Synthesis of 2′-β-Fluoro- and 3′-α-Fluoro-Substituted Guanine Nucleosides. Effects of Sugar Conformational Shifts on Nucleophilic Displacement of the 2′-Hydroxy and 3′-Hydroxy Group with DAST[1]

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Tritylation of 2-*N*-acetyl-6-*O*-((4-nitrophenyl)ethyl)guanosine (**4**) with TrCl/DMAP followed by TrCl/$AgNO_3$ afforded a mixture of isomeric 3′,5′-di-*O*-trityl and 2′,5′-di-*O*-trityl derivatives **6** and **7**, which were separated on a silica gel column to give **6** and **7** in 40% and 50% yield, respectively. Upon treatment with DAST, **6** was converted into the corresponding 2′-β-fluoro nucleoside **8** in 43% yield. Deprotection of the 2-*N*-acetyl group occurred during the reaction. Removal of the 6-*O*-NPE group from **8** with DBU/pyridine, followed by detritylation with $CF_3COOH/CHCl_3$, gave F-ara-G (**1b**) in good yield. The same treatment of **7** with DAST did not lead to nucleophilic substitution with fluoride ion, but only decomposition took place. Treatment of the 2′,5′-di-*O*-trityl nucleoside **7** with CF_3SO_2Cl/DMAP in CH_2Cl_2, followed by $PhCO_2K$/HMPA, afforded the corresponding *xylofuranosyl* derivative **16** along with 6-O-deprotected nucleoside **19**. The 6-*O*-NPE group was completely removed in the reaction of triflate nucleoside **15** with CH_3CO_2Na/HMPA. The obtained diacetyl nucleoside **20** under hydrolysis with $Et_3N/MeOH/H_2O$ gave 9-(2,5-di-*O*-trityl-β-D-xylofuranosyl)guanine (**22**). Upon reaction of derivative **22** with DAST no formation of the desired 3′-fluoro nucleoside **23** was observed, but only decomposition took place. When, however, the triflate nucleoside **15** was treated with CH_3COONa in DMF instead of HMPA the corresponding diacetyl nucleoside **17** with intact 6-*O*-NPE group was obtained. This compound was hydrolyzed with $Et_3N/MeOH/H_2O$ to give the 2-*N*-acetyl derivative **18**, which was smoothly converted into the desired 3′-α-fluoro-substituted nucleoside **24** in 76% yield. Again, removal of the 2-*N*-acetyl group occurred during the reaction with DAST. Compound **24** was deprotected with DBU/pyridine followed by $CF_3COOH/CHCl_3$ to give 3′-fluoro-3′-deoxyguanosine in good yield (**3b**). In a similar manner the O^2,O^5,N^6-tritrityladenosine (**25**) was converted into the corresponding 3′-deoxy-3′-fluoroadenosine (**3a**).

Since it was established that introduction of fluorine into the 2′-β-position of nucleosides in general, and of purine nucleosides in particular (**1**, Figure 1), inhibits chemical and phosphorylase (PNP) catalyzed hydrolyses,[2] several 2′-β-fluoropurine dideoxynucleosides have recently been prepared[3-6] as potential anti-HIV-1 agents. Also, the 2′-β-fluoro analogues of fludarabine and other 2-halo derivatives of 9-β-D-arabinofuranosyladenine have been synthesized in order to improve their metabolic stability.[7,8] Very recently, studies of the hammerhead ribozyme sequences containing 2′-fluoro-2′-deoxyadenosine (**2a**) and -guanosine (**2b**) have been reported.[9,10] The 3′-fluoro-3′-deoxyadenosine (**3a**)[11-14] and -guanosine (**3b**)[14,15] have been synthesized, and their antiviral as well as cytostatic properties were evaluated.[13,14,16] The adenosine analogue **3a** was incorporated[17] into 2′,5′-oligoadenylate 5′-triphosphate, but the activity of the modified oligomer as potential interferon inducer has not been reported yet. Nucleosides **1–3**, where incorporated into oligonucleotides, may alter their physicochemical properties and consequently their interactions with biopolymers and enzymes.

Although the fluorinated sugar purine nucleosides have attracted attention in recent years, the methods for their synthesis are neither simple nor efficient. For example, 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)guanine (**1b**, **F-ara-G**) was synthesized in very low yield by coupling the 2-deoxy-2-fluoro-D-arabinofuranosyl bromide[18,19] with 2-acetamido-6-chloropurine[20] or 2,6-dichloropurine[21] followed by conversion of the aglycon into guanine. **F-ara-G** was found to exhibit selective T-cell toxicity.[20-22]

A method of direct introduction of a 2′-β-fluoro substituent into performed purine nucleosides has recently been reported from our laboratory.[1,23] We have shown that if the sugar moiety of a purine nucleoside was in the C-2′-endo conformation nucleophilic displacement of 2′-

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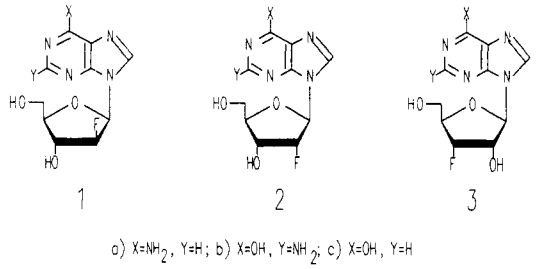


a) X=NH_2, Y=H; b) X=OH, Y=NH_2; c) X=OH, Y=H

Figure 1.

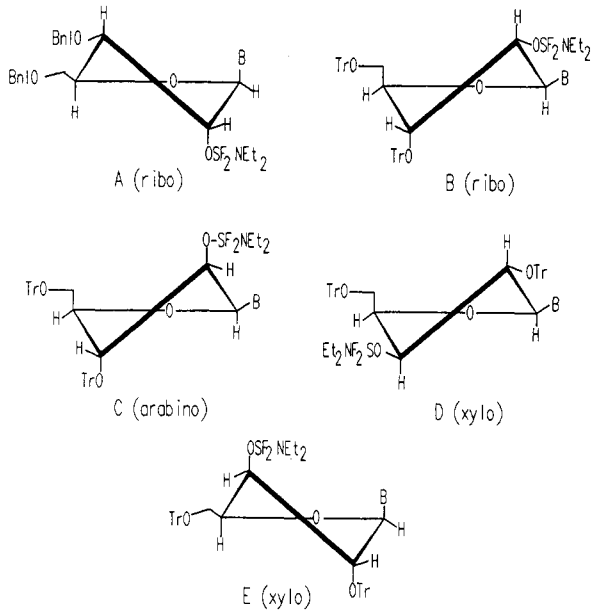
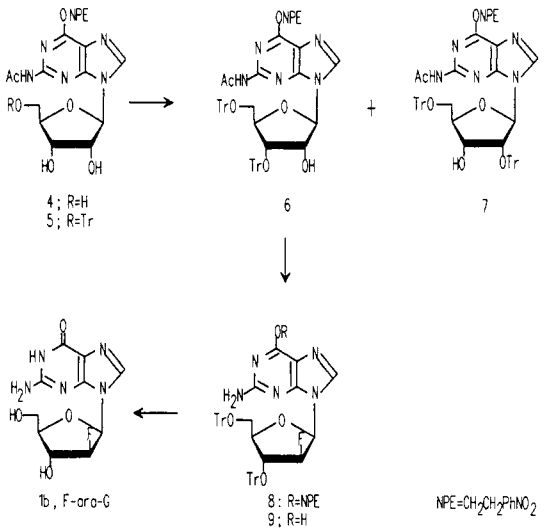


Figure 2.

