A Synthesis of 9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)adenine and Hypoxanthine. An Effect of C3'-Endo to C2'-Endo Conformational Shift on the Reaction Course of 2'-Hydroxyl Group with DAST[1]

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$O^{3'},O^{5'},N^6$-Tritrityladenosine (**6**), 3',5'-di-*O*-trityl-N^1-benzylinosine (**15**), and 3',5'-di-*O*-tritylinosine (**18**) were prepared and subjected to nucleophilic reaction with DAST. Thus, **6** afforded 2'-β-fluorine-substituted nucleoside **11** along with the isomeric 2-deoxy-2-(*N*-trityladenin-3-yl)-3,5-di-*O*-trityl-α-D-arabinofuranosyl fluoride (**12**). Nucleoside **15**, under the same treatment with DAST, gave the desired 2'-fluoroarabino derivative **16** exclusively in high yield. Although **18** was converted into the 2'-β-fluoro product **19** under the similar conditions, the yield was low. A plausible mechanism of formation of **12** is discussed. Deprotection of **11** and **16** afforded the desired 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (**1**) and -hypoxanthine (**2**), respectively, in high yield. The conformational influence of sugar protecting groups on the rate of nucleophilic substitution against elimination is discussed. Treatment of $O^{3'},O^{5'},N^1$-benzylinosine (**20**) with DAST afforded only the elimination products 9-(3',5'-di-*O*-benzyl-β-D-*erythro*-pent-2-enofuranosyl)-1-benzylhypoxanthine (**22**) and 3-(benzyloxy)-2-[(benzyloxy)methyl]furan (**23**). On the other hand, 9-(3,5-di-*O*-trityl-β-D-arabinofuranosyl)adenine (**26**) (prepared from **6** by triflyation followed by NaOAc treatment and deacetylation) afforded a mixture from which 2'-deoxy-2'-fluoroadenosine (**27**) and 9-(2-deoxy-3,5-di-*O*-trityl-D-*erythro*-pent-1-enofuranosyl)-N^6-tritylladenine (**28**) were isolated in 60 and 30% yield, respectively. $O^{2'},O^{5'},N^6$-Tritrityladenosine (**7**) was selectively detritylated with HCO_2H/Et_2O to give $O^{2'},N^6$-ditrityladenosine (**30**), which, upon treatment with benzyl chloride/KOH, afforded 3',5'-di-*O*-benzyl-$O^{2'},N^6$-ditrityladenosine (**31**). 9-(3,5-Di-*O*-benzyl-β-D-arabinofuranosyl)adenine (**35**) was prepared from **31** by further detritylation with $CF_3CO_2H/CHCl_3$ and triflylation followed by NaOAc treatment and deacetylation of the product. Treatment of **35** with DAST followed by hydrogenolytic debenzylation afforded 2'-deoxy-2'-fluoroadenosine (**3**) in high yield. The three-step synthesis described herein, albeit about 10% overall yield, is far superior to the currently available multistep procedures which give the desired 2'-fluoroarabinosylpurines in much less overall yields.

The synthesis of numerous pyrimidine[2] and purine[3] nucleosides containing fluorine in the C2' (β) (arabino) configuration have been in recent years reported from our laboratory. In contrast to parent deoxynucleosides these 2'(β)-fluoro analogues exhibit dramatically different biological activity. For example, many 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)pyrimidines are potent antiherpes virus agents,[2] the guanine nucleoside (F-ara-G) exhibits selective T-Cell toxicity,[3,4] and the hypoxanthine nucleoside possesses an antiparasitic activity.[5] Replacement of the hydrogen by fluorine causes not only change in biological activity but also increases chemical and metabolic stability of these nucleosides. Due to the powerful electron-withdrawing nature of fluorine, the 2'-fluoro-2'-deoxynucleosides are resistant to chemical and phosphorylase-catalyzed hydrolysis.[6-8] The conformation of the sugar moiety of these analogues is strongly affected by the influence of the fluorine substituent and is different from that of natural deoxynucleosides.

The physicochemical and biochemical properties of oligonucleotides containing 2'(β)-fluoro-substituted nucleosides with the above-mentioned characteristics have attracted our attention. In order to synthesize such oligomers, an efficient procedure for the synthesis of 2'-(β)-fluoro-substituted nucleosides must be available. Although, the procedure for large-scale synthesis of 2'(β)-fluoro pyrimidine nucleosides[2,9] has been developed in our laboratory, the corresponding 2'(β)-fluoro-substituted purine nucleosides were synthesized by us[3] and others[4,6] only in minute amounts.

All reported 2'(β)-fluorinated nucleosides were synthesized by glycosylation of a purine base with an appropriate sugar halide.[9,10] In contrast to the simple and efficient glycosylation of pyrimidines, the condensation of purines with 2-deoxy-2-fluoro-D-arabinofuranosyl halide is extremely difficult. In fact, some purine bases do not

(1) Nucleosides 161. Studies directed toward the synthesis of 2'-deoxy-2'-substituted arabinonucleosides. 9. Presented in part at the 200th National Meeting of the American Chemical Society, Washington, DC, Aug 1990; CARB 19. Relevant paper in this series: Krzeminski, J.; Nawrot, B.; Pankiewicz, K. W.; Watanabe, K. A. *Nucleosides Nucleotides* **1991**, *10*, 781. Also: Pankiewicz, K. W.; Nawrot, B.; Gadler, H.; Price, R. W.; Watanabe, K. A. *J. Med. Chem.* **1987**, *30*, 2314.

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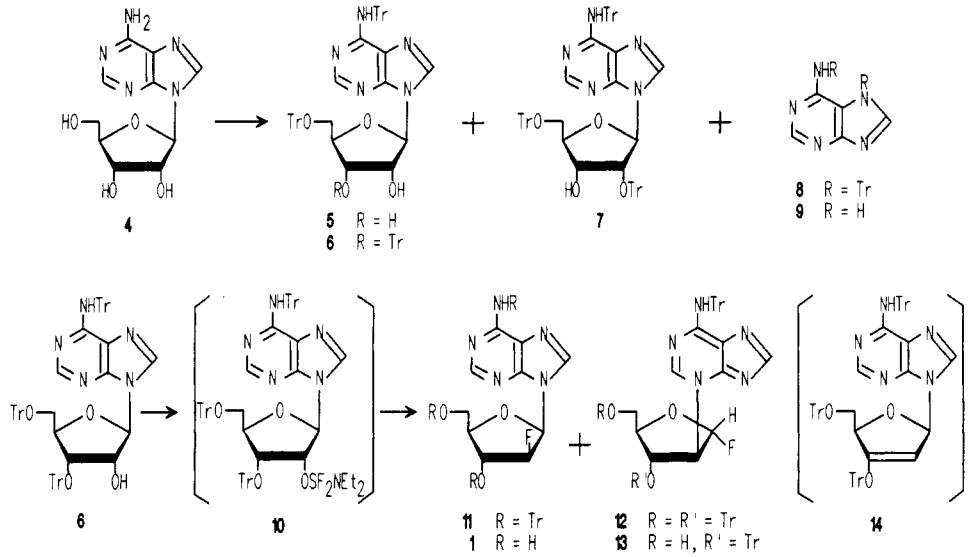
Scheme I



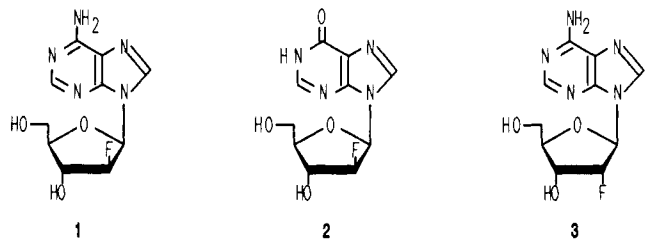


Figure 1.

react with the sugar halides. For example, the adenosine derivative 1 (F-ara-A) has been recently prepared[6] by condensation of 6-chloropurine with 2-deoxy-2-fluoro-D-arabinofuranosyl bromide followed by conversion of the purine into adenine. The glycosylation reaction afforded a mixture of four isomers from which the desired isomer was separated in very low yield. Thus, it is evident that a method of direct introduction of the fluorine into preformed purine nucleosides is of great interest.

