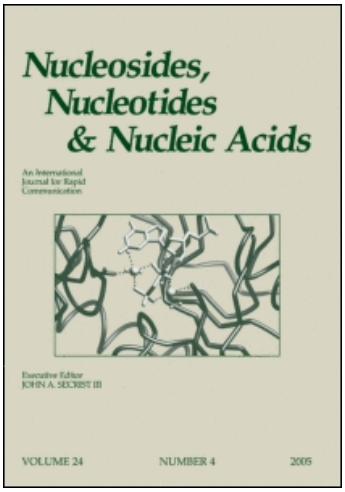

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Synthesis of 9-(2-Deoxy-2-Fukuoro-β-D- Abinoruranosyl)Hypoxhine. The First Direct Introduction of A 2'-β-Fldoro Substituent in Ppepormed Purine Nucleosides. Studies Directed Toward the Synthesis of 2'-DEOXY-2'-Substituted Arabppmocebosides. 8.[1]

Jacek Krzeminski[a]; Barbara Nawrot[a]; Krzysztof W. Pankiewicz[a]; Kyoichi A. Watanabe[a]
[a] Laboratory of organic chemistry, sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Graduate School of Medical. Sciences, Cornell University, New York, NY

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SYNTHESIS OF 9-(2-DEOXY-2-FLUORO-β-D-ARABINOFURANOSYL)HYPOXANTHINE. THE FIRST DIRECT INTRODUCTION OF A 2'-β-FLUORO SUBSTITUENT IN PREFORMED PURINE NUCLEOSIDES. STUDIES DIRECTED TOWARD THE SYNTHESIS OF 2'-DEOXY-2'-SUBSTITUTED ARABINONUCLEOSIDES. 8.[1]

Jacek Krzeminski, Barbara Nawrot, Krzysztof W. Pankiewicz*
and Kyoichi A. Watanabe

Laboratory of Organic Chemistry, Sloan-Kettering Institute
for Cancer Research, Sloan-Kettering Division of Graduate School
of Medical Sciences, Cornell University, New York, NY 10021.

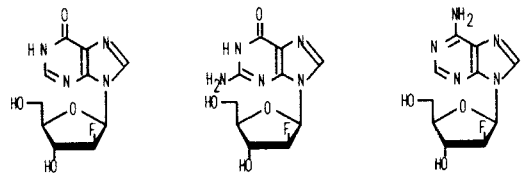
Abstract. The 3',5'-di-O-acetyl-, 3',5'-di-O-benzyl-, 3'-O-acetyl-5'-O-trityl- and 3',5'-di-O-trityl-2'-O-triflyl-1-benzylinosine (**8c, 15, 20c,** and **27**, respectively) were prepared and subjected to nucleophilic reaction with TASF. Thus, 3',5'-O-(1,1,3,3-tetraisopropyldisiloxanyl)-1-benzylinosine (**5c**) was triflylated, desilylated, and then acetylated to give **8c**. Also, **5c** was converted into the 2'-O-tetrahydropyranyl (THP) derivative **11** which was desilylated and then benzylated to give 2'-O-tetrahydropyranyl-$O^{3'}$,$O^{5'}$,N^{1}-tribenzylinosine (**13**). Removal of the THP group from **13** followed by triflylation afforded 2'-O-triflyl-$O^{3'}$,$O^{5'}$,N^{1}-tribenzylinosine (**15**). 3'-O-Acetyl-2'-O-triflyl-5'-O-trityl-1-benzylinosine (**20**) was prepared from 5'-O-trityl-1-benzylinosine (**18c**) by conversion into the 2',3'-O-(di-n-butylstannylene) derivative which was treated with triflyl chloride and then acetylated. Treatment of 1-benzylinosine (**4c**) with trityl chloride in pyridine containing p-dimethylaminopyridine afforded a mixture of 2',5'- and 3',5'-di-O-trityl-1-benzylinosine (**25** and **26**, respectively). These regioisomers were chromatographically separated. Triflylation of **26** gave 2'-O-triflyl-3',5'-di-O-trityl-1-benzylinosine (**27**).

The triflates **8c** and **15** only afforded elimination products upon treatment with TASF. However, the triflate group in **20c** and **27** was displaced by fluoride with formation of the 2'-fluoro-arabino nucleosides, **21c** and **28**, in 10 and 30% yield, respectively. After deprotection of **28**, 9-(2-deoxy-2-fluoro-ß-D-arabinofuranosyl)hypoxanthine (**1**, F-ara-H) was obtained in good yield. The conformational influence of the sugar protecting groups on the rate of nucleophilic substitution against elimination is discussed.

The synthesis of several 9-(2-deoxy-2-fluoro-ß-D-arabinofuranosyl)-9H-purines has recently been reported from our laboratory.[2] Some of these nucleosides exhibit interesting biological activity. For example, the hypoxanthine nucleoside **1** (F-ara-H, Figure **1**) showed potent inhibitory

activity against the growth of Leishmania tropica promastigotes,[3] and the guanine nucleoside (**2**, F-ara-G) was found to be selectively toxic to T-cells.[2,4,5] The 2'-fluoro-arabinosylpurines in these studies were prepared by condensation of 3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide[6] with N^6-benzoyladenine, 6-chloropurine,

Figure 1



1. F-ara-H 2. F-ara-G 3. F-ara-A

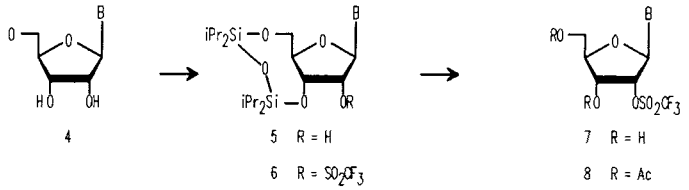
2,6-dichloropurine, or 2-acetamido-6-chloropurine, followed by appropriate functional group replacement and deprotection. The overall yield was generally very low. For example, F-ara-H (**1**) was prepared by deamination of 9-(2-deoxy-2-fluoro-ß-D-arabinofuranosyl)adenine (**3**, F-ara-A), but the overall yield from the bromo sugar was only 7%.

We have recently developed[7] a method of synthesis of 5-(2-deoxy-2-fluoro-ß-D-arabinofuranosyl)-1-methyluracil by direct displacement of the 2'-triflate group in 4,5'-anhydro-2'-O-triflyl-1-methylpseudouridine by fluorine on treatment with tris(dimethylamino)sulfur (trimethylsilyl)-difluoride (TASF).

In the purine series, several 9-(2-deoxy-2-substituted-ß-D-arabino-furanosyl)adenine derivatives (except F-ara-A) have been prepared[8] by direct displacement of the 2'-triflate group of the adenosine derivative with nucleophiles. We prepared 3',5'-di-O-acetyl-2'-O-triflyl derivatives of adenosine, inosine, and 1-benzylinosine (**8a**, **8b** and **8c**) by the procedure shown in Scheme **1**.

Treatment of adenosine 2'-triflate (**8a**) with KF/DMF, Amberlyst A26 (F^-) in acetonitrile, or TASF in methylene chloride always resulted in the formation of a mixture of adenine and 9-(2,3,5-tri-O-acetyl-ß-D-arabino-furanosyl)adenine (**10a**). No fluorinated nucleoside was detected. Compound **10a** was isolated in yield of 40% in the reaction with KF/DMF.

