'}$ = 6.3 Hz), 7.00 (1H, d, H-1'), 7.56 (1H, d, H-5, $J_{4,5}$ = 9.3 Hz), 8.88 (1H, dd, H-4, $J_{2,4}$ = 2.2 Hz), 9.16 (1H, d, H-2). Anal. Calcd for $C_{12}H_{16}N_2O_8S$: C, 41.38; H,4.63; N, 8.04. . Found: C, 41.32; H, 4.65; N, 7,89.

Compound **1a** (348 mg, 1 mmol) was dissolved in H_2O (2 mL), and the solution was passed through a column of Dowex-1 (Cl^- form). The column was washed with H_2O (50 mL), and the solution was concentrated in vacuo. The residue was crystallized from EtOH to give **1a** (Cl^- form) (28 mg, 97.3 %),

mp 195-198 °C. The ^{1}H NMR spectrum of this sample was identical with that for **1a** (MsO^- form) except that the Ms signal at δ 2.37 was absent.

In a similar manner, **1b** (MsO^- form) was converted into the **1b** (Cl^- form) in almost quantitative yield, mp 205-207 °C (EtOH).

1-ß-D-Arabinofuranosyl-2(1H)-pyridone-3-carboxamide and 1-ß-D-arabinofuranosyl-6(1H)-pyridone-3-carboxamide (10a and 10b). Compound **1a** (Cl^- form, 150 mg, 0.52 mmol) was dissolved in 0.1 N NaOH (5.0 mL) stirred at room temperature for 15 min, and the solution was neutralized with 0.5 N HCl. The mixture was concentrated in vacuo and the residue was chromatographed on a silica gel ($CHCl_3$-MeOH, 7:3 v/v) to give **10a** (140 mg, quantitative yield), mp 225-228 °C (EtOH). ^{1}H NMR (Me_2SO-d_6) δ 3.64-3.70 (2H, m, H-5',5"), 3.94-3.97 (2H, m, H-3',4'), 4.18 (1H, dd, H-2', $J_{1',2'}$= 3.8 Hz, $J_{2',3'}$= 2.2 Hz), 5.14 (1H, t, OH exchg.), 5.42-5.49 (2H, m, 2xOH exchg.), 6.32 (1H, d, H-1'), 6.52 (1H, dd, H-5, $J_{4,5}$= 6.8 Hz, $J_{5,6}$=7.4 Hz), 7.57 (1H, brs, NH exchg.), 8.06 (1H, dd, H-4, $J_{4,6}$= 2.2 Hz), 8.33 (1H, dd, H-6), 8.94 (1H, brs, NH exchg.). Anal Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.36. Found: C, 48.88; H, 5.41; N, 10.27.

In a similar alkaline treatment of **1b** (, Cl^- form, 150 mg, 0.55 mmol) **10b** (141 mg, quantitative yield) was obtained, mp 234-236 °C (EtOH). ^{1}H NMR (Me_2SO-d_6) δ 3.60-3.67 ((2H, m, H-5',5"), 3.86-4.08 (3H, m, H-2',3',4'), 5.05 (1H, t, OH exchg.), 5.39-5.46 (2H, m, 2xOH exchg.), 6.20 (1H, d, H-1', $J_{1',2'}$= 3.8 Hz), 6.36 (1H, d, H-5, $J_{4,5}$= 9.3 Hz), 7.80, 7.30 (two brs, 2xNH exchg.), 7.88 (1H, dd, H-4, $J_{2,4}$= 2.5 Hz), 8.30 (1H, d, H-2). Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.36. Found: C, 49.01; H, 5.31; N, 10.11.

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References and Footnotes

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35. In contrast to **5a** compound **5b** could not be converted into the corresponding carboxamide derivative **6** at room temperature without pressure

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