We published[1] the first example of direct introduction of the 2′(β)-fluoro substituent into preformed pyrimidine *C*-nucleoside. Displacement of the triflate group of 3′-*O*-acetyl-4,5′-anhydro-1-methyl-2′-*O*-triflyl-ψ-uridine with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) afforded, after deprotection, 2′-deoxy-2′-fluoro-1-methyl-ψ-uridine (C-FMAU). Subsequently, we discovered[1] that the similar reaction of 2′-*O*-triflyl-3′,5′-di-*O*-trityl-1-benzylinosine with TASF gave the desired 2′-fluoroarabino derivative in 30% yield. The latter study showed that conformational shift of the nucleoside triflate toward C2′-endo was required for successful displacement of the 2′-triflate function with TASF.

In this paper, we report the practical, three-step synthesis of F-ara-A and F-ara-H (1 and 2, Figure 1) via displacement of the 2′-hydroxyl group of $O^{3'},O^{5'},N^6$-tritrityladenosine and $O^{3'},O^{5'}$-ditritylinosine with diethylaminosulfur trifluoride[11] (DAST). Also, we report herein the synthesis of 9-(2-deoxy-2-fluoro-β-D-ribofuranosyl)-adenine (3, Figure 1) from $O^{2'},O^{5'},N^6$-tritrityladenosine as an example of possible utilization of 2′,5′-di-*O*-trityl purine nucleoside in the synthesis of the corresponding 2′(α)-fluoro-substituted (ribo) analogues of nucleosides. Conformational influence of the sugar protecting groups on the reaction course of the 2′-OH group with DAST is discussed.

Treatment of adenosine (4, Scheme I) with trityl chloride in pyridine containing 4-(dimethylamino)pyridine[12] (DMAP) at 80 °C for 2–3 days[13] afforded a mixture of $O^{5'},N^6$-dityladenosine[14] (5), $O^{3'},O^{5'},N^6$-tritrityladenosine[14] (6), $O^{2'},O^{5'},N^6$-tritrityladenosine[14] (7), and N^6,N^7-ditrityladenine (8). These compounds were separated on a silica gel column. Compound 8 was detritylated with CF_3COOH–$CHCl_3$[15] to give adenine. Nucleosides 6 and 7 were obtained in crystalline form in 20.5% and 25.5% yield, respectively. Further tritylation[13] of 5 under the same conditions afforded additional amounts of 6 and 7, increasing the total yield of 6 and 7 up to 35% and 45%, respectively.

Treatment of the tritrityladenosine 6 with DAST gave a mixture of two products. A minor and less polar product 11 (Scheme I), which was isolated in 30% yield, was detritylated with CF_3COOH–$CHCl_3$[15] to give the desired 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (1). To our surprise the major, more polar derivative was not the expected elimination product 14 but an isomer of 11 containing the fluorine atom. Its structure was established on a basis of spectral and elemental analysis as 2-deoxy-2-(N^6-trityladenin-3-yl)-3,5-di-*O*-trityl-α-D-arabinofuranosyl fluoride (12). The MS and elemental analysis indicate the isomeric nature of nucleosides 11 and 12. The ^{1}H NMR spectrum of 12 shows an anomeric proton doublet at $\delta = 5.63$ with a large geminal coupling constant ($J_{1'F} = 60.6$ Hz) indicating that the fluorine atom is attached to C1′. Since there is no H1′–H2′ coupling, the fluorine should be in the α configuration if the aglycon is linked to the C2′ position from the β side. This is strongly suggested by a small H2′–H3′ coupling constant ($J_{2'3'} = 3.2$ Hz). The dramatic change in the UV spectrum of 12 versus 11 is also fully consistent with the proposed structure for isonucleoside 12. Attempts at detritylation

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(12) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *95*.

(13) Tritylation reaction should be quenched with EtOH before the entire amount of 5 was consumed. Although more stringent conditions allowed for complete conversion of 5 into a mixture of 6 and 7, excessive depurination with formation of 8 occurred.

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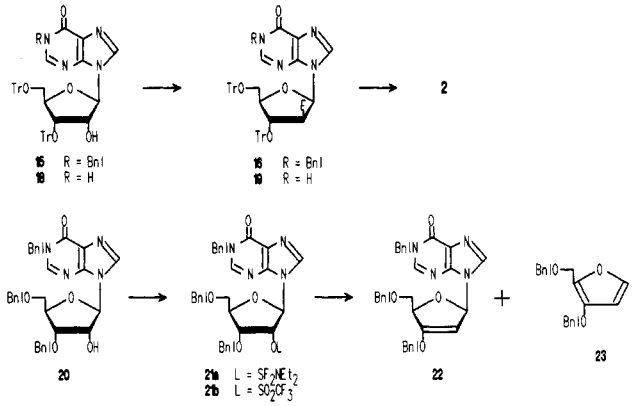
(15) MacCoss, M.; Cameron, D. J. *Carbohyd. Res.* **1978**, *60*, 206.

Scheme II



of **12** with CF_3COOH–$CHCl_3$ caused decomposition to give adenine. Under milder conditions ($HCOOH$–Et_2O[16]), however, a partially deprotected $O^{3'},N^6$-dityrityl derivative **13** was obtained.

A possible mechanism of **6** to **12** conversion is as follows: attack of N3 of the aglycon on the activated 2'-carbon atom of the alkoxy (dimethylamino)sulfur difluoride intermediate[17] may result in the formation of a carbocation via cleavage of the glycosyl bond. Subsequently, the fluoride ion attacks from the less hindered α-side to give **12**. Alternatively, the fluoride ion may cleave the glycosyl bond with inversion of configuration at the anomeric carbon atom.

It is well established that adenine N3 participation in sugar transformation in the adenosine series results in undesired formation of intramolecular cyclization products between N3 and the sugar moiety.[18-25] Recently, the attack of N3 on C3' of the sugar of 5'-*O*-(monomethoxytrityl)-2'-deoxyadenosine under DAST treatment has been reported.[21] In this case almost all the starting material was converted into the N^3,3'-cyclonucleoside.

Neither the base migration nor cyclization to the N^3,2'-cyclonucleoside would be possible for 3',5'-di-*O*-trityl-1-benzylinosine[1] (**15**, Scheme II). Indeed, the desired 9-(2-deoxy-2-fluoro-3,5-di-*O*-trityl-β-D-arabinofuranosyl)-1-benzylinosine (**16**) was obtained in 63% yield when **15** was treated with DAST. After deprotection of **16**, **2** was prepared in high yield. When 3',5'-di-*O*-tritylinosine (**18**) was treated with DAST the yield of 2'(β)-fluoro derivative **19** became lower (30% yield) probably due to N3 participation in the reaction.