Apparently, some **8a** decomposed during the reaction, releasing acetate ion which displaced the triflate group, giving rise to **10a** (Scheme 2). The



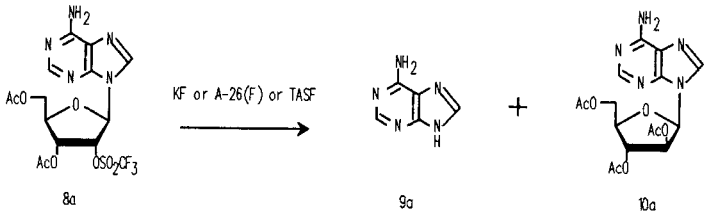
4 5 R = H 6 R = SO_2CF_3 7 R = H 8 R = Ac

a Series: B = adenine, b Series: B = hypoxanthine, c Series: B = 1-benzylhypoxanthine

Scheme 1

triflates, **8b** and **8c**, when treated with TASF, also afforded a mixture of the corresponding purine base and peracetylated arabino nucleosides. We made a similar observation[7] when 4,5'-anhydro-3'-O-acetyl-2'-O-triflyl-1-methylpseudouridine was treated with CsF/DMF or Amberlyst A26/CH_2Cl_2.

In order to avoid the problems caused by acetate displacement of triflate, we synthesized 3',5'-di-O-benzyl-2'-O-triflyl-1-benzylinosine



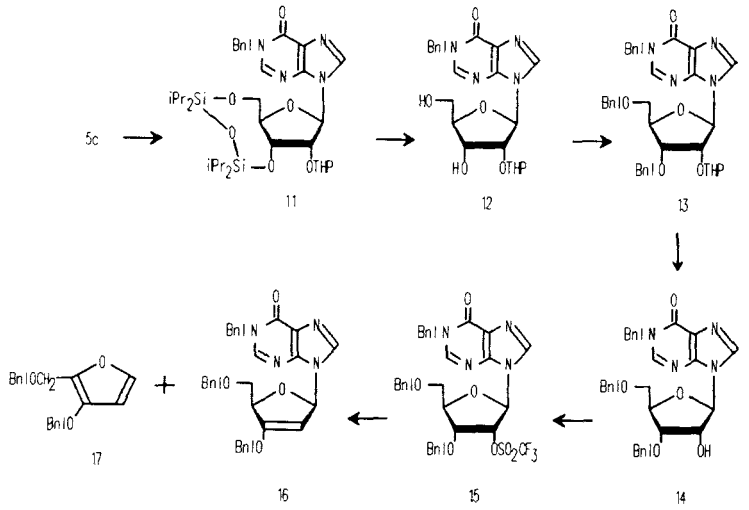
8a 9a 10a

Scheme 2

(**15**). Thus, 3',5'-O-(1,1,3,3-tetraisopropyl)disiloxanyl-1-benzylinosine (**5c**, Scheme 3) was treated with dihydropyran (DHP)/TsOH, and then desilylated with Et_3NHF/THF to obtain **12**. Benzylation of **12** followed by 2'-deprotection and triflylation afforded **13-15**. Contrary to our expectation, treatment of **15** with TASF only afforded the elimination products **16** and **17**, and no trace of F-ara-H was detected in the reaction mixture.

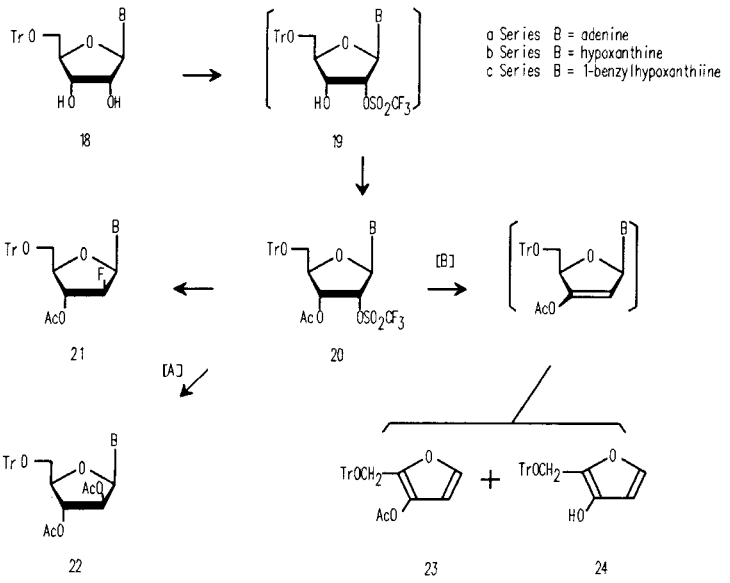
Facile elimination of trifluoromethanesulfonic acid from **15** with the formation of the olefin **16** is probably due to the fact that the sugar has the C_3, endo conformation, in which the triflate group on C_2, and the hydrogen on C_3, are almost in a trans di-axial configuration. Ikehara et

al. reported[9] that the amount of C_3, endo conformer in 2'-substituted adenosines increases linearly with the electronegativity of the 2'-substituent. Thus, the presence of the electronegative 2'-triflate group may force **15** to assume the C_3, endo conformation, which favors elimination.

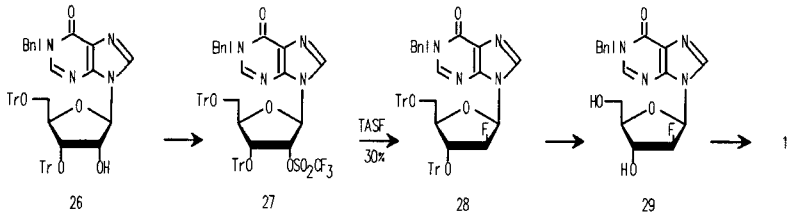


Scheme 3

The furanose ring conformation may be altered by using different protecting groups at C5' and C3' of the purine nucleoside 2'-triflate. It has been suggested that bulky trityl groups may force the furanose ring to assume an unfavorable conformation[10,11] for trans elimination. We therefore synthesized 5'-O-trityl-3'-O-acetyl-2'-O-triflyl nucleosides **20** (Scheme **4**) from 5'-O-trityl-adenosine[12] (**18a**), -inosine[13] (**18b**), and -1-benzylinosine (**18c**). Treatment of compounds **18** with Bu_2SnO/MeOH followed by CF_3SO_2Cl yielded the corresponding 2'-O-triflates **19**, which, without isolation, were acetylated to **20**. Treatment of **20a** and **20c** with TASF in CH_2Cl_2 afforded the desired protected F-ara-A and F-ara-H (**21a** and **21c**) in 4% and 10% yield, respectively. The reaction of **20b** with TASF, however, gave an unseparable mixture of the sugar fluorinated product **21b** and 2',3'-di-O-acetylated derivative **22b** along with the furan derivatives **23** and **24** and hypoxanthine. It has been recently reported [14] that treatment of 5'-O-tritylcordycepin with diethylamino sulfur trifluoride (DAST) followed by detritylation afforded 9-(2-fluoro-2,3-dideoxy-ß-D-threo-pentofuranosyl)-adenine in 10% yield. According to authors comment this fluorination was



Scheme 4



Scheme 5

facilitated by the absence of an oxygen function on the adjacent 3'-carbon atom.