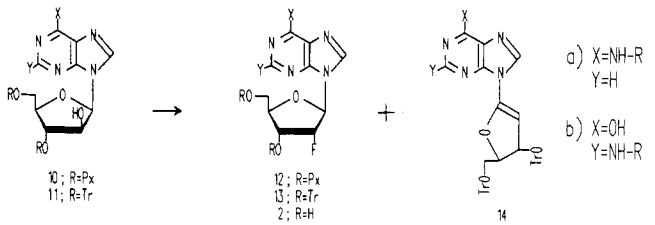
α-leaving group with fluoride ion took place. Little competitive, base-catalyzed elimination was observed. Using bulky 3′,5′-protecting groups, such as trityl groups, which promote the C3′-endo to C2′-endo conformational shift (**A** to **B**, Figure 2) and DAST as the fluorinating agent, we were able to displace the 2′-hydroxy function of 3′,5′-di-*O*-tritylinosine and -adenosine in 70% and 30%, respectively. After deprotection, 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)hypoxanthine (**1c, F-ara-H**) and -adenine (**1a, F-ara-A**) were obtained.[1,23]

Guanosine has not been converted into **F-ara-G** directly, due to difficulties in preparing the corresponding 3′,5′-di-*O*-trityl derivative. Although treatment of adenosine with trityl chloride (TrCl) in pyridine in the presence of 4-(dimethylamino)pyridine (DMAP) afforded the corresponding 2′,5′-di-*O*-trityl- and 3′,5′-di-*O*-trityl-N^6-trityladenosine[1] in good yield, a similar reaction of guanosine with TrCl gave decomposition products due presumably to the preferential N^7-tritylation. Thus, we prepared the 2-*N*-isobytyrylguanosine,[24] 2-((*N*-dimethylamino)-methylene)guanosine,[21] and 1-benzyl-2-((*N*-dimethylamino)methylene)guanosine[25] for tritylation. None of these derivatives afforded the desired di-O-tritylated nucleosides. However, when 2-*N*-acetyl-6-((4-nitrophenyl)-ethyl)guanosine[26,27] (**4**, Scheme I) was tritylated with

Scheme I



Scheme II



TrCl/DMAP (3 days at 80 °C with a large excess of TrCl), a mixture of the 5′-*O*-trityl-, 2′,5′-di-*O*-trityl-, and 3′,5′-di-*O*-tritylguanosine derivatives (**5, 6**, and **7**, respectively) was obtained. This mixture was separated on a column of silica gel to give **5, 6**, and **7** in 9%, 15%, and 20% yield, respectively. More stringent conditions to allow for complete conversion of **5** into a mixture of **6** and **7** produced excessive decomposition.

We found, however, that the di-O-tritylated guanosine derivatives **6** and **7** could be prepared effectively when **4** was treated first with TrCl/DMAP at room temperature for 3–4 days to give the 5′-*O*-trityl derivative **5** in 99% yield, which was then treated further with approximately 2 molar excess of TrCl and $AgNO_3$ in DMF containing 2,4,6-collidine[28,29] (overnight at room temperature). After chromatographic separation on a silica gel column, the 3′,5′-di-*O*-trityl derivative **6** and 2′,5′-regioisomer **7** were obtained in 40% and 50% yield, respectively.

Compound **6** was converted smoothly into 6-*O*-((4-nitrophenyl)ethyl)-9-(2-deoxy-2-fluoro-3,5-di-*O*-trityl-β-D-ribofuranosyl)guanosine (**8**) in 43.5% yield upon treatment with DAST. Apparently, the 2-*N*-acetyl protecting group was removed during the reaction. Further deprotection with DBU in pyridine[30] followed by $CF_3CO_2H/CHCl_3$[31]

(24) This compound was prepared by general procedure for N-acetylation by transient protection; see ref 26, p 25.

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(27) During the preparation of this manuscript, a paper entitled "N^2-Isobutyryl-O^6-[2-(p-Nitrophenyl)ethyl]guanine: A New Building Block for the Efficient Synthesis of Carbocyclic Guanosine Analogs" (Jenny, T. F.; Schneider, K. C.; Benner, S. A. *Nucleosides Nucleotides* **1992**, *11*, 1257 was published. The authors found that the title compound, in contrast to other guanine derivatives and precursors tested, allows the synthesis of different types of carbocyclic analogs of guanosine under Mitsunobu conditions. Only the desired N^9-substituted derivatives of guanine were formed. Although no explanation of this phenomenon was provided, it seems to be apparent from this and our studies that the 6-*O*-NPE group of the guanine prevents the possible involvement of N^7 during reaction.

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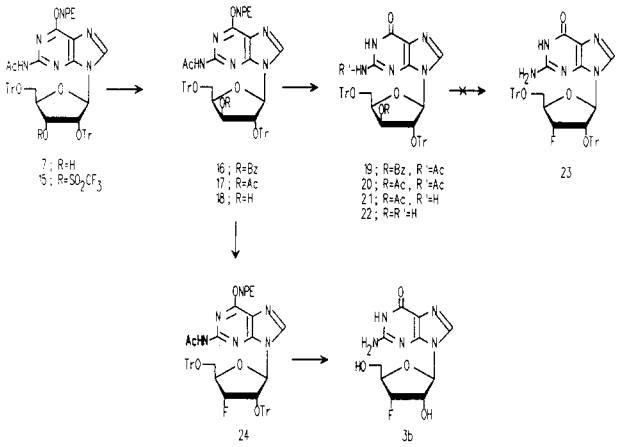
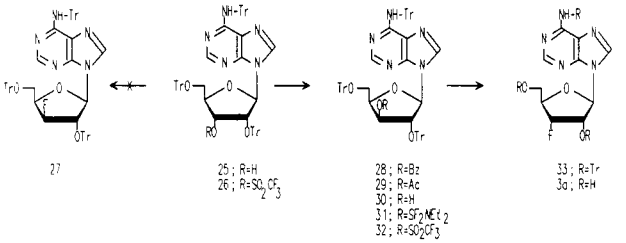
Scheme III



Scheme IV



gave **F-ara-G (1b)** in good yield.

In comparison to direct introduction of fluorine at C-2′ of preformed purine nucleosides from the β-side of the sugar ring by nucleophilic reaction, substitution at C-2′ from the α-side is much less difficult. Recently, Eckstein et al.[9] published the synthesis of **2a** and **2b** (Scheme II) via DAST treatment of the corresponding tripixyl derivatives **10a** and **10b**. The reported yield of **2a** was 43%. This is in agreement with our observation[1] on the conversion of N^6,$O^{3'}$,$O^{5'}$-tritrityl-9-β-D-ara-A (**11a**) into the 2′-α-fluoro-substituted derivative **13a** with DAST. The reaction gave a 2:1 mixture of the desired nucleoside **13a** and elimination product **14a**. Detritylation of **13a** with $CF_3CO_2H/CHCl_3$ afforded a good yield of 2′-fluoro-2′-deoxyadenosine (**2a**). Examination of the ^1H NMR spectrum of the tritrityl-protected arabino nucleoside **11a** revealed that inversion of configuration at C-2′ (ribo to arabino conversion) did not affect the sugar conformation of **11a**, which remains in the same C2′-endo conformation as its ribo precursor.[1] Since the anomeric proton and the leaving group at C-2′ are in the trans diaxial disposition as in **C** (Figure 2), elimination occurred to some extent even when nucleophilic substitution with fluoride ion is executed from the less hindered α-side of the sugar ring.

Earlier we demonstrated[1] the utilization of $O^{2'}$,$O^{5'}$,N^6-tritrityladenosine (formed as a byproduct) in the synthesis of 2′-α-fluoro-substituted adenosine. Although the corresponding $O^{2'}$,$O^{5'}$-ditrityl guanosine derivative **7** may also be converted into the 2′-α-fluoro-substituted guanosine in a similar manner, we focused our attention on the synthesis of the 3′-α-fluoro-substituted guanosine (**3b**) with **7** as the starting material. There are two published procedures for the synthesis of **3b**, but they are extremely laborious and inefficient. For example, Imbach[15] synthesized 3′-deoxy-3′-fluoroguanosine (**3b**) in 2% yield by treatment of 9-(2-*O*-(methoxytetrahydropyranyl)-5-*O*-(monomethoxytrityl)-β-D-xylofuranosyl)-2-*N*-(monomethoxytrityl)-guanine with DAST followed by deprotection. Also Mikhailopulo[14] obtained **3b** via condensation of 1-*O*-acetyl-2,5-di-*O*-benzoyl-3-fluoro-3-deoxy-α,β-D-ribofuranose with N^2-protected guanine. The formation of anomers (α,β) and regioisomers (N^7,N^9) made the condensation procedure inefficient.