It is interesting to note that treatment of $N^1,O^{3'},O^{5'}$-tribenzylinosine[1] (**20**, Scheme II) with DAST did not give the corresponding 2'(β)-fluoro-substituted nucleoside, but instead elimination products **22** and **23** were obtained

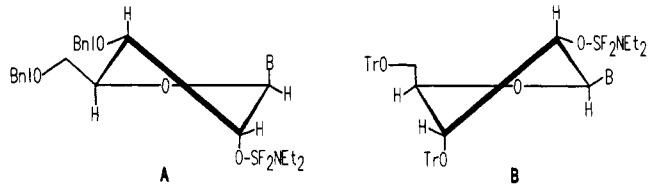
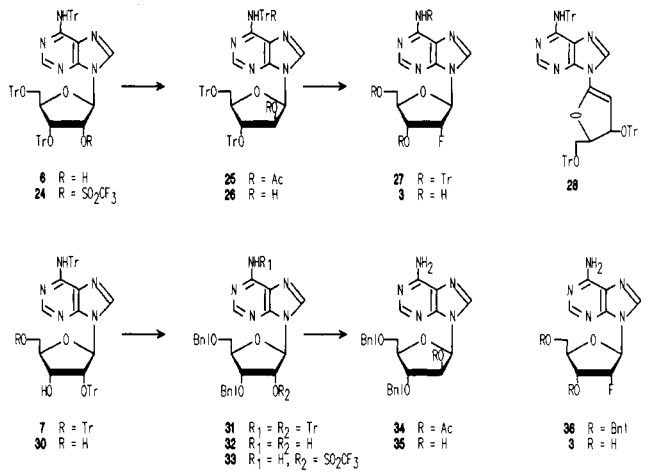


Figure 2.

Scheme III



exclusively. Facile elimination of an activated 2'-hydroxyl group [$COSF_2(NEt_2)$] from intermediate **21a** with formation of the olefins **22** and **23** is probably due to the C3' endo conformation of the sugar ring of **21a**, in which the hydrogen on C3' and the leaving group on C2' are in almost a trans diaxial configuration (Figure 2, A) favoring elimination over substitution. The same elimination products **22** and **23** were obtained when 2'-triflate **21b**[1] was treated with TASF. Ikehara et al.[26] reported that the amount of C3' endo conformer in 2'-substituted adenosines increases linearly with the electronegativity of the 2'-substituent. Thus, although **20** is in the C2' endo conformation, indicated by its rather large 1',2'-coupling constant (5.2 Hz), the conformation of 2'-triflate **21b** ($J_{1',2'}$ = 2.5 Hz) is rather C3' endo, favoring elimination.

The differences in the course of the reaction of the activated 2'-OH group of the corresponding *trityl*-protected nucleosides **6**, **15**, and **18** versus *benzyl*-protected derivative **20** may be explained on the basis of C3'-endo to C2'-endo conformational shift of these purine nucleosides. Thus, the two bulky trityl groups at O3' and O5' do shift the conformation of **6** ($J_{1',2'}$ = 7.4 Hz), **15** ($J_{1',2'}$ = 7.2 Hz),[1] and **18** ($J_{1',2'}$ = 7.1 Hz) toward C2'-endo (Figure 2, B) and probably preserve their C2'-endo conformation even after introduction of the electronegative 2'-*O*-triflyl group. Indeed, the sugar conformation of the 2'-triflate of **15** ($J_{1',2'}$ = 6.8 Hz)[1] is similar to that of the 3',5'-di-*O*-trityl derivative **15** but quite different from that of 3',5'-di-*O*-benzyl-2'-triflate **21b** ($J_{1',2'}$ = 2.5 Hz).[1] In order to ensure that similar conformational shift is responsible for elimination or nucleophilic displacement (by fluoride) of the activated 2'-hydroxyl group ($COSF_2NEt_2$) of the tribenzyl and tritrityl intermediates (**21a** and **10**, respectively), we performed molecular dynamics simulation and minimized energy structure for **21a** and **10** to determine their conformation at various temperatures. In the energy-minimized conformation of **21a** and **10**, the dihedral angle between H3' and O2' is 129.45° and 116.14°, respectively,

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(17) Detection of the alkoxy (dimethylamino) sulfur difluoride intermediate of 2'-deoxy-5'-*O*-(dimethoxytrityl)cytidine has been recently reported by: Agyei-Aye, K.; Yan, S.; Hebbler, A. K.; Baker, D. C. *Nucleosides Nucleotides* **1989**, *8*, 327.
(18) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1970**, *35*, 2319 and 2868.
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(24) MacCoss, M.; Ryu, E. K.; White, R. S.; Last, R. L. *J. Org. Chem.* **1980**, *45*, 788.
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(26) Uesugi, S.; Niki, H.; Ikehara, M.; Iwahashi, H.; Kyogoku, Y. *Tetrahedron Lett.* **1979**, 4073.

indicating that the latter is closer to diequatorial orientation than the former. Examination of the dynamic data set for equilibration and simulation of both **21a** and **10** at heating from 0 to 300 K showed that the dihedral angle between H3′ and O2′ in the average structure for **10** is 103° whereas that for **21a** is 121°. These results clearly endorse our prediction that **10** might undergo nucleophilic displacement to a certain extent, while **21a** yields predominantly the elimination products **22** and **23**. In the C2′-endo conformation, the hydrogen at C3′ and the 2′-leaving group are now in quasi *diequatorial* disposition as in B, which, as less amenable to β-elimination, should facilitate nucleophilic substitution with fluoride ion.

An examination of the ^{1}H NMR spectrum of the isomeric $O^{2'},O^{5'},N^6$-tritrityladenosine (**7**, Scheme III) revealed that the conformation of this nucleoside is the same as that of **6**, i.e., C2′-endo, as evidenced by ^{1}H NMR in $CDCl_3$ ($J_{1',2'}$ = 6.2 Hz, $J_{2',3'}$ = 4.2 Hz, and $J_{3',4'}$ = 0 Hz, i.e., dihedral angles between H1′ and H2′, H2′ and H3′, and H3′ and H4′ are approximately 145, 130 and 90°, respectively). Cook and Moffatt[27] found that 2′,5′-di-*O*-trityl-3′-ketouridine is much more stable than the free 3′-ketouridine. They attributed such a stability to the steric distortion of the furanose ring caused by the presence of bulky trityl groups *at both* C2′ and C5′ positions. We found, however, that selective 5′-*O*-detritylation of **7** did not change the C2′-endo conformation of the parent nucleoside **30** (vide infra). The unusual upfield shift of the H3′ signal both in **7** (δ 2.85) and **30** (δ 2.98) indicates a restricted rotation of the 2′-*O*-trityl group. This large diamagnetic shift of H3′ is, apparently, caused by an anisotropic effect of one of the phenyl groups of the 2′-*O*-trityl located just above the H3′. We found the same C2′-endo conformation and similar upfield shift of H3′ for 3′,5′-di-*O*-benzyl-2′-*O*-trityl-N^6-trityladenosine (**31**) and 2′,5′-di-*O*-tritylinosine (**17**). Cook and Moffatt also reported the similar diamagnetic shift of the resonance of H3′ for 2′,5′-di-*O*-trityluridine.[27] Thus, although steric repulsion of closely located 3′,5′-*O*-trityl groups seems to be responsible for enforcement of C2′-endo conformation for **6**, **15**, and **18**, other factors also play an important role in preserving the same C2′-endo conformation in 2′-*O*-trityl derivatives **7**, **17**, **30**, and **31**.

Direct introduction of fluorine at C2′ of purine nucleosides from the α-side of the sugar moiety is much less difficult than such nucleophilic substitution from the β-side. There are a number of reports on the synthesis of 2′-deoxy-2′-fluoroadenosine, -guanosine, and -inosine.[7,28-36] The tetrahydrofuranyl or the tetrahydropyranyl group was generally used for protection of the 3′- and 5′-hydroxyl groups, and usually the triflate group at C2′ in arabino configuration was displaced with fluoride ion ($Bu_4N^+F^-$) under mild conditions.