Detailed examination of the reaction of triflates **20** with TASF revealed depurination to be the major course of the reaction. Displacement of the triflate group by acetate also occurs to give 9-(2,3-di-O-acetyl-5-O-trityl-β-D-arabinofuranosyl)purines (**22**, path **A**, Scheme **4**). Although nucleophilic displacement of the triflate group with fluoride ion takes place to some extent, a facile double elimination of triflate and the purine base (path **B**) affords the furan derivatives **23** and **24**. Compound **24** was converted into **23** by acetylation. Similar triflate elimination from carbohydrates in the presence of fluoride ion is known.[15,16] The above

data appear to support our concept that the $C_{3'}$-endo to $C_{2'}$-endo conformational change prevents triflate elimination so that nucleophilic displacement of 2'-triflate by fluoride nucleophile becomes possible. In order to further promote conformational shift toward $C_{2'}$-endo and prevent formation of acetate ion during the reaction, we prepared 3',5'-di-O-trityl-2'-O-triflyl-1-benzylinosine (**27**). The relatively large $J_{1',2'}$ value of 7.1 Hz (in $CHCl_3$) for the 3',5'-di-O-trityl derivative **27** versus small 1',2' coupling (2.5 - 4.1 Hz) in **8**, **15** and **20** indicates that trityl groups did cause the desired conformational change in **27** toward $C_{2'}$-endo. When **27** was treated with TASF, the yield of the desired 2'-fluorinated arabino nucleoside **28** was increased to 30%.

Detritylation of **28** with $CF_3CO_2H/CHCl_3$[17] followed by hydrogenolysis afforded a good yield of F-ara-H (**1**, Scheme **5**).

Studies directed toward the synthesis of other 2'-fluoro-arabinosylpurines are in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on silica gel G60 (70-230 mesh, ASTM, Merck). TLC was performed on Analtech Uniplates with short-wavelength UV light for visualization. Elementary analyses were performed by M-H-W Laboratories, Phoenix, AZ. ^1H and ^{19}F NMR spectra were recorded on a JEOL FX90Q spectrometer with Me_4Si and $CFCl_3$ as the internal standards. Chemical shifts are reported in ppm (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet) and dd (double doublet). Values given for coupling constants are first order.

1-Benzylinosine (4c). To a suspension of inosine (**4b**, 10.7 g, 40 mmol) in DMF (400 mL) and DBU (8.96 mL, 60 mmol) was added benzyl bromide (7.13 mL, 60 mmol), and the mixture was stirred at room temperature for 4 h. The mixture was concentrated in vacuo, and the residue was crystallized from EtOH (200 mL) to obtain **4c** (13.5 g, 94%), mp 220-222 °C (lit.[18] mp 219-222 °C).

3',5'-O-(1,1,3,3-Tetraisopropyldisiloxan-1,3-yl)-1-benzylinosine (5c). A mixture of **4c** (9.9 g, 27.6 mmol) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (10.0 g, 31.7 mmol) in pyridine (100 mL) was stirred at room temperature overnight. The pyridine was removed in vacuo, and the residue partitioned between $CHCl_3$ (300 mL) and H_2O (50 mL). The organic layer was washed with H_2O (2 x 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/EtOH, 40:1 v/v) to obtain **5c** (13.2 g, 81%). ^{1}H NMR (Me_2SO-d_6) δ 0.94-1.02 (28H, m, i-Pr), 3.95-4.02 (3H, m, H4',5',5"), 4.49-4.54 (2H, m, H2',3'), 5.25 (2H, s, CH_2Ph), 5.67 (1H, d, 2'-OH, exchangeable), 5.85 (1H, s, H1'), 7.32 (5H, s, CH_2Ph), 8.19, 8.52 (two 1H singlets, H2 and H8). Anal. Calcd for $C_{29}H_{44}N_4O_6Si_2$: C, 59.76; H, 7.38; N, 9.32. Found: C, 60.05; H, 7.38; N, 9.15.

2'-O-Triflyladenosine (7a). To a mixture of **5a**[19] (500 mg, 1.0 mmol), DMAP (120 mg, 1.0 mmol) and Et_3N (240 μL, 2.0 mmol) in CH_2Cl_2 (10 mL) was added CF_3SO_2Cl (212 μL, 2.0 mmol), and the mixture was stirred at room temperature for 0.5 h. After concentration of the mixture in vacuo, the residue was dissolved in 1 N Et_3NHF in THF (3 mL). The mixture was kept overnight at room temperature, and then concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/EtOH, 9:1 v/v) to obtain **7a** (300 mg, 75%) as a foam. ^{1}H NMR (Me_2DO-d_6) δ 3.66-3.88 (2H, m, H5',5"), 4.02-4.13 (1H, m, H4'), 4.48-4.64 (1H, m, H3', became dd at 4.61 on addition of D_2O, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 5.5 Hz), 5.89 (1H, dd, H2', $J_{1',2'}$ = 4.4, $J_{2',3'}$ = 5.0 Hz), 6.40 (1H, d, H1', $J_{1',2'}$ = 4.4 Hz), 7.61 (2H, bs, NH_2), 8.20, 8.42 (two 1H singlets, H2, H8). This compound was too unstable for combustion analyses.

2'-O-Triflylinosine (7b). A mixture of **4b** (268 mg, 1 mmol) and Bu_2SnO[20] (249 mg, 1 mmol) in MeOH (50 mL) was heated under reflux until a clear solution was obtained, and then concentrated in vacuo. The residue was dissolved in DMF (15 mL), and treated with CF_3SO_2Cl (185 mg, 1.1 mmol) at room temperature for 1 h. The mixture was concentrated in vacuo, and the residue chromatographed on silica gel ($CHCl_3$/EtOH, 9:1 v/v) as the eluent to obtain **7b** (148 mg, 37%) as a foam. ^{1}H NMR (Me_2SO-d_6) δ 3.64-3.74 (2H, m, H5',5"), 3.99-4.08 (1H, m, H4'), 4.59 (1H, dd, H3', $J_{2',3'}$ = 4.4, $J_{3',4'}$ = 5.5 Hz), 5.77 (1H, dd, H2', $J_{1',2'}$ = 4.1, $J_{2',3'}$ = 4.4 Hz), 6.38 (1H,

d, H1', $J_{1',2'}$ = 4.1 Hz), 8.12 (1H, d, H2, collapsed to a singlet upon addition of D_2O), 8.37 (1H, s, H8), 12.40 (1H, bs, NH). This compound decomposed in the mail sent for combustion analyses.