Since the conformation of **7** is C2′-endo, we hoped that inversion of configuration at C3′ of the ditrityl derivative **7** (ribo to xylo conversion) would not alter dramatically (as it was the case in ribo to arabino conversion) the conformation of the inverted product **20** (Scheme III). If the xylo nucleoside **20** remains in the same C2′-endo conformation (**D**, Figure 2) in which the hydroxyl group at C3′ and H2′ are in cis, and H4′ and 3′-OH are in quasi diequatorial disposition, the possibility of elimination with formation of the 3′,4′-double bond should be markedly reduced.

The tritylated 9-β-D-xylofuranosylguanine **22** was prepared from **7** as shown in Scheme III. Tritylation of **7** gave **15**, which upon treatment with $PhCO_2K$/HMPA (12 h) was converted into a mixture of 2-*N*-acetyl-6-*O*-((4-nitrophenyl)ethyl)-9-(2,5-di-*O*-trityl-3-*O*-benzoyl-β-D-xylofuranosyl)guanine (**16**) and 2-*N*-acetyl-9-(2,5-di-*O*-trityl-3-*O*-benzoyl-β-D-xylofuranosyl)guanine (**19**). Apparently, the reaction medium was basic enough for β-elimination of the NPE protecting group. Deprotection of **16** with pyridine/DBU afforded a good yield of nucleoside **19**. Debenzoylation of **19** with $MeOH/NH_3$ gave a poor yield of deprotected nucleoside **22**, due to formation of elimination products and decomposition. When nucleoside triflate **15** was treated with CH_3CO_2Na/HMPA for 3 days, the NPE-deprotected diacetyl derivative **20** was obtained exclusively in good yield. Surprisingly, treatment of the diacetyl nucleoside **20** with Et_3N–MeOH–H_2O (4 h) removed only the 2-*N*-acetyl group, giving **21** with the intact 3′-*O*-acetyl function. Further hydrolysis (48 h) afforded the desired deacetylated product **22**.

Contrary to our expectations, the sugar conformation of nucleosides **16**, **19–22** was C3′-endo (**E**, Figure 2). The ^1H NMR spectrum of **22** revealed sharp singlets at δ 5.47, 4.54, and 3.77 for H1′, H2′, and H3′, respectively, showing that the dihedral angles between these hydrogen atoms were approximately 90°. Thus, we expected that elimination rather than nucleophilic substitution with fluoride ion would take place due to unfavorable trans diaxial disposition of the 3′-β-leaving group and H4′. Indeed, the tritylated 9-β-D-xylofuranosylguanine **22**, upon treatment with DAST, gave a host of decomposition products and no traces of the protected 3′-fluoro-3′-deoxyguanosine **23** was detected in the reaction mixture.

It was rather surprising that the reaction of tritylated 9-β-D-xylofuranosyladenine **30** with DAST afforded the desired 3′-fluoro-3′-deoxy compound **33** in 72% yield, as recently reported by Herdewijn et al.[12,13] The authors[12] commented that: "It is well known that changes in the conformations of the ribose ring upon protection may alter the course of the reaction. Therefore the reaction with DAST was tested on tritylated 9-β-D-xylofuranosyladenine" and then concluded[13] that: "a trityl group at 2′-O-position allowed nucleophilic displacement at the 3′-position with limited side reaction."

Our results, however, suggested that tritylated 9-β-D-xylofuranosylguanine **22** remains mainly in the undesired C3′-endo conformation which should make elimination imminent.

In order to investigate these differences we synthesized the adenine nucleoside **30** and compared its reaction with DAST with that of guanosine derivative **22**. As is depicted in Scheme IV, the 2′,5′-di-*O*-trityl-N^6-trityladenosine[1] (**25**)

(30) See ref 26, p 178.
(31) MacCoss, M.; Cameron, D. J. *Carbohydr. Res.* **1978**, *60*, 206.

was treated with triflyl chloride followed by BzONa/HMPA to give the 3′-*O*-benzoyl derivative **28**. Similar to debenzoylation of guanosine nucleoside **19**, hydrolysis of adenosine derivative **28** with $MeOH/NH_3$ gave a poor yield of deprotected nucleoside **30**, apparently due to formation of elimination products and decomposition. Fortunately, the conversion of the triflate **26** with AcONa to the 3′-*O*-acetyl derivative **29**, followed by mild hydrolysis with Et_3N–$MeOH$–H_2O, afforded **30** in good yield. Treatment of **30** with DAST gave the desired 3′-α-fluoro derivative **33** in 70% yield, as reported.[12] Detritylation of **33** with $CF_3COOH/CHCl_3$ afforded the 3′-fluoro-3′-deoxyadenosine (**3a**) in almost quantitative yield. This procedure using commercially available adenosine instead of xylofuranosyladenine is superior to the currently available methods in terms of steps involved and yields of reactions.

Examination of the ^1H NMR spectra of **28–30** revealed that the sugar conformation of all these adenosine nucleosides was the same as that of guanosine derivative **22**, i.e., C3′-endo. Sharp singlets in the spectrum of **30** at δ 5.45 and 4.57 for H1′ and H2′ (doublets for H1′ and H2′ were reported by Herdewijn et al.) as well as a doublet ($J_{3'-4'}$ = 3.1 Hz) at δ 3.95 for H3′, respectively, show that the dihedral angles between H1′ and H2′, H2′ and H3′, and H3′ and H4′ are approximately 90°, 90°, and 50°, respectively.

In order to find out if the conformation of the DAST-activated intermediate **31** remains the same as that of nucleoside **30**, the latter was converted into the triflate **32**. The triflate **32** was viewed as an analogue of **31**, since it contains a strongly electronegative leaving group. The ^1H NMR spectrum of **32** did not shown any conformational change. Sharp singlets at δ 6.42 and 4.38 and a doublet at δ 3.61 ($J_{3'-4'}$ = 2.0 Hz) confirmed the C3′-endo conformation of this triflate derivative.

Thus, since the conformation of the sugar moiety of nucleosides **22** and **30** is identical, some other factors must be responsible for the differences in reactivity of these nucleosides with DAST. The presence of the unprotected oxygen atom at the 6 position has long been correlated with degradation of guanine nucleosides. Therefore, we decided to check if the reaction of the 6-*O*-NPE protected derivative **18** with DAST would give the desired 3′-α-fluoro-substituted derivative. When the nucleoside triflate **15** was treated with CH_3COONa in DMF instead of HMPA, the 2-*N*-acetyl-3′-*O*-acetyl xylofuranosyl nucleoside (**17**) with intact 6-*O*-NPE protection was obtained. In contrast to the hydrolysis of **20** (removal of 2-*N*-acetyl group), treatment of **17** with $Et_3N/MeOH/H_2O$ removed the 3′-*O*-acetyl group to give nucleoside **18**. Compound **18** was smoothly converted into the desired 3′-α-fluoro-substituted nucleoside **24** in 76% yield. Again, removal of the 2-*N*-acetyl group occured during the reaction with DAST. Finally, compound **24** was deprotected with DBU/pyridine followed by $CF_3COOH/CHCl_3$ to give 3′-fluoro-3′-deoxyguanosine in good yield (**3b**).

In conclusion, it appears that conformational factors play an important role in reaction of DAST with the activated hydroxyl groups in the ribo configuration of purine nucleosides, but they are not that crucial in displacement of the 2′-β (arabino) and 3′-β (xylo) hydroxyl functions with fluoride ion. Nucleophilic attack by fluoride ion from the β-side of the sugar is extremely difficult, due to steric hindrance, which is why the C2′-endo conformation of 3′,5′-di-*O*-tritylinosine, -adenosine, and -guanosine derivatives (in which H3′ and 2′-OH are in the cis quasi diequatorial orientation) is absolutely essential for the displacement of the 2′-α-OH (ribo) with DAST.