As mentioned earlier, we were also interested in preparing 2′-fluororibonucleosides from arabinosylpurines. It should be noted that in nucleophilic displacement of a 2′-β (arabino) function to introduce substituent to C2′ in the α (ribo) configuration, conformational factors also play an important role. In this case, the C2′-endo conformation of the starting nucleoside is not advantageous for fluorination with DAST, since the anomeric proton and C2′ leaving group are in trans diaxial disposition, making elimination imminent. Indeed, such elimination has been reported[28] when 9-(2-*O*-triflyl-3,5-di-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine was treated with Bu_4NF in THF. The expected 2′-deoxy-2′-fluoroadenosine was obtained in 50% yield, along with 9-(3,5-di-*O*-tetrahydropyranyl-2-deoxy-*erythro*-pent-1-enofuranosyl)-adenine, in 30% yield.[28] We converted the 3′,5′-di-*O*-trityl ribonucleoside **6** at C-2′ to the corresponding arabino nucleoside **26** (Scheme III), which was then treated with DAST. The reaction, however, resulted in the formation of a 2:1 mixture of 2′-deoxy-2′-fluoro-3′,5′-di-*O*-trityl-N^6-trityladenosine (**27**) and 9-(3,5-di-*O*-trityl-2-deoxy-*erythro*-pent-1-enofuranosyl)-N^6-trityladenosine (**28**). We therefore decided to use a smaller protecting group (such as benzyl) than trityl. As a starting material we used $O^{2'},O^{5'},N^6$-tritrityladenosine (**7**, Scheme III), which was formed as a byproduct in our synthesis of $O^{3'},O^{5'},N^6$-tritrityladenosine. Thus, nucleoside **7** was selectively 5′-detritylated[16] with HCOOH–Et_2O to give the $O^{2'},N^6$-ditrityl derivative **30**, which under treatment with BnlCl/KOH afforded the fully protected nucleoside **31**. Further detritylation of **31** with CF_3COOH–$CHCl_3$[17] gave 3′,5′-di-*O*-benzyladenosine (**32**). The attempted inversion of the ribo configuration of **32**, as well as **6** into **26** conversion, via oxidation–reduction[37] were in our hands unsuccessful. Although the oxidation reactions were accomplished we had difficulties in reduction of the corresponding keto nucleosides with $NaBH_4$. Since the reduction of the 2′,5′-di-*O*-trityl-3-keto- and 3′,5′-di-*O*-trityl-2-ketouridine was reported by Cook and Moffatt[27] as poorly selective reaction (xylo–ribo and arabino–ribo derivative ratio was 66:34 and 82:18, respectively) we abandoned this approach. Instead, the triflate nucleoside **33** was treated with sodium acetate to give 9-(2-*O*-acetyl-3,5-di-*O*-benzyl-β-D-arabinofuranosyl)adenine (**34**), and then the acetyl group of **34** was removed with methanolic ammonia. Finally, the nucleoside **35**, under treatment with DAST, afforded the desired fluoroadenosine derivative **36** in high yield without formation of the corresponding elimination product. Hydrogenolytic debenzylation of **36** gave the quantitative yield of 2′-deoxy-2′-fluoroadenosine (**3**).

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. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. ^{1}H NMR spectra were recorded on a JEOL FX90Q 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), bs (broad singlet), and (dd) (double doublet). Values given for coupling constants are first order.

Tritylation of Adenosine. A mixture of adenosine (**4**, 20 g, 75 mmol, dried by coevaporation with pyridine), DMAP (7.7 g, 63 mmol), and TrCl (70 g, 251 mmol) in pyridine (1 L) was heated at 80 °C. [The progress of the reaction was followed by TLC (MePh–EtOAc (85:15)).] Additional amounts of TrCl (20 g each) were added on the 2nd and 3rd day. The reaction was quenched with EtOH (300 mL) when **6** and **7** were in high concentrations and a small amount of **8** started appearing on TLC. The reaction

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mixture was concentrated in vacuo and coevaporated with MePh (3 × 500 mL). The residue was suspended in MePh (500 mL), shaken well, and filtered. The filtrate was concentrated in vacuo, the residue was dissolved in a mixture of MePh and EtOAc (85:15, 150 mL), and the solution was kept at room temperature until crystallization occurred (1–2 h). The crystalline **5** (8.4 g), mp 213–215 °C (lit.[14] mp 215–216 °C) was filtered, and the filtrate was applied on a column of silica gel (40 × 15 cm). The column was eluted with MePh–EtOAc (95:5) followed by MePH–EtOAc (85:15) and MePh–EtOAc–EtOH (4:1:1 v/v/v).

Compound **8** (4.5 g), mp 250–252 °C (EtOH), was eluted first: ^{1}H NMR (Me_2SO-d_6) δ 7.08–7.45 (30 H, m, 2 × Tr), 7.60, 7.90 (two 1 H, s, H2, 8); UV λ_{max} (MeOH) 276.5 (ε 19 281), λ_{max} (0.1 M HCl) 280.5, λ_{max} (0.1 M NaOH) 277.5; MS (FAB) *m/e* 620 (MH^+, 15), 376 (N^6-Tr-adenine ion, 45), 243 [$(C_6H_5)_3C^+$, 100], 165 [$(C_6H_5)_2CH^+$, 65, 136 (adenine-H^+, 45). Anal. Calcd for $C_{43}H_{33}N_5$: C, 83.33; H, 5.36; N, 11.30. Found: C, 83.22; H, 5.48; N, 11.29.

Compound **6** (15.3 g, 20.5%), mp 153–156 °C (EtOH) (lit.[14] mp 155–158 °C) was eluted next: ^{1}H NMR (Me_2SO-d_6) δ 2.56–2.63 (2 H, m, H5′,5″), 3.01–3.08 (1 H, m, H4′), 4.12–4.15 (1 H, m, H3′), 4.14 (1 H, t, H2′, $J_{2',3'}$ = 7.0 Hz), 6.10 (1 H, d, H1′, $J_{1',2'}$ = 7.4 Hz), 7.16–7.38 (45 H, m, 3 × Tr), 7.75, 8.29 (two 1 H, s, H2, 8); UV λ_{max}(MeOH) 275.5 (ε 23 670), λ_{max}(0.1 M HCl/MeOH) 276.5, λ_{max} (0.1 M NaOH/MeOH) 275.0); MS (FAB) *m/e* 994 (MH^+, 80), 376 (N^6-Tr-adenine, 20), 243 [$(C_6H_5)_3C^+$, 100], 165 [$(C_6H_5)_2CH^+$, 60], 136 (adenine-H^+, 100). Anal. Calcd for $C_{67}H_{55}N_5O_4$: C, 80.94; H, 5.57; N, 7.04. Found: C, 80.75; H, 5.49; N, 6.98.

Compound **7** (19.0 g, 25.5%) was then eluted, mp 151–154 °C (EtOH) (lit.[14] 153–157 °C): ^{1}H NMR (Me_2SO-d_6) δ 2.95–3.17 (3 H, m, H4′,5′,5″), 3.95–3.99 (1 H, m, H3′), 4.99–5.04 (1 H, m, H2′), 5.90 (1 H, d, H1′, $J_{1',2'}$ = 6.0 Hz), 7.08–7.42 (45 H, m, 3 × Tr), 7.59, 8.10 (two 1 H singlets, H2,8); MS (FAB) *m/e* 994 (MH^+, 30), 376 (N^6-Tr-adenine, 35), 243 [$(C_6H_5)_3C^+$, 100], 165 [$(C_6H_5)_2CH^+$, 80], 136 (adenine-H^+, 70). Anal. Calcd for $C_{67}H_{55}N_5O_4$: C, 80.94; H, 5.57; N, 7.04. Found: C, 80.80; H, 5.51; N, 6.95.

Finally, compound **5** (3.1 g, 20.5%) was eluted from the column, mp 213–215 °C (EtOH) (lit.[14] mp 215–216 °C).

Compound **5** (11.5 g, 153 mmol) was retritylated in a similar manner, and after silica gel column separation of **5**–**8**, additional amounts of **6** (10.8 g) and **7** (14.5 g) were obtained, increasing the overall yield of **6** and **7** to 35% and 45%, respectively.