1-Benzyl-2'-O-triflylinosine (7c). In a similar manner to the conversion of **5a** into **7a**, 1-benzylinosine (**5c**, 584 mg, 1 mmol) was converted into **7c** (295 mg, 60%) after chromatographic purification ($CHCl_3$/EtOH, 40:1 v/v) and crystallization from EtOH; mp 143-145 °C (dec). ^{1}H NMR (Me_2SO-d_6) δ 3.65-3.67 (2H, m, H5',5"), 3.99-4.06 (1H, m, H4'), 4.54-4.67 (1H, m, H3'), 5.24 (2H, s, CH_2Ph), 5.80 (1H, t, H2', $J_{1',2'} = J_{2',3'}$ = 3.6 Hz), 6.39 (1H, d, H1', $J_{1',2'}$ = 3.6 Hz), 7.35 (5H, s, CH_2Ph), 8.40, 8.67 (two 1H singlets for H2 and H8). Anal. Calcd for $C_{18}H_{17}F_3N_4O_7S$: C, 44.08; H, 3.50; N, 11.42; S, 6.54. Found: C, 44.32; H, 3.91; N, 11.23; S, 6.52.

3',5'-Di-O-acetyl-2'-O-triflyladenosine (8a). A mixture of **7a** (399 mg, 1.0 mmol) and Ac_2O (0.8 mL, 10 equiv.) in pyridine (10 mL) was left standing for 4 h, and then concentrated in vacuo. The residue was dried by azeotropical distillation of toluene (2 x 10 mL) and EtOH (2 x 10 mL) to obtain quantitative yield of **8a** as a foam. ^{1}H NMR (Me_2SO-d_6) δ 1.98 (3H, s, Ac), 2.16 (3H, s, Ac), 4.11-4.51 (3H, m, H4',5',5"), 5.87 (1H, t, H-3', $J_{2',3'} = J_{3'4'}$ = 5.9 Hz), 6.35 (1H, dd, H-2', $J_{1',2'}$ = 4.1, $J_{2',3'}$ = 5.9 Hz), 6.53 (1H, d, H-1', $J_{1',2'}$ = 4.1 Hz), 7.44 (2H, bs, NH_2), 8.18, 8.57 (two 1H singlets, H2 and H8).

3',5'-Di-O-acetyl-2'-O-triflylinosine (8b) and **3',5'-di-O-acetyl-2'-O-triflyl-1-benzylinosine (8c).** These compounds were prepared similarly. **8b:** ^{1}H NMR (Me_2SO-d_6) δ 2.01 (3H, s, Ac), 2.16 (3H, s, Ac), 4.13-4.54 (3H, m, H4',5',5"), 5.78 (1H, dd, H3', $J_{2',3'}$ = 5.6, $J_{3',4'}$ = 6.0 Hz), 6.21 (1H, dd, H2', $J_{1',2'}$ = 4.1, $J_{2',3'}$ = 5.6 Hz), 6.54 (1H, d, H1', $J_{1',2'}$ = 4.0 Hz), 8.13 (1H, d, H2, collapsed to a singlet upon addition of D_2O), 8.34 (1H, s, H8), 12.10 (bs, NH). **8c:** ^{1}H NMR (Me_2SO-d_6) δ 1.98 (3H, s, Ac), 2.15 (3H, s, Ac), 4.19-4.53 (3H, m, H4',5',5"), 5.24 (2H, s, CH_2Ph), 5.84 (1H, dd, H3', $J_{2',3'}$ = 5,8, $J_{3',4'}$ = 6.0 Hz), 6.21 (1H, dd, $J_{1',2'}$ = 4.0, $J_{2',3'}$ = 5.8 Hz), 6.57 (1H, d, H1', $J_{1',2'}$ = 4.0 Hz), 7.53 (5H, s, CH_2Ph), 8.34, 8.68 (two 1H singlets, H2, H8).

Compounds **8a - 8c** decomposed before combustion analyses.

9-(2,3,5-Tri-O-acetyl-ß-D-arabinofuranosyl)adenine (10a). A mixture of **8a** (50 mg, 0.1 mmol) and NaOAc (10 mg) in DMF (2 mL) was stirred at room temperature overnight, and then concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$-EtOH 19:1 v/v) to obtain **10a** (22 mg), mp 142 °C (EtOH). (Lit.[21] mp 142 °C.)

Reaction of 8a with KF/DMF, Amberlyst A-26 (F^-)/MeCN, and TASF/CH_2Cl_2. Formation of (10a). (a). A mixture of **8a** (50 mg, 0.1 mmol) and KF (10 mg) in DMF (1 mL) was stirred at room temperature for 3 days, and then concentrated in vacuo. The residue was partitioned between $CHCl_3$ (20 mL) and H_2O (5 mL). The organic layer was separated, dried ($MgSO_4$), concentrated, and the residue chromatographed on silica gel column $CHCl_3$/EtOH (19:1 v/v) as the eluent. Unreacted **8a** (5 mg) was eluted first, followed by **10a** (17 mg, 41%). This sample was identical with **10a** prepared above.

(b). A mixture of **8a** (50 mg) and Amberlyst A-26 (F^-) (150 mg) in CH_2Cl_2 (2 mL) was heated under reflux for 10 h. After cooling, the resin was removed by filtration, the filtrate concentrated in vacuo, and the residue chromatographed ($CHCl_3$/EtOH, 19:1 v/v) to give **10a** (17 %).

(c). To a cold (-70 °C) and stirred solution of **8a** (52 mg, 0.1 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of TASF (90 mg, 0.3 mmol) in CH_2Cl_2 (0.6 mL) under argon. The mixture was allowed to warm to room temperature and stirring was continued for 24 h. An additional amount of TASF (90 mg) was added, and the mixture was stirred for another 24 h. The reaction was quenched by addition of H_2O (1 mL). The organic layer was separated, washed with H_2O (0.5 mL), dried ($MgSO_4$), concentrated in vacuo, and the residue chromatographed on silica gel ($CHCl_3$/EtOH, 19:1 v/v) to obtain **10a** (4 mg) and adenine (7 mg).

2'-O-(Tetrahydropyran-2-yl)-1-benzylinosine (12). A mixture of **5c** (9.0 g, 15.4 mmol), DHP (2.8 mL, 31.0 mmol), and TsOH (2.85 mg, 15 mmol) in CH_2Cl_2 (50 mL) was stirred overnight at room temperature. An additional amount of DHP (1 mL) was added, and the mixture was stirred at room temperature for 24 h, and then neutralized with satd. $NaHCO_3$ (50 mL). The organic layer was separated, washed (satd. $NaHCO_3$), dried (Na_2SO_4), and concentrated in vacuo. The residue (crude **11**, 10.0 g, 87%) was dissolved in 1M Et_3NHF in THF (40 mL), and the solution was kept at room temperature

for 24 h. Excess Et_3NHF was decomposed by addition of satd. $NaHCO_3$. The mixture was concentrated in vacuo, and the residue was dried by repeated coevaporation with pyridine. Finally, the residue was suspended in pyridine, insoluble inorganic salts were removed by filtration, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/EtOH, 19:1 v/v) to give **12** (6.67 g, 98%) as a diastereomeric mixture.