The importance of conformational requirements in displacement of the 3′-α (ribo) hydroxy group of purine nucleosides with DAST may be illustrated by our unsuccessful experiments. We attempted to convert the 2′,5′-di-*O*-tritylguanosine and -adenosine derivatives (**7** and **25**, respectively, both with 3′-α-OH) into their corresponding 3′-β-fluoro (xylo) substituted analogues. These compounds upon treatment with DAST afforded a host of decomposition products. Since the conformation of **7** and **25** is C-2′-endo (see their ^1H NMR spectra in Experimental Section), in which H2′ and 3′-OH are in the trans quasi diaxial disposition, elimination instead of substitution took place preferentially.

When steric factors are in favor of the S_N2 conversion, as in the case of nucleophilic attack by fluoride ion from the less hindered α-side of nucleosides, the displacement of the 2′-β (arabino) as well as 3′-β (xylo) hydroxyl groups is not very troublesome. There are, however, differences in reactivity of the arabino and the xylo hydroxyl groups with DAST. It was reported[12] that the reaction of 3′-OH of 9-(2-deoxy-β-D-xylofuranosyl)adenine with DAST was completed within 1 h, whereas the same reaction with 2′-OH of 9-(3-deoxy-β-D-arabinofuranosyl)adenine required 14 h. Unfavorable electronic factors at C-2′, due to proximity to the anomeric center, are most probably responsible for such differences in reactivity.

Thus, when the tritylated ara-A derivative **11** was treated with DAST, substitution as well as elimination took place. Since nucleoside **11** remains in the C2′-endo conformation, in which the anomeric proton and 2′-OH are in the trans quasi diaxial disposition, elimination occurred to some extent even when the fluoride nucleophile attacked from the less hindered α-side. On the other hand, sterically and electronically favored nucleophilic displacement of the 3′-β (xylo) hydroxyl group of nucleosides **22** and **30** proceeds smoothly even in the unfavorable C3′-endo conformation.

Experimental Section

Melting points are 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. ^1H NMR spectra were recorded on a Bruker AMX-400 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 2-*N*-Acetyl-6-*O*-((4-nitrophenyl)ethyl)-guanosine (4). A. Procedure with DMAP. A mixture of **4** (9.48 g, 20 mmol, dried by coevaporation with pyridine), DMAP (4.8 g, 40 mmol), and TrCl (16.74 g, 60 mmol) was heated at 80–100 °C. Additional amounts of TrCl (5.6 g) and DMAP (2.4 g) were added on the second, third, and fourth day. The reaction mixture was cooled to room temperature and filtered. The filtrate was coevaporated with PhMe, and the residue was chromatographed on a silica gel column using $CHCl_3$–EtOH (1%), followed by $CHCl_3$–EtOH (2%) and $CHCl_3$–EtOH (4%) as the eluents. 2′,5′-Di-*O*-trityl derivative **7** (3.8 g, 20%) was eluted first: ^1H NMR ($CDCl_3$) δ 2.25 (3 H, s, Ac), 2.92 (1 H, d, H3′, $J_{2',3'}$ = 4.5 Hz), 2.97 (1 H, dd, H5′, $J_{4',5'}$ = 2.3 Hz, $J_{5',5''}$ = 10.6 Hz), 3.28 (1 H, dd, H5″, $J_{4',5''}$ = 2.3 Hz), 3.36 (2 H, t, (nitrophenyl)*ethyl*, J = 6.7 Hz), 4.04 (1 H, m, H4′), 4.84 (2 H, t, (nitrophenyl)*ethyl*), 4.97 (1 H, dd, H2′, $J_{1',2'}$ = 7.5 Hz, $J_{2',3'}$ = 4.5 Hz), 6.29 (1 H, d, H1′), 7.08–7.32 (30 H, m, 2×Tr), 7.54 (2 H, d, (*nitrophenyl*)ethyl, J = 8.6 Hz), 7.63 (1 H, s, NH), 8.02 (1 H, s, H8), 8.18 (2 H, d, (*nitrophenyl*)ethyl). Anal. Calcd for $C_{58}H_{50}N_6O_8$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.50; H, 5.36; N, 8.80.

3′,5′-Di-*O*-trityl nucleoside **6** (2.9 g, 15%) was then eluted: ^1H NMR ($CDCl_3$) δ 2.32 (3 H, s, Ac), 2.50 (1 H, d, H5′, $J_{5',5''}$ = 10.4

Hz), 3.15 (1 H, d, H5″), 3.30 (3 H, m, H4′, (nitrophenyl)*ethyl*), 4.25 (1 H, d, H3′, $J_{2',3'}$ = 3.6 Hz), 4.73 (1 H, dd, H2′, $J_{1',2'}$ = 6.1 Hz), 4.79 (2 H, t, (nitrophenyl)*ethyl*, J = 6.8 Hz), 6.10 (1 H, d, H1′), 7.06–7.45 (30 H, m, 2×Tr), 7.48 (2 H, d, (*nitrophenyl*)ethyl, J = 8.7 Hz), 7.85 (1 H, s, NH), 8.05 (1 H, s, H8), 8.13 (2 H, d, (*nitrophenyl*)ethyl). Anal. Calcd for $C_{58}H_{50}N_6O_8$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.48; H, 5.41; N, 8.78.

Finally, compound **5** (1.3 g, 9%) was eluted from the column. ^{1}H NMR ($CDCl_3$) δ 2.26 (3 H, s, Ac), 3.17 (1 H, dd, H5′, $J_{4',5'}$ = 2.9 Hz, $J_{5',5''}$ = 10.6 Hz), 3.30 (2 H, t, (nitrophenyl)*ethyl*, J = 6.7 Hz), 3.40 (1 H, dd, H5″, $J_{4',5''}$ = 3.3 Hz), 4.38 (1 H, d, H3′, $J_{2',3'}$ = 5.2 Hz), 4.46–4.47 (1 H, m, H4′), 4.80 (2 H, t, (nitrophenyl)*ethyl*, J = 6.7 Hz), 4.93 (1 H, dd, H2′, $J_{1',2'}$ = 6.2 Hz), 5.91 (1 H, d, H1′), 7.48 (2 H, d, (*nitrophenyl*)ethyl, J = 8.6 Hz), 8.13 (1 H, s, H8), 8.15 (2 H, (*nitrophenyl*)ethyl). Anal. Calcd for $C_{39}H_{36}N_6O_8$: C, 65.36; H, 5.06; N, 11.72. Found: C, 65.20; H, 5.09; N, 11.72.

B. Procedure with $AgNO_3$. A mixture of **4** (18.96 g, 40 mmol, dried by coevaporation with pyridine), TrCl (33.4 g, 120 mmol), and DMAP (4.8 g) was dissolved in pyridine (800 mL) and stirred at room temperature for 4 days. The mixture was concentrated in vacuo and coevaporated with PhMe (2 × 250 mL), and the residue was chromatographed on a silica gel column using $CHCl_3$–EtOH (1%) followed by $CHCl_3$–EtOH (3%) as eluents to give **5** (27.5 g, 98%) as a foam. To a mixture of **5** (33.0 g, 46 mmol) and TrCl (16.0 g, 57 mmol) in DMF (330 mL) containing 2,4,6-collidine (7.26 g, 60 mmol) was added $AgNO_3$ (9.2 g, 60 mmol), and the mixture was stirred at room temperature. Additional amounts of TrCl (16.0 g) and $AgNO_3$ (10.0 g) were added after 2 h and then again after 3 h [TrCl (8.0 g) and $AgNO_3$ (5.0 g)], and the stirring was continued overnight. The precipitated AgCl was removed by filtration, and the mixture was concentrated in vacuo. The residue was dissolved in $CHCl_3$ (500 mL), and the solution was washed with water (3 × 100 mL) and concentrated. The residue was chromatographed on a silica gel column using CCl_4–EtOAc (4:1 v/v) followed by CCl_4–EtOAc (3:1 v/v) and then CCl_4–EtOAc (1:1 v/v) to give **7** (22.1 g, 50.0%) followed by **6** (17.6 g, 40.0%).