Reaction of 6 with DAST. To a solution of DAST (8.06 g, 50 mmol, Aldrich) in dry CH_2Cl_2 (33 mL) containing pyridine (100 mmol, 10 mL) was added a solution of **6** (9.9 g, 10 mmol) in CH_2Cl_2 (66 mL). The mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 (200 mL), and the reaction was quenched by addition of 5% $NaHCO_3$ (50 mL). The organic layer was separated, washed with H_2O, and concentrated in vacuo, and the residue was chromatographed on a silica gel column with MePh–EtOAc (95:5) followed by CH_2Cl_2 containing 2.5% of EtOH to give **11** (3.0 g, 30.0%), mp 148–152 °C (EtOH): ^{1}H NMR δ (Me_2SO-d_6) 2.99–3.06 (2 H, m, H5′, 5″) 4.32 (1 H, m, H3′, $J_{3',F}$ = 15.1 Hz), 4.35 (1 H, m, H2′, $J_{2',F}$ = 51.1 Hz), 4.41 (1 H, m, H4′), 6.38 (1 H, m, H1′, $J_{1',F}$ = 20.0 Hz), 7.20–7.40 (45 H, m, 3 × Tr), 7.59 (1 H, s, NH), 7.85–7.89 (2 H, m, H-2, H-8); UV λ_{max}(MeOH) 274.0 (ε 17 800), λ_{max} (0.1 M HCl/MeOH) 275.5, λ_{max} (0.1 M NaOH/MeOH) 274.0; MS (FAB) *m/e* 997 (MH^+, 90), 755 (MH^+ – 243, 5), 376 (N^6-Tr-adenine, 50), 243 [$(C_6H_5)_3C^+$, 55], 165 [$(C_6H_5)_2CH^+$, 23]. Anal. Calcd for $C_{67}H_{54}FN_5O_3$: C, 80.78; H, 5.46; N, 7.03. Found: C, 80.71; H, 5.50; N, 7.00.

Compound **12** (5.08 g, 51%) was eluted next, mp 188–192 °C (EtOH): ^{1}H NMR δ ($CDCl_3$) 3.68 (1 H, dd, H-5′, $J_{4',5'}$ = 1.2 Hz, $J_{5',5''}$ = 11.0 Hz), 3.75 (1 H, dd, H-5″, $J_{4',5''}$ = 1.9 Hz), 4.80–4.90 (2 H, m, H-3′,4′), 5.00 (1 H, dd, H-2′, $J_{2',3'}$ = 3.2, $J_{2',F}$ = 14.6 Hz), 6.0 (1 H, d, H-1′, $J_{1',F}$ = 60.0 Hz), 6.90–7.40 (46 H, m, 3 × Tr, H-2), 8.00 (1 H, s, H-8); UV λ_{max} (MeOH) 304.0 (ε 14 050), λ_{max} (0.1 M HCl/MeOH) 298.0, λ_{max} (0.1 M NaOH/MeOH) 304.0. MS (FAB) *m/e* 997 (MH^+, 90), 755 [$(MH - 243)^+$, 10), 376 (N^6-Tr-adenine, 10), 243 [$(C_6H_5)_3C^+$, 100], 165 [$(C_6H_5)_2CH^+$, 40]. Anal. Calcd for $C_{67}H_{54}FN_5O_3 \cdot C_2H_5OH$. C, 79.51; H, 5.80; N, 6.72. Found: C, 79.55; H, 5.98; N, 6.65. Contamination of 1 mmol of C_2H_5OH was detected in the ^{1}H NMR spectrum at δ 1.22 (t) and 3.70 (q) of this sample, which was dried at 60 °C in vacuo for 4 h.

Detritylation of 8, 11, and 12. Compound **8** (100 mg) was dissolved in a mixture (1 mL) of CF_3COOH–$CHCl_3$ (1:9, v/v) and kept at room temperature for 1 h. The mixture was diluted with MePh (10 mL) and concentrated in vacuo. The residue was chromatographed on a silica gel column with $CHCl_3$–EtOH (3:1, v/v) to give adenine **9** (22 mg), the ^{1}H NMR spectrum of which was identical with that of an authentic sample.

Compound **11** (2.6 g, 2.6 mmol) was dissolved in a mixture (27 mL) of CF_3COOH and $CHCl_3$ (1:9 v/v) and kept at room temperature for 1 h. Toluene (100 mL) was added to the reaction mixture and concentrated in vacuo. The residue was coevaporated with toluene (2 × 100 mL) and dissolved in EtOH (200 mL), and the solution was neutralized by addition of Amberlite IRA-45. The resin was filtered, and the solution was concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–EtOH (19:1 v/v) followed by $CHCl_3$–EtOH (5:1, v/v) to give **1** (675 mg, 96%), mp 232–234 °C (lit.[2] mp 232–234 °C). The ^{1}H NMR spectrum of this sample was identical with that of authentic sample.[3]

Compound **12** (100 mg, 0.1 mmol) was treated with CF_3COOH–$CHCl_3$ as above. The residue was chromatographed on silica gel with $CHCl_3$–EtOH (3:1, v/v) to give adenine (17 mg).

Compound **12** (500 mg, 0.5 mmol) was dissolved in a mixture (10 mL) of HCOOH–Et_2O (1:1, v/v) and kept at room temperature for 30 min. The mixture was diluted with Et_2O (100 mL), washed with 10% $NaHCO_3$ (2 × 20 mL) and H_2O (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a silica gel column with $CHCl_3$ containing 1% of EtOH to give **13** (340 mg, 90%) as a foam: ^{1}H NMR ($CDCl_3$) δ 3.54 (1 H, dd, H5′, $J_{4',5'}$ = 1.0, $J_{5',5''}$ = 13.1 Hz), 4.03 (1 H, dd, H5″, $J_{4',5''}$ = 1.0 Hz), 4.69 (1 H, dd, H2′, $J_{2',F}$ = 14.5, $J_{2',3'}$ = 3.2 Hz), 4.86 (1 H, dd, H-4′, $J_{3',4'}$ = 5.4 Hz), 5.16 (1 H, dd, H-3′), 5.68 (1 H, d, H-1′, $J_{1',F}$ = 61.2 Hz), 6.76 (1 H, s, H-2), 6.98–7.31 (30 H, m, 2 × Tr), 7.80 (1 H, s, H-8); MS (FAB) *m/e* 755 (MH^+, 100), 512 [$(MH - 243)^+$, 15], 376 (N^6-Tr-adenine, 10), 243 [$(C_6H_5)_3C^+$, 100], 165 [$(C_6H_5)_2CH^+$, 40]. Anal. Calcd for $C_{48}H_{40}FN_5O_3$: C, 76.47; H, 5.35; N, 9.29. Found: C, 76.50; H, 5.36; N, 9.19.

Reaction of 15 with DAST. The solution of 3′,5′-di-*O*-trityl-N^1-benzylinosine[1] (2.0 g, 2.37 mmol) in CH_2Cl_2 (10 mL) containing pyridine (24 mmol, 2.4 mL) was treated with DAST (1.83 g, 11.3 mmol) as described for **6**. Purification on a silica gel column with CCl_4–EtOAc (3:1, v/v) afforded **16** (1.26 g, 63%) as a foam: ^{1}H NMR (Me_2SO-d_6) δ 3.00–3.02 (2 H, m, H5′,5″), 4.27 (1 H, d, H3′, $J_{3',F}$ = 19.0 Hz), 4.38 (1 H, s, H4′), 4.44 (1 H, dd, H2′, $J_{2',F}$ = 48.3, $J_{1',2'}$ = 3.0 Hz), 5.24 (2 H, s, CH_2Ph), 6.37 (1 H, dd, H1′, $J_{1',F}$ = 22.0 Hz), 7.27–7.32 (35 H, m, CH_2*Ph*, 2 × Tr), 7.72 (1 H, d, H8, $J_{8,F}$ = 2.2 Hz), 8.56 (1 H, s, H-2). Anal. Calcd for $C_{55}H_{45}FN_4O_4$: C, 78.18; H, 5.37; N, 6.63. Found: C, 78.25; H, 5.43; N, 6.63.