Analytical samples of pure diastereomers were obtained by rechromatography of **12** (500 mg) using the same solvent system. The less polar isomer of **12** was obtained as a foam. ^1H NMR (Me_2SO-d_6) δ 1.45-1.75 (6H, m, THP), 3.18-3.20 (2H, m, THP), 3.55-3.60 (2H, m, H5',5"), 3.95-4.00 (1H, m, H4'), 4.23 (1H, m, H3'), 4.57-4.69 (1H, m, THP), 5.07-5.22 (2H, m, 2 x OH), 5.22 (2H, s, CH_2Ph), 6.02 (1H, d, H1', $J_{1',2'}$ = 5.8 Hz), 7.32 (5H, s, $CH_2\underline{Ph}$), 8.40, 8.63 (two 1H singlets, H2, H8). Anal. Calcd for $C_{22}H_{26}N_4O_6$: C, 59.97; H, 5.92; N, 12.16. Found: C, 59.95; H, 6.07; N, 12.40.

The more polar isomer of **12** was also obtained as a foam. ^1H NMR (Me_2SO-d_6) δ 1.32-1.54 (6H, m, THP), 3.06-3.10 (2H, m, THP), 3.55-3.61 (2H, m, H5',5"), 3.98-4.01 (1H, m, H4'), 4.28-4.31 (1H, m, H3'), 4.60-4.72 (1H, m, THP), 5.04-5.30 (2H, m, 2 x OH), 5.23 (2H, s, CH_2Ph), 6.04 (1H, d, H1', $J_{1',2'}$ = 6.3 Hz), 7.31 (5H, s, $CH_2\underline{Ph}$), 8.37, 8.63 (two 1H singlets, H2, H8). Anal. Found: 60.15; H, 6.10; N, 12.38.

3',5'-Di-O-Benzyl-1-benzylinosine (14). To a solution of NaH (980 mg, 40 mmol) in Me_2SO (20 mL) was added, under argon, a solution of **12** (6.0 g, 13.6 mmol) in dry Me_2SO (50 mL). The mixture was stirred for 30 min and benzyl chloride (4.6 mL) was added dropwise. After 4 h, the mixture was poured into ice-water (400 mL), and the product was extracted into Et_2O (4 x 200 mL). The ether extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in MeOH (50 mL) containing TsOH (2.2 g, 13 mmol), and the mixture was stirred overnight at room temperature. The mixture was neutralized (NH_4OH), and then concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 4:1 v/v) to give **14** (4.68 g, 64%) as a foam. ^1H NMR (Me_2SO-d_6) δ 3.56-3.66 (2H, m, H5',5"), 4.09-4.29 (2H, m, H3',4'), 4.51 (2H, s, CH_2Ph), 4.64-4.83 (3H, m, H2', CH_2Ph), 5.23 (2H, s, CH_2Ph), 5.70 (1H, d, 3-OH), 5.93 (1H, d, H1', $J_{1',2'}$ = 5.2 Hz), 7.29-7.34 (15H, m, $CH_2\underline{Ph}$), 8.25,

8.59 (two 1H singlets for H2 and H8). Anal. Calcd for $C_{31}H_{30}N_4O_5$: C, 69.13; H, 5.61; N, 10.40. Found: C, 69.33; H, 5.82; N, 10.21.

3',5'-Di-O-benzyl-2'-O-triflyl-1-benzylinosine (15). To a mixture of **14** (538 mg, 1 mmol), DMAP (122 mg, 1 mmol) and Et_3N (202 mg, 2 mmol) in CH_2Cl_2 (15 mL) was added CF_3SO_2Cl (336 mg, 2 mmol). The mixture was stirred for 15 minutes, and then concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3/Me_2CO$, 20:1 v/v) to give **15** (630 mg, 94%) as a foam. ^1H NMR (Me_2SO-d_6) δ 3.58 (1H, dd, H5', $J_{4',5'}$ = 4.4, $J_{5',5''}$ = 12.0 Hz), 3.70 (1H, dd, H5", $J_{4',5''}$ = 4.0, $J_{5',5''}$ = 12.0 Hz), 4.28-4.44 (1H, m, H4'), 4.44 (2H, s, CH_2Ph), 4.64 (2H, s, CH_2Ph), 4.64-4.77 (1H, m, H3'), 5.23 (2H, s, CH_2Ph), 6.08-6.16 (1H, m, H2'), 6.45 (1H, d, H1', $J_{1',2'}$ = 2.5 Hz), 7.26-7.33 (15H, m, CH_2Ph), 8.23, 8.61 (two 1H singlets for H2, H8). This compound decoposed prior to elemental analyses.

Reaction of 15 with TASF. Synthesis of 3',5'-Di-O-benzyl-2'-deoxy-2',3'-didehydro-1-benzylinosine (16). A solution of **15** (670 mg, 1 mmol) in dry CH_2Cl_2 (10 mL) was cooled to -70 °C in a dry ice/acetone bath. To this solution was added a solution of TASF (900 mg, 3 mmol) in CH_2Cl_2 (6 mL) under argon. The mixture was allowed to warm to room temperature, and stirring was continued for 24 h. An additional amount of TASF (900 mg in 6 mL of CH_2Cl_2) was added, and the stirring continued for 24 h. The reaction was quenched by addition of satd $NaHCO_3$ (10 mL). The organic layer was separated, washed with H_2O (5 mL), dried ($MgSO_4$), and concentrated to dryness in vacuo. The residue chromatographed on silica gel ($CHCl_3/Me_2CO$, 20:1 v/v). **3-Benzyloxy-2-benzyloxymethylfuran (17)** (47 mg, 16%) was eluted first from the column followed by **16** (320 mg, 62%).

Compound **17** was obtained as a foam. ^1H NMR (Me_2SO-d_6) δ 4.39 (2H, s, CH_2Ph), 4.40 (2H, s, CH_2Ph), 5.03 (2H, s, CH_2OCH_2Ph), 6.60 (1H, d, H4, $J_{4,5}$ = 2.2 Hz), 7.29 (5H, s, CH_2Ph), 7.36 (5H, s, CH_2Ph), 7.49 (1H, d, H5). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.28; H, 6.37.

Compound **16** was also obtained as a foam. ^1H NMR (Me_2SO-d_6) δ 3.58-3.63 (2H, m, H5',5"), 4.44 (2H, s, CH_2Ph), 4.83 (1H, m, H4'), 5.11 (2H, s, CH_2Ph), 5.20 (1H, s, H1'), 5.24 (2H, s, H1', CH_2Ph), 6.87 (1H, s, H2'), 7.21, 7.32, 7.39 (each 5H singlets for CH_2Ph), 8.06, 8.62 (two 1H singlets for H2, H8). Anal. Calcd for $C_{31}H_{28}N_4O_4$: C, 71.94; H, 5.45; N, 10.24. Found: C, 71.67; H, 5.50; N, 10.27.