Reaction of 6 with DAST. To a solution of DAST (4 mL, 6 equiv) in dry CH_2Cl_2 (70 mL) containing pyridine (4 mL) was added a solution of **6** (4.8 g, 5.0 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2 (500 mL). The solution was washed with 5% $NaHCO_3$ (100 mL) and water (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a silica gel column [CCl_4–EtOAc (4:1, v/v)] to give **8** (2.0 g, 43.5%) as a foam: ^{1}H NMR ($CDCl_3$) δ 3.14 (1 H, dd, H5′, $J_{4',5'}$ = 2.9 Hz, $J_{5',5''}$ = 10.1 Hz), 3.25–3.29 (3 H, m, H5″, (nitrophenyl)*ethyl*), 3.73 (1 H, dd, H2′, $J_{1',2'}$ = 2.2 Hz, $J_{2',F}$ = 50.1 Hz), 4.22 (1 H, dd, H3′, $J_{3',4'}$ = 2.4 Hz, $J_{3,F}$ = 15.4 Hz), 4.47 (1 H, m, H4′), 4.71–4.78 (2 H, m, (nitrophenyl)*ethyl*), 4.84 (2 H, brs, NH_2), 6.27 (1 H, dd, H1′, $J_{1',F}$ = 25.0 Hz), 7.21–7.40 (30 H, m, 2×Tr), 7.47 (2 H, d, (*nitrophenyl*)ethyl, J = 8.7 Hz), 7.71 (1 H, d, H8, $J_{8,F}$ = 3.6 Hz), 8.15 (2 H, d, (*nitrophenyl*)ethyl). Anal. Calcd for $C_{56}H_{47}N_6O_6F$: C, 73.18; H, 5.15; N, 9.14. Found: C, 73.35; H, 5.15; N, 9.11.

3′,5′-Di-*O*-trityl-F-ara-G (9). Compound **8** (919 mg, 1 mmol) was dissolved in a mixture of pyridine (20 mL) and DBU (10 mmol, 1.52 g) and kept at room temperature for 15 h. The reaction mixture was neutralized with AcOH (pH = 6) and concentrated in vacuo. The residue was coevaporated with PhMe, dissolved in CH_2Cl_2 (50 mL), washed with water (2 × 10 mL), and concentrated in vacuo. The residue was chromatographed on a silica gel column using $CHCl_3$–EtOH (5%, v/v) to give **9** (734 mg, 95%): ^{1}H NMR (Me_2SO-d_6) δ 2.99–3.08 (2 H, m, H5′,5″), 4.07 (1 H, d, H-2′, $J_{2',F}$ = 51.0 Hz), 4.22 (1 H, d, H3′, $J_{3',F}$ = 15.7 Hz), 4.36–4.37 (1 H, m, H4′), 6.09 (1 H, d, H1′, $J_{1',F}$ = 25.0 Hz), 6.62 (2 H, brs, NH_2), 7.27–7.44 (31 H, m, H8, 2×Tr), 10.69 (1 H, s, NH). Anal. Calcd for $C_{48}H_{40}N_5O_4F$: C, 74.88; H, 5.24; N, 9.10. Found: C, 75.00; H, 5.34; N, 8.94.

F-ara-G (1b). Compound **9** (5.0 g, 6.5 mmol) was dissolved in a mixture of CF_3CO_2H–$CHCl_3$ (1:9, v/v, 60 mL) and kept at room temperature for 3 h. The mixture was diluted with PhMe (50 mL) and concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O (300 mL:300 mL), and the aqueous layer was separated, neutralized with 5% $NaHCO_3$, and concentrated in vacuo. The crystalline **1b** (**F-ara-G**, 1.68 g, 91%, mp 250–251 °C (lit.[20] 250–251 °C)) was collected by filtration. The ^{1}H NMR spectrum of this sample was identical with that of an authentic sample.

2-*N*-Acetyl-6-*O*-((4-nitrophenyl)ethyl)-9-(2,5-di-*O*-trityl-3-*O*-triflyl-β-D-ribofuranosyl)guanine (15). To a solution of **7** (9.6 g, 10 mmol) and DMAP (1.2 g, 10 mmol) in CH_2Cl_2 (200 mL) containing Et_3N (2.8 mL, 20 mmol) was added dropwise a solution of CF_3SO_2Cl (2.12 mL, 20 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 30 min and then concentrated in vacuo. The residue was chromatographed on a silica gel column [CCl_4–EtOAc (2:1, v/v)] as the eluent to give **15** (9.6 g, 88%): ^{1}H NMR ($CDCl_3$) δ 2.20 (3 H, s, Ac), 3.16 (1 H, dd, H5′, $J_{4',5'}$ = 4.1 Hz, $J_{5',5''}$ = 10.7 Hz), 3.30–3.37 (3 H, m, H5″, (nitrophenyl)*ethyl*, 4.23–4.27 (1 H, m, H4′), 4.48 (1 H, d, H3′, $J_{2',3'}$ = 4.2 Hz), 4.78–4.84 (2 H, m, (nitrophenyl)*ethyl*), 5.53 (1 H, dd, H2′, $J_{1',2'}$ = 7.6 Hz), 6.04 (1 H, d, H1′), 7.03–7.36 (30 H, m, 2×Tr), 7.54 (2 H, d, (*nitrophenyl*)ethyl, J = 8.7 Hz), 7.82 (1 H, s, H8), 8.19 (2 H, d, (*nitrophenyl*)ethyl). Anal. Calcd for $C_{59}H_{49}N_6O_{10}SF_3$: C, 64.99; H, 4.53; N, 7.70. Found: C, 64.72; H, 4.52; N, 7.49.

2-*N*-Acetyl-6-*O*-((4-nitrophenyl)ethyl)-9-(2,5-di-*O*-trityl-3-*O*-benzoyl-β-D-xylofuranosyl)guanine (16) and 2-*N*-acetyl-9-(2,5-di-*O*-trityl-3-*O*-benzoyl-β-D-xylofuranosyl)-guanine (19). A mixture of **15** (3.0 g, 2.75 mmol) and $C_6H_5CO_2K$ (2.0 g) in HMPA (50 mL) was stirred at room temperature overnight and then partitioned between EtOAc (400 mL) and water (200 mL). The organic layer was separated, washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a silica gel column [$CHCl_3$–Me_2CO, 1%] to give **16** (800 mg, 37%): ^{1}H NMR ($CDCl_3$) δ 2.40 (3 H, s, Ac), 3.23 (1 H, dd, H5′, $J_{4',5'}$ = 5.7 Hz, $J_{5',5''}$ = 9.9 Hz), 3.29 (2 H, t, (nitrophenyl)*ethyl*, J = 6.7 Hz), 3.37 (1 H, dd, H5″, $J_{4',5''}$ = 6.3 Hz), 4.71–4.76 (3 H, m, H4′, (nitrophenyl)*ethyl*), 5.01 (1 H, s, H2′), 5.47 (1 H, d, H3′, $J_{3',4'}$ = 3.5 Hz), 5.75 (1 H, s, H1′), 7.08–7.47 (35 H, m, 2×Tr, Bz), 7.49 (2 H, d, (*nitrophenyl*)ethyl, J = 8.8 Hz), 7.69 (1 H, s, H8), 8.18 (2 H, d, (*nitrophenyl*)ethyl). Anal. Calcd for $C_{65}H_{54}N_6O_9$: C, 73.43; H, 5.12; N, 7.90. Found: C, 73.20; H, 5.13; N, 7.65.

Further elution of the column with $CHCl_3$–Me_2CO (5%) gave **19** (1.4 g, 56%): ^{1}H NMR ($CDCl_3$) δ 2.12 (3 H, s, Ac), 3.26 (1 H, dd, H5′, $J_{4',5'}$ = 6.0 Hz, $J_{5',5''}$ = 9.8 Hz), 3.36 (1 H, dd, H5″, $J_{4',5''}$ = 6.3 Hz), 4.85 (1 H, td, H4′, $J_{3',4'}$ = 3.3 Hz), 5.20 (1 H, s, H2′), 5.45 (1 H, d, H3′), 5.47 (1 H, s, H1′), 7.13–7.51 (36 H, 2×Tr, Bz, H8), 7.91 (1 H, s, NH), 11.63 (1 H, s, NH). Anal. Calcd for $C_{57}H_{47}N_5O_7$: C, 74.90; H, 5.18; N, 7.66. Found: C, 74.72; H, 5.25; N, 7.60.