Tritylation of Inosine. Inosine (13.4 g, 50 mmol, dried by coevaporation with pyridine) was dissolved in the mixture of DMF (175 mL) and pyridine (100 mL), TrCl (42 g, 3 equiv) and DMAP (3.7 g) were added, and the mixture was heated at 80 °C for 16 h. The mixture was concentrated in vacuo and coevaporated with MePh (2 × 300 mL), and the residue was dissolved in $CHCl_3$ (500 mL). The solution was washed with H_2O (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a column of silica gel with AcOEt–hexane (40:60) followed by AcOEt–hexane (60:40), then AcOEt–hexane (70:30), and finally by AcOEt to give 2′,5′-di-*O*-tritylinosine (**17**, 6.3 g, 16.7%), mp 196–198 °C (EtOH): ^{1}H NMR (Me_2SO-d_6) δ 3.01–3.16 (3 H, m, H4′,5′,5″), 4.02 (1 H, m, H3′), 4.85–4.92 (2 H, m, H2′, OH) 5.94 (1 H, d, H1′, $J_{1',2'}$ = 6.03 Hz), 7.16–7.26 (30 H, m, 2 × Tr), 7.73, 8.01 (two 1 H s, H2,8), 12.15 (1 H, bs, NH). Anal. Calcd for $C_{46}H_{40}N_4O_5$: C, 76.57; H, 5.35; N, 7.44. Found: C, 76.32; H, 5.41; N, 7.39.

3′,5′-Di-*O*-tritylinosine (**18**, 4.6 g, 12.2%) was then eluted and obtained as a crystalline compound, mp 200–202 °C (EtOH): ^{1}H NMR (Me_2SO-d_6) δ 2.60–2.68 (2 H, m, H5′,5″), 3.04 (1 H, m, H4′), 4.10–4.14 (1 H, m, H3′), 4.74–4.78 (1 H, m, H2′), 6.09–6.14 (2 H, m, H1′, OH, become d, $J_{1',2'}$ = 7.14 Hz upon addition of D_2O), 7.07–7.65 (30 H, m, 2 × Tr), 7.95, 8.14 (two 1 H, s, H2,8), 12.21 (1 H, bs, NH). Anal. Calcd for $C_{46}H_{40}N_4O_5$: C, 76.57; H, 5.35; N, 7.44. Found: C, 76.40; H, 5.96; N, 7.40.

Reaction of 18 with DAST. The solution of **18** (753 mg, 1 mmol) in CH_2Cl_2 (5 mL) containing pyridine (10 mmol, 1 mL) was treated with DAST (806 mg, 5 mmol) as described for **15**. The residue was chromatographed on a silica gel column with CH_2Cl_2–MeOH (27:1 v/v) to give **19** (223 mg, 29.6%) as a foam:

^{1}H NMR (Me_2SO-d_6) δ 3.00–3.04 (2 H, m, H5′,5″), 4.29 (1 H, dd, $J_{3',F}$ = 16.5 Hz, $J_{3',4'}$ = 1.5 Hz), 4.34 (1 H, dd, H2′, $J_{2',F}$ = 51.5 Hz, $J_{1',2'}$ = 2.0 Hz), 4.38 (1 H, m, H4′), 6.35 (1 H, dd, H1′, $J_{1',F}$ = 20.0 Hz), 7.23–7.28 (30 H, m, 2 × Tr), 7.68 (1 H, d, H-8, $J_{F,8}$ = 2.7 Hz), 8.06 (1 H, s, H-2). Anal. Calcd for $C_{48}H_{39}FN_4O_4$·1.5 H_2O: C, 73.73; H, 5.23; N, 7.17. Found: C, 73.79; H, 5.43; N, 7.29. Approximately 1.5 mol of H_2O was detected in the ^{1}H NMR spectrum of this sample even after drying in vacuo overnight.

Reaction of 20 with DAST. 3′,5′-Di-*O*-benzyl-*N*^{1}-benzylinosine[1] (100 mg, 0.18 mmol) was treated with DAST (75 μL) as described for **15**. The residue was chromatographed on a silica gel column with $CHCl_3$–Me_2CO (20:1, v/v) to give **23**[1] (9 mg, 16%) followed by **22**[1] (40 mg, 41%). ^{1}H NMR spectra of **22** and **23** were identical with those of authentic samples.[1]

2′-*O*-Trifyl-3′,5′-di-*O*-trityl-*N*^{6}-trityladenosine (24). To a mixture of **6** (994 mg, 1 mmol), DMAP (120 mg, 1 mmol), and Et_3N (280 μL, 2 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of CF_3SO_2Cl (212 μL). The reaction mixture was stirred at room temperature, and the progress of the reaction was checked by TLC (MePh–EtOAc (95:5)). After the reaction was completed (30–40 min), the mixture was concentrated in vacuo, and the residue was chromatographed on a column of silica gel with MePh–EtOH (98:2) to give **24** (1.0 g, 88%) as a foam: ^{1}H NMR (Me_2SO-d_6) δ 2.83–2.95 (2 H, m, H5′,5″), 3.70–3.80 (1 H, m, H4′), 4.45–4.54 (1 H, m, H3′), 6.06 (1 H, m, H2′), 6.66 (1 H, d, H1′, $J_{1',2'}$ = 5.5 Hz), 7.15–7.27 (45 H, m, 3 × Tr), 7.54, 7.59 (two 1 H s, H2,8). Anal. Calcd for $C_{68}H_{54}F_3N_5O_6S$: C, 72.52; H, 4.83; N, 6.22. Found: C, 72.70; H, 5.00; N, 6.02.

9-(3,5-Di-*O*-trityl-β-D-arabinofuranosyl)-*N*^{6}-trityladenine (26). A mixture of **24** (1.13 g, 1 mmol) and AcONa (1.0 g, dried in vacuo at 60 °C overnight) in HMPA (20 mL) was stirred at room temperature for 3–4 h (TLC, MePh–EtOAc (95:5)) and then partitioned between EtOAc (200 mL) and H_2O (50 mL). The organic layer was separated, washed (H_2O, 3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was suspended in MeOH/NH_3 (100 mL), stirred 24 h, and concentrated in vacuo. TLC analysis showed a complete conversion of **25** into **26**, which surprisingly migrates faster than the starting acetyl derivative **25**. The residue was purified on a silica gel column (MePh–EtOAc (95:5)) to give **26** (875 mg, 88%) as a foam: ^{1}H NMR ($CDCl_3$) δ 3.00 (1 H, dd, H5′, $J_{4',5'}$ = 3.3 Hz, $J_{5',5''}$ = 10.3 Hz), 3.38 (1 H, dd, H5″, $J_{4',5''}$ = 2.5 Hz), 3.60 (1 H, dd, H-2′, $J_{1',2'}$ = 2.5 Hz, $J_{2',OH}$ = 9.33 Hz; collapsed to a doublet upon addition of D_2O), 3.96 (2 H, m, H3′,4′), 4.51 (1 H, d, OH), 6.28 (1 H, d, H1′), 6.95 (1 H, s, NH), 7.15–7.37 (45 H, m, 3 × Tr), 8.02, 8.28 (two 1 H s, H2,8). Anal. Calcd for $C_{67}H_{55}N_5O_4$: C, 80.94; H, 5.57; N, 7.04. Found: C, 80.81; H, 5.60; N, 7.00.