5'-O-Trityl-1-benzylinosine (18c). A mixture of **4c** (3.58 g, 10 mmol) and TrCl (3.3 g, 12 mmol) in pyridine (50 mL) was stirred at room temperature. An additional amount of TrCl (3.3 g, each) was added on the 2nd and 3rd day, and stirring was continued until all the starting material was consumed. The mixture was concentrated in vacuo, and traces of pyridine were removed by coevaporations with toluene and EtOH. The residue was chromatographed on silica gel ($CHCl_3$/EtOH, 19:1 v/v) to give **18c** which was crystallized from EtOH (5.40 g, 90%), mp 208-209 °C. ^{1}H NMR (Me_2SO-d_6) δ 3.20-3.24 (2H, m, H5',5"), 4.10-4.29 (2H, m, H3',4'), 4.61-4.67 (1H, m, H2', collapsed to dd upon addition of D_2O, $J_{2',3'}$ = 5.0, $J_{1',2'}$ = 5.6 Hz), 5.21-5.27 (3H, m, CH_2Ph, OH, became s at 5.24 upon addition of D_2O), 5.57 (1H, d, OH), 5.92 (1H, d, H1', $J_{1',2'}$ = 5.6 Hz), 7.06-7.32 (20H, m, Tr, $CH_2\underline{Ph}$), 8.23, 8.51 (two 1H singlets for H2, H8). Anal. Calcd for $C_{36}H_{32}N_4O_5$: C, 71.98; H, 5.37; N, 9.33. Found: C, 71.86; H, 5.44; N, 9.18.

3'-O-Acetyl-2'-O-triflyl-5'-O-trityladenosine (20a). A mixture of 5'-O-trityladenosine[12] (497 mg, 1 mmol) and Bu_2SnO[20] (249 mg, 1 mmol) in MeOH (50 mL) was heated under reflux until a clear solution was obtained (45 minutes). The solution was concentrated in vacuo, and the residue dissoved in DMF (20 mL). The solution was cooled in an ice bath, and CF_3SO_2Cl (190 mg, 1.1 mmol) was added. After being stirred for 1.5 h at room temperature, the solution was concentrated in vacuo, the residue was dissolved in pyridine (20 mL) and then treated with Ac_2O (1.5 mL). The mixture was stirred for 3 h, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/EtOH, 33:1 v/v) to obtain **20a** (208 mg, 31%) as a foam. ^{1}H NMR (Me_2SO-d_6) δ 2.12 (3H, s, Ac), 3.36-3.49 (2H, m, H5',5"), 4.36-4.40 (1H, m, H4'), 5.90-5.95 (1H, m, H3'), 6.45-6.54 (2H, m, H1',2'), 7.20-7.57 (17H, m, Tr, NH_2), 8.06, 8.35 (two 1H singlets for H2, H8). Anal. Calcd for $C_{32}H_{28}F_3N_5O_7S$: C, 56.22; H, 4.13; N, 10.24. Found: C, 56.08; H, 4.30; N, 10.11.

In a similar manner, 5'-O-tritylinosine[13] (740 mg, 1.45 mmol) was converted into **3'-O-acetyl-2'-O-triflyl-5'-O-tritylinosine (20b)** (foam, 445 mg, 45%). The eluent used for chromatography was $CHCl_3$/EtOH (19:1 v/v). ^{1}H NMR (Me_2SO-d_6) δ 2.11 (3H, s, Ac), 3.30-3.35 (2H, m, H5',5"), 4.38-4.43 (1H, m, H4'), 5.99 (1H, t, H3', $J_{2',3'} = J_{3',4'}$ = 5.7 Hz), 6.32 (1H, dd, H2', $J_{1',2'}$ = 4.1, $J_{2',3'}$ = 5.7 Hz), 6.55 (1H, d,H1',$J_{1',2'}$ = 4.1 Hz),

7.15-7.37 (15H, m, Tr), 8.15, 8.37 (two 1H singlets for H2, H8). Anal. Calcd for $C_{32}H_{27}F_3N_4O_8S$: C, 56.17; H, 3.98; N, 8.19. Found: C, 55,98; H, 4.05; N, 8.07.

Likewise, **3'-O-acetyl-2'-O-triflyl-5'-O-trityl-1-benzylinosine (20c)** was obtained from **18c** (700 mg, 1.16 mmol) as a foam (580 mg, 64%), using CH_2Cl_2/EtOAc (16:1 followed by 8:1 v/v) as the eluents for column chromatography. ^{1}H NMR (Me_2SO-d_6) δ 2.11 (3H, s, Ac), 3.32-3.36 (2H, m, H5',5"), 4.41-4.45 (1H, m, H4'), 5.24 (2H, s, CH_2Ph), 5.88 (1H, t, H3', $J_{2',3'} = J_{3',4'} = 6.0$ Hz), 6.30 (1H, dd, H2', $J_{1',2'} = 4.1$, $J_{2',3'} = 6.0$ Hz), 6.57 (1H, d, H1', $J_{1',2'} = 4.1$ Hz), 7.18-7.36 (20H, m, Tr, CH_2Ph), 8.34, 8.51 (two 1H singlets for H2 and H8). Anal. Calcd for $C_{39}H_{33}F_3N_4O_8S$: C, 60.46; H, 4.29; N, 7.23. Found: C, 60.39; H, 4.37; N, 7.20.

Treatment of 20 with TASF. a) To a cold solution (-70 °C) of **20a** (1.0 g, 1.46 mmol) in dry CH_2Cl_2 (15 mL) was added a solution of TASF (1.2 g, 4.35 mmol) in CH_2Cl_2 (9 mL) under argon. The reaction mixture was allowed to warm to room temperature while being stirred. After 24 h, an additional amount of TASF (1.2 g) in CH_2Cl_2 (9 mL) was added, and the stirring was continued for 24 h. The reaction was quenched by addition of H_2O (15 mL). The organic layer was washed with H_2O (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel by successive elution with 99:1, 97:3, and 95:5 $CHCl_3$-EtOH (v/v). **2-Triphenylmethyloxymethyl-3-acetoxyfuran (23)** (220 mg, 37%) was eluted first from the column followed by **2-triphenylmethyloxymethyl-3-hydroxyfuran (24)**, **9-(3-O-acetyl-2-deoxy-2-fluoro-5-O-trityl-β-D-arabinofuranosyl)adenine (21a)**, **9-(2,3-di-O-acetyl-5-O-trityl-β-D-arabinofuranosyl)adenine (22a)** and adenine.

Compound **23** was crystallized from hexane-Et_2O, mp 79-83 °C. ^{1}H NMR (Me_2SO-d_6) δ 2.17 (3H, s, Ac), 3.89 (2H, s, CH_2OTr), 6.55 (1H, d, H4, $J_{4,5} = 2.2$ Hz), 7.25-7.43 (15H, m, Tr), 7.63 (1H, d, H1, $J_{1,2} = 2.2$ Hz). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.40; H, 5.60.

Compound **24** was obtained as crystals (80 mg, 15%), mp 119-120 °C (hexane-Et_2O). The ^{1}H NMR spectrum was identical with that reported.[22] Upon acetylation of **24** (45 mg) with Ac_2O (45 uL) in pyridine (1 mL), **23** (50 mg) was obtained.

Compound **21a** was isolated as a foam (33 mg, 4%). ^{1}H NMR (Me_2SO-d_6) δ 2.10 (3H, s, Ac), 3.38-3.40 (2H, m, H5',5"), 4.20-4.24 (1H, m, H4'), 5.36

(1H, dm, H3', $J_{3',F}$ = 17.1 Hz), 5.57 (1H, dm, H2', $J_{2',F}$ = 51.3 Hz), 6.49 (1H, dd, H1', $J_{1',2'}$ = 3.8, $J_{1',F}$ = 17.0 Hz), 7.25-7.36 (15H, m, Tr), 8.07 (1H, d, H8, $J_{8,F}$ = 2.5 Hz), 8.15 (1H, s, H2). ^{19}F NMR (Me_2SO-d_6) δ -189.5 (dt, $J_{1',F}$ = $J_{3',F}$ = 17.1, $J_{2',F}$ = 51.3 Hz). Anal. Calcd for $C_{31}H_{28}FN_5O_4$: C, 67.26; H, 5.10; N, 12.65. Found: C, 67.30; H, 5.21; N, 12.50.