Deprotection of 16. Nucleoside **16** (1.0 g, 1 mmol) was dissolved in pyridine (10 mL) containing DBU (1 g), and the mixture was stirred for 3 h. After neutralization with AcOH, the mixture was concentrated in vacuo and coevaporated with PhMe. The residue was chromatographed on a silica gel column [$CHCl_3$–EtOH, 2%] to give **19** (810 mg, 94%). The ^{1}H NMR spectrum of this sample was identical with that reported above.

2-*N*-Acetyl-6-*O*-((4-nitrophenyl)ethyl)-9-(2,5-di-*O*-trityl-3-*O*-acetyl-β-D-xylofuranosyl)guanine (17). A mixture of **15** (5.5 g, 5.0 mmol) and AcONa (5 g) in DMF (80 mL) was stirred for 3 days, and then the mixture was stirred at 70 °C for 5 h. The reaction mixture was partitioned between EtOAc (500 mL)–H_2O (250 mL), and the organic layer was separated, washed with water (2 × 150 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a column of silica gel with toluene–EtOAc (15%) to give **17** (4.3 g, 86%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.62 (3 H, s, OAc), 2.52 (3 H, s, NAc), 3.10 (1 H, dd, H5′, $J_{4',5'}$ = 5.7 Hz, $J_{5',5''}$ = 9.9 Hz), 3.27–3.33 (3 H, m, H5″, (nitrophenyl)*ethyl*), 4.52 (1 H, s, H2′), 4.57–4.61 (1 H, m, H4′), 4.79 (2 H, t, (nitrophenyl)*ethyl*, J = 6.7 Hz), 4.95 (1 H, d, H3′, $J_{3',4'}$ = 3.3 Hz), 6.06 (1 H, s, H1′), 7.13–7.40 (30 H, m, 2×Tr), 7.50 (2 H, d, (*nitrophenyl*)ethyl, J = 8.8 Hz), 7.70 (1 H, s, H8), 8.17 (2 H, d, (*nitrophenyl*)ethyl, J = 8.8 Hz. Anal. Calcd for $C_{60}H_{52}N_6O_9$: C, 71.98; H, 5.23; N, 8.39. Found: C, 71.67; H, 5.40; N, 8.40.

2-*N*-Acetyl-6-*O*-((4-nitrophenyl)ethyl)-9-(2,5-di-*O*-trityl-β-D-xylofuranosyl)guanine (18). Compound **17** (5 g, 5 mmol) was dissolved in a mixture of Et_3N–MeOH–H_2O (300 mL:300 mL:100 mL) and kept at room temperature overnight. The mixture was concentrated in vacuo, and the residue was used in the next step without purification. An analytical sample was obtained by silica gel column purification of crude **18** with

$CHCl_3$–acetone (5%) as the eluent: ^1H NMR ($CDCl_3$) δ 2.28 (3 H, s, NAc), 3.23 (2 H, t, (nitrophenyl)*ethyl*, J = 6.8 Hz), 3.39 (1 H, dd, H5′, $J_{4',5'}$ = 4.4 Hz, $J_{5',5''}$ = 10.6 Hz), 3.52 (1 H, dd, H5″, $J_{4',5''}$ = 6.4 Hz), 3.70 (1 H, s, H3′), 4.26 (1 H, dd, H4′), 4.51 (1 H, s, H2′), 4.69 (2 H, t, (nitrophenyl)*ethyl*, J = 6.8 Hz), 5.65 (1 H, s, H1′), 7.11–7.39 (30 H, m, 2×Tr), 7.41 (2 H, d, (*nitrophenyl*)ethyl, J = 8.7 Hz), 7.67 (1 H, s, H8), 8.09 (2 H, dd, (*nitrophenyl*)ethyl). Anal. Calcd for $C_{58}H_{50}N_6O_8$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.72; H, 5.31; N, 8.75.

2-*N*-Acetyl-9-(2,5-di-*O*-trityl-3-*O*-acetyl-β-D-xylofuranosyl)guanine (20). A mixture of **15** (3.0 g, 2.75 mmol) and CH_3CO_2Na (2.0 g) in HMPA (50 mL) was stirred at room temperature for 3 days and then partitioned between EtOAc (400 mL) and water (200 mL). The organic layer was separated, washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a silica gel column [$CHCl_3$–EtOH, 2%] to give **20** (2.18 g, 93%): ^1H ($CDCl_3$) δ 1.61 (3 H, s, Ac), 2.23 (3 H, s, Ac), 3.13 (1 H, dd, H5″, $J_{4',5'}$ = 5.5 Hz, $J_{5',5''}$ = 9.9 Hz), 3.28 (1 H, dd, H5″, $J_{4',5''}$ = 6.3 Hz), 4.54 (1 H, s, H2′), 4.88 (1 H, d, H3′, $J_{3',4'}$ = 3.2 Hz), 5.85 (1 H, s, H1′), 7.17–7.39 (30 H, m, 2×Tr), 7.54 (1 H, s, H8), 8.23 (1 H, s, NH), 11.88 (1 H, s, NH). Anal. Calcd for $C_{52}H_{45}N_5O_7$: C, 73.31; H, 5.35; N, 8.65. Found: C, 73.48; H, 5.43; N, 8.03.

9-(2,5-Di-*O*-trityl-3-*O*-acetyl-β-D-xylofuranosyl)guanine (21). A solution of **20** (852 mg, 1 mmol) in a mixture of Et_3N–MeOH–H_2O (3:3:1, v/v, 50 mL) was kept at room temperature for 4 h and then concentrated in vacuo. The residue was crystallized from MeOH to give **21** (600 mg, 74%): mp 255–256 °C; ^1H NMR ($CDCl_3$) δ 1.65 (3 H, s, Ac), 3.12 (1 H, dd, H5′, $J_{4',5'}$ = 6.0 Hz, $J_{5',5''}$ = 9.8 Hz), 3.31 (1 H, dd, H5″, $J_{4',5''}$ = 6.0 Hz), 4.52–4.55 (2 H, m, H2′,4′), 4.91 (1 H, d, H3′, $J_{3',4'}$ = 3.1 Hz), 5.92 (1 H, s, H1′), 6.25 (2 H, brs, NH_2-exchg), 7.16–7.43 (31 H, m, 2×Tr, H8), 11.98 (1 H, s, NH-exchg). Anal. Calcd for $C_{50}H_{43}N_5O_6$: C, 74.15; H, 5.35; N, 8.65. Found: C, 74.08; H, 5.50; N, 8.50.

9-(2,5-Di-*O*-trityl-β-D-xylofuranosyl)guanine (22). A solution of **20** (8.5 g, 10 mmol) in Et_3N–MeOH–H_2O was left standing for 48 h and then concentrated in vacuo. The residue was chromatographed on a silica gel column with $CHCl_3$–EtOH (3%) and then crystallized from CH_2Cl_2–MeOH to give **22** (6.3, 82%): mp 253–255 °C; ^1H NMR ($CDCl_3$) δ 3.44 (1 H, dd, H5′, $J_{4',5'}$ = 4.6 Hz, $J_{5',5''}$ = 10.4 Hz), 3.51 (1 H, dd, H5″, $J_{4',5''}$ = 6.4 Hz), 3.78 (1 H, d, H3′, $J_{3',4'}$ = 2.6 Hz), 4.25 (1 H, m, H4′), 4.54 (1 H, s, H2′), 5.48 (1 H, s, H1′), 6.99 (1 H, s, H8), 7.16–7.42 (30 H, m, 2×Tr). Anal. Calcd for $C_{48}H_{41}N_5O_5$: C, 75.08; H, 5.38; N, 9.12. Found: C, 74.98; H, 5.46, N, 9.15.