2′-Deoxy-2′-fluoro-3′,5′-di-*O*-trityl-*N*^{6}-trityladenosine (27) and 9-(3,5-Di-*O*-trityl-2-deoxy-*erythro*-pent-1-enofuranosyl)-*N*^{6}-adenine (28). Compound **26** (420 mg, 0.42 mmol) was treated with DAST (5 equiv) in the same manner as described for **6**. The reaction products were separated on a column of silica gel to give the faster migrating nucleoside **28** (125 mg, 30%) followed by derivative **27** (250 mg, 59.5%).

Compound **27** was obtained as a foam: ^{1}H NMR ($CDCl_3$) δ 2.83 (1 H, dd, H5′, $J_{4',5'}$ = 5.2 Hz, $J_{5',5''}$ = 11.0 Hz), 3.26 (1 H, dd, H5″, $J_{4',5''}$ = 1.6 Hz), 3.83–3.90 (1 H, m, H4′), 4.41 (1 H, ddd, H3′, $J_{2',3'}$ = 4.6 Hz, $J_{3',4'}$ = 7.5 Hz, $J_{3',F}$ = 14.3 Hz), 4.80 (1 H, ddd, H2′, $J_{1',2'}$ = 3.6 Hz, $J_{2',F}$ = 56.4 Hz), 6.22 (1 H, dd, H1′, $J_{1',F}$ = 14.6 Hz), 6.90 (1 H, s, NH), 7.10–7.41 (45 H, m, 3 × Tr), 7.71, 7.91 (two 1 H s, H2,8). Anal. Calcd for $C_{67}H_{54}FN_5O_3$: C, 80.78; H, 5.46; N, 7.03. Found: C, 80.70; H, 5.56; N, 6.93.

Compound **28** was isolated as a foam: ^{1}H NMR ($CDCl_3$) δ 2.54 (1 H, dd, H5′, $J_{4',5'}$ = 5.7, $J_{5',5''}$ = 10.5 Hz), 2.75 (1 H, dd, H5″, $J_{4',5''}$ = 2.2 Hz), 4.24–4.30 (1 H, m, H4′), 4.73–4.79 (1 H, m, H3′), 5.52 (1 H, d, H2′, $J_{2',3'}$ = 2.7 Hz), 6.97 (1 H, s, NH), 7.11–7.47 (45 H, m, 3 × Tr), 8.14 (2 H, s, H2,8). Anal. Calcd for $C_{67}H_{53}N_5O_3$: C, 82.42; H, 5.47; N, 7.17. Found: C, 82.37; H, 5.59; N, 6.97.

Reduction and Detritylation of 28. Compound **28** (100 mg) was dissolved in MeOH (5 mL), 10% Pd/C (50 mg) was added, and the mixture was shaken in a Parr hydrogenation apparatus for 2 h with an initial pressure of 40 psi. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give an anomeric mixture of 2′-deoxy-3′,5′-di-*O*-trityl-*N*^{6}-trityladenosine (**29**), which without purification was treated with 2 mL of $CHCl_3$/CF_3COOH (10%) for 1 h. The mixture was diluted with MePh (20 mL) and concentrated in vacuo. Several coevaporations with EtOH afforded a white foam. The ^{1}H NMR of this sample was identical with that of 1:1 anomeric mixture of 2′-deoxyadenosine.

2′-*O*-Trityl-*N*^{6}-trityladenosine (30). Compound **7** (16.0 g, 16.1 mmol) was dissolved in a mixture of Et_2O (300 mL) and HCO_2H (100 mL) and kept at room temperature for 24 h. The ethereal solution was decanted from white crystals which were washed with Et_2O (150 mL) and dried to give **30** (8.7 g). The filtrate and washings were combined, diluted with Et_2O (250 mL), and washed with 5% $NaHCO_3$ (5 × 200 mL) and then with water (2 × 200 mL). The solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on a silica gel column with MePh–EtOAc (95:5 followed by 85:15 and 70:30) to give an additional 2.0 g of **30**: yield 88.4%; ^{1}H NMR (Me_2SO_4-d_6) δ 2.98 (1 H, d, H3′, $J_{2',3'}$ = 4.1 Hz), 3.31 (1 H, d, H-5′, $J_{5',5''}$ = 11.8 Hz), 3.72 (1 H, d, H5″), 4.06 (1 H, s, H-4′), 5.06 (1 H, dd, H2′, $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 4.1 Hz), 6.05 (1 H, d, H1′) 7.06–7.41 (30 H, m, 2 × Tr), 7.76, 7.96 (two 1 H s, H2,8). Anal. Calcd for $C_{48}H_{41}N_5O_4$: C, 76.67; H, 5.51; N, 9.31. Found: C, 76.51; H, 5.60; N, 9.21.

3′,5′-Di-*O*-benzyl-2′-*O*-trityl-*N*^{6}-trityladenosine (31). To a solution of **30** (9.0 g, 11.96 mmol) in a mixture of C_6H_6 (115 mL) and dioxane (55 mL) were added powdered KOH (17.4 g, 0.31 mmol) and then BnlCl (8.15 mL, 71.15 mmol). The mixture was heated at reflux in an oil bath for 15 min. After cooling, the solution was decanted, and the solid residue was washed with C_6H_6 (200 mL). The combined organic solutions were washed with H_2O (50 mL), 0.1 N AcOH (2 × 20 mL), and H_2O (2 × 50 mL), then dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on a silica gel column with MePH–EtOAc (95:5) to give **31** (10.4 g, 93%) as a foam: ^{1}H NMR ($CDCl_3$) δ 2.98 (1 H, d, H3′, $J_{2',3'}$ = 4.7 Hz), 3.39 (1 H, dd, H5′, $J_{4',5'}$ = 2.7 Hz, $J_{5',5''}$ = 10.6 Hz), 3.53 (1 H, dd, H5″, $J_{4',5''}$ = 2.7 Hz), 4.19–4.26 (3 H, m, H4′, CH_2Ph), 4.42 (2 H, s, CH_2Ph), 5.12 (1 H, dd, H2′, $J_{1',2'}$ = 7.0 Hz, $J_{2',3,}$ = 4.7 Hz), 6.18 (1 H, d, H1′), 7.02–7.45 (40 H, m, 2 × Tr, 2 × CH_2*Ph*), 7.67, 7.89 (two 1 H s, H2,8). Anal. Calcd for $C_{62}H_{53}N_5O_4$: C, 79.89; H, 5.73; N, 7.51. Found: C, 80.06; H, 5.60; N, 7.29.

3′,5′-Di-*O*-benzyladenosine (32). Compound **31** (9.32 g, 10.0 mmol) was treated with a mixture of CF_3CO_2H in $CHCl_3$ (1:10 v/v, 90 mL) at room temperature for 1 h. The mixture was diluted with $CHCl_3$ (300 mL), washed with 5% $NaHCO_3$ (3 × 100 mL) and H_2O (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed with $CHCl_3$ followed by $CHCl_3$–MeOH (97:3 v/v) to give **32** (3.2 g, 72.4%) as a foam: ^{1}H NMR ($CDCl_3$) δ 3.56 (1 H, dd, H5′, $J_{4',5'}$ = 3.1 Hz, $J_{5',5''}$ = 10.5 Hz), 3.76 (1 H, dd, H5″, $J_{4',5''}$ = 3.0 Hz) 4.27–4.38 (2 H, m, H3′,4′), 4.52 (2 H, s, PhCH_2), 4.66–4.79 (3 H, m, H2′, PhCH_2), 6.06 (1 H, d, H1′, $J_{1',2'}$ = 4.9 Hz), 7.25–7.36 (10 H, 2 × *Ph*CH_2), 8.04, 8.25 (two 1 H s, H2,8). Anal. Calcd for $C_{24}H_{25}N_5O_4$: C, 64.43; H, 5.63; N, 15.65. Found: C, 64.37; H, 5.72; N, 15.71.