Compound **22a** was obtained as a foam, (104 mg, 12%). ^{1}H NMR (Me_2SO-d_6) δ 1.67 (3H, s, Ac), 2.08 (3H, s, Ac), 3.38-3.54 (2H, m, H5',5"), 4.32 (1H, m, H4'), 5.50-5.75 (2H, m, H2',3'), 6.65 (1H, d, H1', $J_{1',2'}$ = 5.5 Hz), 7.23-7.34 (15H, m, Tr), 8.37 and 8.52 (each 1H, s, H2 and H8). Anal. Calcd for $C_{33}H_{31}N_5O_6$: Calcd: C, 66.77; H, 5.26; N, 11.79. Found: C, 66.59; H, 5.35; N, 11.54.

b) Compound **20b** (1.0 g, 1.46 mmol) was treated with TASF (2 x 3.0 g) and the products purified as above to obtain **23** (310 mg, 52%), **24** (93 mg, 17%), hypoxanthine (156 mg, 77%), and a mixture of **21b** and **22b** (12 mg).

c) Similar treatment of **20c** (1.0 g, 1.29 mmol) with TASF (2 x 1.06 g) afforded the following compounds, which were separated on silica gel (CH_2Cl_2/EtOAc, 9:1 v/v): **23** (133 mg, 26%), **24** (27 mg, 6%), **21c** (83 mg, 10%, foam): ^{1}H NMR (Me_2SO-d_6) δ 2.09 (3H, s, Ac), 3.21-3.33 (2H, m, H5',5"), 4.20-4.25 (1H, m, H4'), 5.25 (2H, m, CH_2Ph), 5.52 (1H, dm, H3', $J_{3',F}$ = 15.3 Hz), 5.54 (1H, dm, H2', $J_{2',F}$ = 51.0 Hz), 6.48 (1H, dd, H1', $J_{1',2'}$ = 4.1, $J_{1',F}$ = 17.1 Hz), 7.23-7.33 (20H, m, Tr, CH_2Ph), 8.05 (1H, d, H8, $J_{8,F}$ = 2.5 Hz), 8.62 (1H, s, H2). ^{19}F NMR (Me_2SO-d_6) δ -197.6 (sextet). Anal. Calcd for $C_{38}H_{33}FN_4O_5$: C, 70.79; H, 5.16; N, 8.69. Found: C, 70.60; H, 5.23; N, 8.52. Compound **22c** (53 mg, 6%), mp 163-165 °C (AcOEt-hexane). ^{1}H NMR (Me_2SO-d_6) δ 1.69 (3H, s, Ac), 2.06 (3H, s, Ac), 3.34-3.37 (2H, m, H5',5"), 4.44-4.46 (1H, m, H4'), 5.22 (2H, s, CH_2Ph), 5.45-5.62 (2H, m, H2',3'), 6.50 (1H, d, H1', $J_{1',2'}$ = 5.2 Hz), 7.22-7.33 (20H, m, Tr, CH_2Ph), 8.01, 8.54 (two 1H singlets, H2, H8). Anal. Calcd for $C_{40}H_{36}N_4O_7$: C, 70.16; H, 5.30; N, 8.18. Found: C, 70.01; H, 5.41; N, 8.18. 1-Benzylhypoxanthine (205 mg, 71%), mp 264-268 °C (from EtOH). (lit.[23] mp 268-270 °C). ^{1}H NMR of this sample was identical with that of an authentic sample.

2',5'-O-Trityl-1-benzylinosine (25) and 3',5'-O-Trityl-1-benzylinosine (26). A mixture of **4c** (50.0 g, 0.14 mol), DMAP (25.3 g, 0.21 mol) and TrCl (97.2 g, 0.35 mol) in pyridine (550 mL) was stirred for 3 d at 70-80 °C. Additional reagents were added at 24 h (58.3 g of TrCl and 10.0 g of

DMAP) and 48 h (39.0 g of TrCl and 6.0 g of DMAP). The hot mixture was filtered, and concentrated in vacuo. Traces of pyridine were removed by coevaporation with toluene (2 x 300 mL). The residue was placed on the top of a silica gel column (10 x 40 cm), which was eluted with hexane/EtOAc (1:1, 4 L), followed by 1:1 hexane/EtOAc containing 3% EtOH. The amount of EtOH was increased gradually up to 30%. Fractions containing **25** and **26** were collected, and this mixture was rechromatographed on silica gel using hexane/$CHCl_3$/EtOH (20:20:1 v/v/v) followed by hexane/$CHCl_3$/EtOH (10:20:1 v/v/v). Compound **25** was eluted first (28.0 g, 24%), mp 231-233 °C (hexane-EtOAc). ^{1}H NMR (Me_2SO-d_6) δ 3.00-3.06 (2H, m, H5',5"), 3.20-3.24 (1H, m, H4'), 4.05-4.09 (1H, m, H3'), 4.95-5.02 (1H, m, H2'), 5.15-5.22 (1H, m, OH, exchangeable), 5.22 (2H, s, CH_2Ph), 5.96 (1H, d, H1', $J_{1',2'}$ = 6.2 Hz), 7.02-7.64 (35H, m, CH_2Ph, 2 x Tr), 8.08, 8.17 (two 1H singlets, H2, H8). Anal. Calcd for $C_{55}H_{46}N_4O_5$: C, 78.36; H, 5.50; N, 6.65. Found: C, 78.17; H, 5.36; N, 6.40.

Compound **26** was eluted next (22.0 g, 19%), mp 187-188 °C ($CHCl_3$-hexane). ^{1}H NMR (Me_2SO-d_6) δ 2.64-2.68 (2H, m, H5',5"), 3.09-3.11 (1H, m, H4'), 4.12-4.14 (1H, m, H3'), 4.70-4.77 (1H, d, H2'), 5.25 (2H, s, CH_2Ph), 6.10 (1H, d, H1', $J_{1',2'}$ = 7.2 Hz), 7.19-7.40 (35H, m, CH_2Ph, 2 x Tr), 8.15, 8.42 (two 1H singlets for H2 and H8). Anal. Calcd for $C_{55}H_{46}N_4O_5$: C, 78.36; H, 5.50; N, 6.65. Found: C, 78.20; H, 5.41; N, 6.52.