2-*N*-Acetyl-6-*O*-((4-nitrophenyl)ethyl)-9-(2,5-di-*O*-trityl-3-deoxy-3-fluoro-β-D-ribofuranosyl)guanine (24). The solution of **18** (9.6 g, 10 mmol) in CH_2Cl_2 (250 mL) was added into a solution of DAST (4.0 mL, 3 equiv) in CH_2Cl_2 (200 mL) containing pyridine (0.8 mL). The reaction mixture was stirred at room temperature for 4 h then diluted with CH_2Cl_2 (500 mL) and washed with 5% $NaHCO_3$. The organic layer was separated, washed with H_2O, and concentrated in vacuo, and the residue was chromatogaphed on a silica gel column with $CHCl_3$–acetone (1%) to give **24** (7.3 g, 76%): ^1H NMR ($CDCl_3$) δ 2.95 (1 H, dd, H5′, $J_{4',5'}$ = 3.1 Hz, $J_{5',5''}$ = 10.5 Hz), 3.30–3.34 (3 H, m, H5″, (nitrophenyl)*ethyl*), 3.55 (1 H, dd, H3′, $J_{2',3'}$ = 3.9 Hz, $J_{2',F}$ = 53.4 Hz), 4.20 (1 H, two m, H4′, $J_{4',F}$ = 28.1 Hz), 4.80 (2 H, t, (nitrophenyl)*ethyl*, J = 6.7 Hz), 4.95 (1 H, ddd, H2′, $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 3.9 Hz, $J_{2',F}$ = 20.1 Hz), 6.18 (1 H, d, H1′), 7.09–7.37 (30 H, m, 2×Tr), 7.53 (2 H, d, (*nitrophenyl*)ethyl, J = 8.7 Hz), 7.74 (1 H, s, H8), 8.19 (2 H, d, (*nitrophenyl*)ethyl). Anal. Calcd for: $C_{58}H_{49}N_6O_7F$: C, 72.48; H, 5.14; N, 8.74. Found: C, 72.19; H, 5.27, N, 8.68.

3′-Deoxy-3′-fluoroguanosine (3b). Compound **24** (961 mg, 1 mmol) was dissolved in pyridine (10 mL) containing DBU (500 mg), and the mixture was stirred for 3 h. After neutralization with AcOH, the mixture was concentrated in vacuo and coevaporated with PhMe, and the residue was dissolved in a mixture of CF_3CO_2H–$CHCl_3$ (1:9, v/v, 10 mL). The mixture was stirred at room temperature for 4 h and then diluted with PhMe (50 mL) and concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O (200 mL:200 mL), and the aqueous layer was separated, neutralized with 5% $NaHCO_3$ and concentrated in vacuo. The crystalline **3b** (200 mg, 70%, mp 288–290 °C (lit.[14] mp 289–291 °C)) was collected by filtration. The ^1H NMR spectrum of this sample was identical with that of an authentic sample.

9-(2,5-Di-*O*-trityl-3-*O*-triflyl-β-D-ribofuranosyl)-6-trityladenine (26). To a mixture of **25**[1] (8.7 g, 8.75 mmol), DMAP (1.05 g, 8.75 mmol), and Et_3N (2.4 mL, 17.5 mmol) in CH_2Cl_2 (150 mL) was added a solution of CF_3SO_2Cl (1.9 mL, 17.5 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at room temperature for 30 min and then concentrated in vacuo. The residue was chromatographed on a column of silica gel with PhMe–EtOAc (2%) as the eluent to give **26** (9.25 g, 97%) as a foam: ^1H NMR ($CDCl_3$) δ 3.14 (1 H, dd, H5′, $J_{4',5'}$ = 4.8 Hz, $J_{5',5''}$ = 10.3 Hz), 3.34 (1 H, dd, H5″, $J_{4',5''}$ = 7.5 Hz), 4.30–4.34 (2 H, m, H3′,H4′), 5.94 (1 H, dd, H2′, $J_{1',2'}$ = 7.8 Hz, $J_{2',3'}$ = 4.4 Hz), 6.11 (1 H, d, H1′), 6.90–7.38 (45 H, m, 3×Tr), 7.54, 7.87 (two 1 H s, H2, H8). Anal. Calcd for $C_{68}H_{54}N_5O_6SF_3$: C, 72.52; H, 4.83; N, 6.22. Found: C, 72.71; H, 5.02; N, 6.04.

9-(2,5-Di-*O*-trityl-3-*O*-benzoyl-β-D-xylofuranosyl)-6-tritylladenine (28). A mixture of **26** (2.3 g, 2.0 mmol) and $PhCO_2Na$ (2.0 g) in HMPA (50 mL) was stirred overnight and then partitioned between EtOAc (300 mL) and water (100 mL). The organic layer was separated, washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a silica gel column using PhMe–EtOAc (2%) as the eluent to give **28** (1.8 g, 80%) as a foam: ^1H NMR ($CDCl_3$) δ 3.25 (1 H, dd, H5′, $J_{4',5'}$ = 6.3 Hz, $J_{5',5''}$ = 9.7 Hz), 3.37 (1 H, dd, H5″, $J_{4',5''}$ = 6.1 Hz), 4.58–4.62 (1 H, m, H4′), 4.76 (1 H, s, H2′), 5.43 (1 H, d, H3′, $J_{3',4'}$ = 3.0 Hz), 5.98 (1 H, s, H1′), 6.99–7.98 (52 H, m, 3×Tr, Bz, H2, H8). Anal. Calcd for $C_{74}H_{59}N_5O_5$: C, 80.92; H, 5.41; N, 6.38. Found: C, 80.87; H, 5.52: N, 6.43.

9-(2,5-Di-*O*-trityl-3-*O*-acetyl-β-D-xylofuranosyl)-6-tritylladenine (29). Compound **26** (5.5 g, 5.0 mmol) was treated with CH_3CO_2Na (5.0 g) in HMPA (70 mL, 48 h) as described above. After a silica gel column purification [PhMe–EtOAc (3%)], **29** (5.06 g, 97%) was obtained as a foam: ^1H NMR ($CDCl_3$) δ 1.64 (3 H, s, Ac), 3.13 (1 H, dd, H5′, $J_{4',5'}$ = 5.8 Hz, $J_{5',5''}$ = 9.8 Hz), 3.30 (1 H, dd, H5″, $J_{4',5''}$ = 6.0 Hz), 4.47–4.51 (1 H, m, H4′), 4.53 (1 H, s, H2′), 4.89 (1 H, d, H3′, $J_{3',4'}$ = 3.0 Hz), 6.12 (1 H, s, H1′), 7.09–7.38 (45 H, m, 3×Tr), 7.63, 8.02 (two 1 H singlets, H2, H8). Anal. Calcd for $C_{69}H_{57}N_5O_5$: C, 79.97; H, 5.54; N, 6.76. Found: C, 80.14; H, 5.77; N, 6.54.

9-(2,5-Di-*O*-trityl-β-D-xylofuranosyl)-6-tritylladenine (30). Compound **29** (5.0 g, 4.8 mmol) was dissolved in a mixture of Et_3N–MeOH–H_2O (150:100:50 mL), and the solution was stirred for 48 h. The precipitated product was filtered, washed with MeOH, and dried to give crystalline **30** (4.5 g, 98%): mp 222–224 °C (lit.[12] mp 240 °C); ^1H NMR ($CDCl_3$) δ 3.45 (1 H, dd, H5′, $J_{4',5'}$ = 3.9 Hz, $J_{5',5''}$ = 10.8 Hz), 3.55 (1 H, dd, H5″, $J_{4',5''}$ = 7.5 Hz), 3.95 (1 H, d, H3′, $J_{3',4'}$ = 3.1 Hz), 4.29–4.31 (1 H, m, H4′), 4.56 (1 H, s, H2′), 5.45 (1 H, s, H1′), 7.06–7.76 (47 H, m, 3×Tr, H2, H8). Anal. Calcd for $C_{67}H_{55}N_5O_4$: C, 80.94: H, 5.57; N, 7.04. Found: C, 80.75; H, 5.74; N, 6.89.