9-(3,5-Di-*O*-benzyl-2-*O*-triflyl-β-D-ribofuranosyl)adenine (33). Compound **32** (2.5 g, 5.6 mmol) and DMAP (5.6 mmol) were dissolved in CH_2Cl_2 (50 mL) containing Et_3N (1.6 mL, 11.2 mmol), and CF_3SO_2Cl (1.2 mL, 11.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was chromatographed on a silica gel column with $CHCl_3$–EtOH (97:3 v/v) to give **33** (2.8 g, 86%) as a foam: ^{1}H NMR (Me_2SO-d_6) δ 3.51 (1 H, dd, H5′, $J_{4',5'}$ = 3.2 Hz, $J_{5',5''}$ = 11.0 Hz), 3.87 (1 H, dd, H5″, $J_{4',5''}$ = 2.9 Hz), 4.36–4.45 (3 H, m, H4′, CH_2Ph), 4.67–4.84 (3 H, m, H3′, CH_2Ph), 6.06–6.16 (1 H, m, H2′), 6.44 (1 H, d, H1′, $J_{1',2'}$ = 3.5 Hz), 7.27–7.35 (10 H, m, 2 × CH_2*Ph*), 7.27, 7.35 (two 1 H s, H2,8). Anal. Calcd for $C_{25}H_{24}F_3N_5O_6S$: C, 51.81; H, 4.17; N, 12.08. Found: C, 51.68; H, 4.19; N, 11.89.

9-(3,5-Di-*O*-benzyl-β-D-arabinofuranosyl)adenine (35). A mixture of **33** (2.6 g, 4.53 mmol) and NaOAc (2.0 g) in HMPA (50 mL) was stirred overnight. The mixture was partitioned between EtOAc (300 mL) and H_2O (150 mL), and the organic layer was separated, washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The oily residue was dissolved in saturated NH_3/MeOH (100 mL) and kept at room temperature overnight. The mixture was concentrated in vacuo, and the residue was chromatographed on a silica gel column with $CHCl_3$ followed by $CHCl_3$–EtOH (3%) to give **35** (1.5 g, 78%) as a foam: ^{1}H NMR (Me_2SO-d_6) δ 3.68–3.73 (2 H, m, H5′,5″), 4.10–4.15 (2

H, m, H3′,4′), 4.40–4.53 (3 H, m, H2′, CH_2Ph), 4.66, 4.67 (two 1 H s, CH_2Ph), 6.27 (1 H, d, H1′, $J_{1',2'}$ = 4.6 Hz), 7.31–7.35 (10 H, m, 2 × CH_2Ph), 7.27, 7.35 (two 1 H s, H2,8). Anal. Calcd for $C_{24}H_{25}N_5O_4$: C, 64.44; H, 5.63; N, 15.65. Found: C, 64.39; H, 5.71; N, 15.50.

2′-Deoxy-2′-fluoro-3′,5′-di-*O*-benzyladenosine (36). Compound **35** (447 mg, 1 mmol, dried by coevaporation with pyridine) was dissolved in CH_2Cl_2 (5 mL), and this solution was added into a solution of DAST (660 μL, 5 mmol) containing pyridine (880 μL). The mixture was stirred overnight then diluted with CH_2Cl_2 (100 mL), and the reaction was quenched by addition of 5% $NaHCO_3$ (10 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$–EtOH (95:5 v/v) to give **36** (362 mg, 82%) as a foam: ^{1}H NMR ($CDCl_3$) δ 3.62 (1 H, dd, H5′, $J_{4',5'}$ = 3.3 Hz, $J_{5',5''}$ = 11.0 Hz), 3.90 (1 H, dd, H5″, $J_{4',5''}$ = 2.2 Hz), 4.38–5.15 (7 H, m, H2′,3′,4′, 2 × CH_2Ph), 5.78 (2 H, s, NH_2), 6.28 (1 H, dd, H1′, $J_{1',2'}$ = 2.0 Hz, $J_{1',F}$ = 16.7 Hz), 7.25–7.39 (10 H, m, 2 × CH_2Ph), 8.11, 8.50 (two 1 H, s, H2,8). Anal. Calcd for $C_{24}H_{24}N_5O_3F$: C, 64.13; H, 5.38; N, 15.58. Found: C, 63.87; H, 5.22; N, 15.39.

2′-Deoxy-2′-fluoroadenosine (3). To a solution of **36** (450 mg, 1 mmol) in MeOH (20 mL) was added 10% Pd/C (200 mg), and the mixture was shaken in a Parr hydrogenation apparatus (50 psi) overnight. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give **3** (250 mg, 93%), mp 232–234 °C (lit.[32] mp 233 °C). ^{1}H NMR of this sample was identical with that of an authentic sample.[30,31]

Molecular Modeling. Structures of **21a** and **10** were generated on a Silicon Graphics Iris Personal Workstation using the QUANTA software (Polygen Corporation), and the CHARMm progress was used for energy calculation. Each molecule was sketched with the ChemNote software (Polygen) to create a 2D structure with light atoms and bonds. The corrected 3D structure was furnished using a molecular editor. The minimized-energy conformations were obtained in two stages: the structures were initially minimized for 300 iterations with the steepest descents algorithm, followed by a 300-step minimization using the Adopted-basis Newton Raphson algorithm. The dynamics data set was generated in 300 steps from 0 to 300 K, followed by equilibration and simulation (300 iterations each). The time step for this process was 0.001 ps each.

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A New One-Step Synthesis of 8-Aminopurine Nucleoside Analogues from 6-(Glycosylamino)-5-nitrosopyrimidines[1]

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The reaction of 6-[[β-D-(per-*O*-acetyl)glycopyranosyl]amino]-5-nitrosopyrimidines (**1**) with $POCl_3$/formamide furnished 8-amino-9-[(per-*O*-acetyl)glycopyranosyl]purines (**2**) in good yield. In this reaction formamide seems to play a double role, as the source of the C(8)-amino group of the purine and as the agent responsible for the reduction of the C(5)-nitroso group of the pyrimidine to a hydroxylamino group. A mechanism which reflects this belief is presented. Chemical evidence that supports the mechanism is provided.

Introduction

There has been long-standing interest in the development of methods for the synthesis of 8-aminopurine nucleosides[2] because such compounds often display antimicrobial and antitumor activity. For example, lethal effects on the growth of 435 cultured rat hepatoma cells have been observed on treatment of the cells with 8-aminoadenosine 3′,5′-cyclic monophosphate derivatives.[3] Furthermore, 8-aminopurine nucleoside analogues are potent inhibitors of purine nucleoside phosphorylase.[4]

One synthesis of 8-aminopurine nucleosides involves the replacement of the bromine atom of an 8-bromopurine nucleoside precursor. Because the C(8) bromine cannot be directly displaced by ammonia,[2a] in contrast to its easy displacement by primary or secondary amines,[2a,b,5] the amino group must be introduced by treating the bromide with aqueous hydrazine[2] or by hydrogenating the azido group formed on treating the bromide with sodium azide in DMSO.[2a] Furthermore, no methods for producing the title compounds directly from 6-(glycosylamino)pyrimidines are known. The classical route to 8-aminopurines from such precursors, i.e., treating 4,5-diaminopyrimidines with guanidine or cyanogen bromide,[6] fails when a glycosyl moiety is attached to the pyrimidine.

A study of the reaction of 6-(glycosylamino)-5-nitrosopyrimidines with Vilsmeier-type reagents[1] showed that treating such pyrimidines with $POCl_3$/formamide provided 8-amino-9-glycosylpurines. Here we report the results of an investigation of this reaction.

Results and Discussion

The work described here is based on the finding of Yoneda and co-workers[7] that 8-(*N*-alkylamino)purines or

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