2'-O-Triflyl-3',5'-di-O-trityl-1-benzylinosine (27). To a mixture of **26** (2.0 g, 2.4 mmol), DMAP (290 mg, 2.4 mmol) and Et_3N (480 mg, 4.8 mmol) in CH_2Cl_2 (40 mL) was added CF_3SO_2Cl (800 mg, 4.8 mmol), and the solution was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (CCl_4/EtOAc, 5:1 v/v) to obtain **27** (1.82 g, 78%) as a foam. ^{1}H NMR (Me_2SO-d_6) δ 2.92-2.96 (2H, m, H5',5"), 3.62-3.69 (1H, m, H4'), 4.41-4.43 (1H, m, H3'), 5.23 (2H, s, CH_2Ph), 5.92 (1H, d, H2', $J_{1',2'}$ = 6.3 Hz), 6.58 (1H, d, H-1') 7.18-7.34 (35H, m, CH_2Ph and 2 x Tr), 8.29, 8.32 (two 1H singlets for H2 and H8): ($CDCl_3$) δ 2.73 (1H, dd, H5', $J_{4',5'}$ = 3.0, $J_{5',5"}$ = 11.1 Hz), 3.22 (1H, dd, H4', $J_{4',5'}$ = 3.0, $J_{4',5"}$ = 1.9 Hz), 3.41 (1H, m, H4'), 4.42 (1H, dd, H3', $J_{2',3'}$ = 4.3, $J_{3',4'}$ = 1.6 Hz), 5.23 (2H, s, CH_2Ph), 5.83 (1H, dd, H2', $J_{1',2'}$ = 7.1, $J_{2',3'}$ = 4.3 Hz), 6.55 (1H, d, H-1'), 7.15-7.40 (30H, m, 2 x Tr), 7.84, 7.99 (two 1H singlets for H2 and H8). This compound was used directly in the next step.

9-(2-Deoxy-2-fluoro-3,5-di-O-trityl-ß-D-arabinofuranosyl)-1-benzylhypoxanthine (28). To a solution of **27** (3.24 g, 3.32 mmol) in dry CH_2Cl_2 (40 mL) was added a solution of TASF (2.75 g, 10 mmol) in CH_2Cl_2 (20 mL) at -70 °C in an argon atmosphere. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 4 days. An additional amount of TASF in CH_2Cl_2 (5.0 g in 40 mL) was added at -40 °C on the 2nd and 3rd day. The reaction was quenched with H_2O (50 mL), the organic layer was separated, washed (H_2O, 2 x 75 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with hexane/EtOAc (4:1), followed by hexane/EtOAc (2:1) to give **28** (842 mg, 30%) as a foam from $CHCl_3$. ^1H NMR (Me_2SO-d_6) δ 3.00-3.02 (2H, m, H5',5"), 4.27 (1H, d, H3', $J_{3',F}$ = 19.0 Hz), 4.38 (1H, s, H4'), 4.44 (1H, dd, H2', $J_{2',F}$ = 48.3, $J_{1',F}$ = 3.0 Hz), 5.24 (2H, s, CH_2Ph), 6.37 (1H, dd, H1', $J_{1',2'}$ = 3.0, $J_{1',F}$ = 22.0 Hz), 7.27-7.32 (35H, m, CH_2Ph, 2 x Tr), 7.72 (1H, d, H8, $J_{8,F}$ = 2.2 Hz), 8.56 (1H, s, H2). Anal. Calcd for $C_{55}H_{45}FN_4O_4.1/5CHCl_3$: C, 76.31; H, 5.24; N, 6.45. Found: C, 76.45; H, 5.54; N, 6.23. A small amount of $CHCl_3$ was detected in the ^1H NMR spectrum of this sample at 8.31.

9-(2-Deoxy-2-fluoro-ß-D-arabinofuranosyl)-1-benzylhypoxanthine (29). To a solution of TFA (63.1 mL) in $CHCl_3$ (670 mL) was added a solution of **28** (6.63 g, 7.85 mmol) in $CHCl_3$ (30 mL) under argon at -25 °C. The mixture was allowed to warm to room temperature, and stirring was continued for 1 h. The mixture was then recooled to -25 °C, and EtOH (73 mL) was added. The colorless mixture was concentrated in vacuo, and the residue was triturated with hexane/Et_2O (1:1 v/v) (2 x 400 mL). The solid residue was collected, and chromatographed on silica gel ($CHCl_3$/EtOH, 8:1 v/v) to give **29** (2.5 g, 88%) as colorless foam. ^1H NMR (Me_2SO-d_6) δ 3.68-3.92 (3H, m, H4',5',5"), 4.44 (1H, ddd, H3', $J_{2',3'}$ = 4.4, $J_{3',4'}$ = 4.9, $J_{3',F}$ = 18.9 Hz), 5.23 (1H, ddd, H2', $J_{1',2'}$ = 4.7, $J_{2',3'}$ = 4.4, $J_{2',F}$ = 53.7 Hz), 6.39 (1H, dd, H1', $J_{1',2'}$ = 4.7, $J_{1',F}$ = 13.5 Hz), 7.33 (5H, s, CH_2Ph), 8.26 (1H, d, H8, $J_{8,F}$ = 1.9 Hz), 8.62 (1H, s, H2). Anal. Calcd for $C_{17}H_{17}FN_4O_4$: C, 56.66; H, 4.75; N, 15.55. Found: C, 56.68; H, 4.83; N, 15.61.

9-(2-Deoxy-2-fluoro-ß-D-arabinofuranosyl)hypoxanthine (1, F-ara-H). To a solution of **29** (2.0 g, 5.55 mmol) in MeOH (70 mL) was added $Pd(OH)_2/C$[24] (700 mg), and the mixture was shaken in a Parr hydroganation apparatus (50 psi). An additional amount of the catalyst (700 mg) was added on the 2nd,

3rd and 6th day. The reduction required 7 days for completion. The catalyst was removed by filtration, the filtrate was concentrated in vacuo, and the residue was acetylated with Ac_2O (1.7 mL) in pyridine (10 mL) for 4 h. The mixture was concentrated, traces of pyridine were removed by coevaporation with EtOH and toluene, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed (H_2O, 3 x 20 mL), dried ($MgSO_4$), and concentrated. The residue was crystallized from $CHCl_3$-Et_2O to give **9-(3,5-di-O-acetyl-2-deoxy-2-fluoro-ß-D-arabinofuranosyl)hypoxanthine** (1.9 g, 91%), mp 190-191 °C. ^1H NMR ($CDCl_3$) δ 2.13 (3H, s, Ac), 2.19 (3H, s, Ac), 4.29-4.48 (3H, m, H4',5',5"), 5.16 (1H, dd, H2', $J_{2',3'}$ = 0, $J_{1',2'}$ = 2.7, $J_{2',F}$ = 52.4 Hz), 5.37 (1H, d, H3', $J_{3',F}$ = 15.1 Hz), 6.45 (1H, dd, H1', $J_{1',2'}$ = 2.7, $J_{1',F}$ = 21.7 Hz), 8.08 (1H, d, H8, $J_{8,F}$ = 2.7 Hz), 8.31 (1H, s, H2).

The above acetylated derivative (1.75 g, 6.47 mmol) was treated with a solution of Et_3N (4.03 g, 40 mmol) in MeOH (45 mL) at room temperature for 2 days, and then at 55 °C for 24 h. The mixture was concentrated in vacuo, and the residue crystallized from Me_2CO/MeCN to obtain **1** (1.28 g, 96%), mp 206-208 °C (lit.[2] amorphous). The ^1H NMR spectrum of this sample was identical with that of an authentic sample.[2]

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