9-(2,5-Di-*O*-trityl-3-*O*-triflyl-β-D-xylofuranosyl)-6-tritylladenine (32). To a mixture of **30** (136 mg, 0.14 mmol), DMAP (17 mg, 0.14 mmol), and Et_3N (40 μL, 0.28 mmol) in CH_2Cl_2 (5 mL) was added CF_3SO_2Cl (30 μL, 0.28 mmol), and the mixture was stirred at room temperature for 30 min. After concentration of the mixture in vacuo, the residue was chromatographed on a silica gel column with PhMe–EtOAc (3%) as the eluent to give **32** (120 mg, 78%) as a foam: ^1H NMR ($CDCl_3$) δ 3.16 (1 H, dd, H5′, $J_{4',5'}$ = 7.9 Hz, $J_{5',5''}$ = 10.2 Hz), 3.56 (1 H, dd, H5″, $J_{4',5''}$ = 6.5 Hz), 3.61 (1 H, d, H3′, $J_{3',4'}$ = 2.0 Hz), 4.00–4.04 (1 H, m, H4′), 4.38 (1 H, s, H2′), 6.42 (1 H, s, H1′), 7.06–7.36 (45 H, m, 3×Tr), 7.63, 8.02 (two 1 H singlets, H2, H8).

9-(2,5-Di-*O*-trityl-3-deoxy-3-fluoro-β-D-ribofuranosyl)-6-tritylladenine (33). Compound **30** (4.2 g, 4.2 mmol) was treated with DAST (3 equiv, 1.67 mL) in the same manner as described for **6**. A silica gel column purification with CCl_4–EtOAc (5%) afforded the fluoro nucleoside **33** (3.15 g, 75%): ^1H NMR ($CDCl_3$) δ 3.02 (1 H, dd, H5′, $J_{4',5'}$ = 3.7 Hz, $J_{5',5''}$ = 10.4 Hz), 3.28 (1 H, dd, H5″, $J_{4',5''}$ = 4.8 Hz), 3.55 (1 H, dd, H3′, $J_{2',3'}$ = 4.0 Hz, $J_{3',F}$ = 53.1 Hz), 4.20 (1 H, pseudo dt, H4′, $J_{4',F}$ = 27.2 Hz), 5.16 (1 H, ddd, H2′, $J_{1',2'}$ = 7.6 Hz, $J_{2',F}$ = 21.6 Hz), 6.22 (1 H, d, H1′), 7.02–7.43 (45 H, m, 3×Tr), 7.76, 7.83 (two 1 H singlets, H2, H8). Anal. Calcd for $C_{67}H_{54}N_5O_3F$: C, 80.78; H, 5.46; N, 7.03. Found: C, 80.80; H, 5.56; N, 6.98.

3'-Deoxy-3'-fluoroadenosine (3a). Compound **33** (0.3 g, 0.3 mmol) was treated with a mixture of CF_3CO_2H–$CHCl_3$ as described for **1b**. The crystalline **3a** (76.0 mg, 94%) had mp 210–211 °C (lit.[13] mp 205 °C; lit.[14] mp 211–212 °C). ^1H NMR of this sample was identical with that reported earlier.[14]

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Characterization of an Unexpected Product from a Monoamine Oxidase B Generated 2,3-Dihydropyridinium Species

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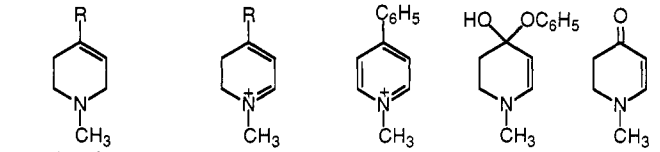
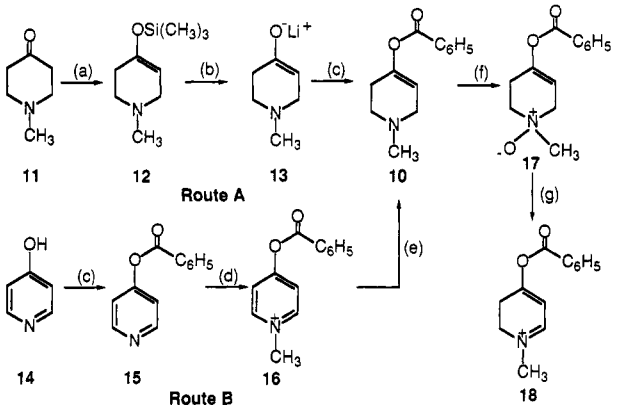
This report summarizes the unexpected properties of the 2,3-dihydropyridinium species generated by the monoamine oxidase B catalyzed oxidation of 4-(benzoyloxy)-1-methyl-1,2,3,6-tetrahydropyridine, an analog of the neurotoxic 4-phenyltetrahydropyridine derivative. Unlike the corresponding 4-aryloxy and 4-carbamoyloxy derivatives which undergo rapid hydrolytic cleavage via a 1,4-addition of water, the benzoyloxy metabolite undergoes a 1,2-addition reaction to yield a carbinolamine that subsequently rearranges to a β-keto aldehyde that was characterized as the corresponding pyrazole. From these results it appears that, under physiological conditions, 2,3-dihydropyridinium species in general may exist in equilibrium with the corresponding carbinolamines and ring-opened amino aldehydes, species which may be of importance in understanding the chemical and biological properties of these heterocyclic systems.

The neurotoxic cyclic allylamine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1**) is an excellent substrate for brain monoamine oxidase B (MAO-B) which catalyzes its bioactivation to the dihydropyridinium species **2**,[1,2] an unstable intermediate that spontaneously oxidizes to the putative ultimate toxin **3**.[3] In contrast to this behavior, the corresponding phenoxy derivative **4** generates the dihydropyridinium metabolite **5** which rapidly hydrolyzes, presumably via the hemiketal **6**, to yield the amino enone **7** and phenol. Analogous behavior has been observed with carbamoyloxy analogs (**8**, R' = CH_3 and C_6H_5) which are converted via **9** to **7** and dimethylamine or *N*-methylaniline.[4] The possibility of developing tetrahydropyridine derivatives bearing biologically active moieties that are released in the central nervous system following enzymatic bioactivation has prompted the chemical and metabolic studies on 4-(benzoyloxy)-1-methyl-1,2,3,6-tetrahydropyridine (**10**) reported in this paper.



Our initial synthetic approach to **10** (Scheme I, route A) involved treatment of the (trimethylsilyl)oxy derivative **12**, obtained from 1-methyl-4-piperidone (**11**) and trimethylsilyl chloride, with methyllithium in THF/HMPA to generate the corresponding lithium enolate **13**.[5] Reaction of **13** with benzoic anhydride afforded a moderate yield of the desired product **10**. An improved synthesis of the target compound (Scheme I, route B) proceeded through O-benzoylation of 4-hydroxypyridine (**14**) followed by treatment of the resulting 4-(benzoyloxy)pyridine (**15**) with iodomethane to yield the corresponding *N*-methylpyridinium species **16**. Reduction of **16** with sodium borohydride[6] gave the desired tetrahydropyridine **10** in 61% overall yield.

Scheme I. Synthetic Pathways to (Benzoyloxy)tetrahydropyridine 10[a]



[a] (a) $ClSi(CH_3)_3$, $(CH_3CH_2)_3N$; (b) CH_3Li, THF/HMPA; (c) $(C_6H_5O)_2O$; (d) CH_3I; (e) $NaBH_4$; (f) *m*-CPBA; (g) $(CF_3CO)_2O$.

Incubation of **10** with purified MAO-B isolated from beef liver led to the rapid formation of a compound with λ_{max} 283 nm to which we initially assigned the expected dihydropyridinium structure **18**. The formation of this product was completely inhibited by pretreatment of the enzyme preparation with 10^{-6} M deprenyl, a potent inactivator of MAO-B.[7] Furthermore, treatment of the

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