Synthesis of 9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (FddA) via a Purine 3′-Deoxynucleoside

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A synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA) via a 6-chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (**9**), which was readily obtained from inosine (**5**), is described. Fluorination at the C2′-β position of the purine 3′-deoxynucleoside with diethylaminosulfur trifluoride was improved by the introduction of a 6-chloro group and proceeded in moderate yield. Purine 3′-deoxynucleoside derivatives were also subjected to nucleophilic reactions with triethylamine trihydrofluoride and gave the desired fluorinated nucleoside in good yield. The safety and yield of the fluorination process were greatly improved by the use of triethylamine trihydrofluoride. The influence of the sugar ring conformation and 6-chloro group on the rate of the nucleophilic reaction against elimination are also discussed.

Introduction

9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA, lodenosine) is an anti-human immunodeficiency virus (HIV) agent characterized by a C2′-β fluorinated dideoxy nucleoside.[1−4] This nucleoside analogue acts as an inhibitor of HIV reverse transcriptase (RT), like other nucleoside derivatives such as 3′-azido-3′-deoxythymidine (AZT, zidovudine), 2′,3′-dideoxyinosine (**3**, ddI, didanosine), and 2′,3′-dideoxyadenosine (**4**, ddA). This class of nucleoside derivatives is known not only for its effectiveness, but also for its toxicity and the development of resistant strains. However, they are considered to be effective therapeutic agents based on their successful use in combination with other nucleoside or non-nucleoside RT inhibitors or with HIV protease inhibitors.[5] Among the deoxynucleoside analogues, FddA is important due to its effectiveness against strains resistant to other dideoxy nucleosides,[6,7] its improved stability under acidic conditions[1,2] which decompose 2′,3′-dideoxyinosine (**3**) and 2′,3′-dideoxyadenosine (**4**), and its ability to penetrate the blood−brain barrier.[8−11] FddA is currently under clinical trials for the treatment of AIDS.[4,12,13]

Since the biological activity and chemical or metabolic stability of FddA have received considerable attention in antiviral research,[2,14] many groups have striven to develop better methods for obtaining C2′-β fluorinated purine deoxynucleosides. While the condensation of fluorinated sugar derivatives with a nucleoside base is a conventional approach to synthesize C2′-β fluorinated nucleosides,[15−17] the synthesis of fluorinated sugar derivatives requires many steps and condensation remains subject to α-anomer formation.[2,18] Consequently, the total yield of FddA has been limited.

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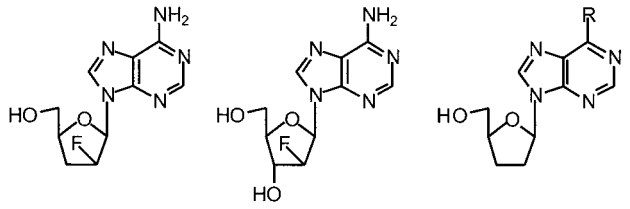
Chart 1



1: FddA **2**: F-ara-A **3**: ddI (R=OH) **4**: ddA (R=NH_2)

Watanabe, Pankiewicz, and their co-workers reported,[19−21] an excellent method for fluorination of riboside at the C2′-β position taking advantage of the control of conformation to synthesize F-ara-A (**2**). They found that C2′-β fluorinated compound was obtained from $O^{2'}$,$O^{5'}$,N^6-tritrityladenosine in 30% yield, but an unexpected isonucleoside was also obtained in 51% yield. Recently, Maruyama et al. also reported[22] a synthesis of F-ara-A (**2**) using 6-chloropurine riboside derivatives with an excellent fluorination yield. They found that 3′,5′-di-*O*-trityl-6-chloropurine riboside gave C2′-β fluorinated compound in 87% yield. We applied this method to the synthesis of FddA through protected F-ara-A.[23] However, this F-ara-A route requires deoxygenation of the 3′-hydroxyl group after the crucial fluorination step, and it loses a precious fluorinated compound. This method also requires a multistep synthesis and an expensive reagent for deoxygenation. Recently, a new synthetic approach to FddA via deoxygenation of 2′-deoxy-2′-fluoroadenosine and subsequent hydrogenation of the vinyl intermediate has been reported.[12,24] However, the preparation of 2′-deoxy-2′-fluoroadenosine from expensive 9-(β-D-arabinofuranosyl)adenine still requires a multistep synthesis. Again, deoxygenation and hydrogenation loses a precious fluorinated compound. We intended to develop a more direct approach to the synthesis of FddA, which would be suitable for large-scale synthesis.

Accordingly, direct fluorination at the C2′-β position of a purine 3′-deoxynucleoside might be a more attractive approach. Marquez studied[1] the fluorination of protected 3′-deoxy adenosine with tetrabutylammonium fluoride; however, a fluorinated compound was not obtained. Herdewijn[25] and Shiragami[26] reported the fluorination of 5′-*O*-tritylated and 5′-*O*-acetylated 3′-deoxy adenosine, respectively, with diethylaminosulfur trifluoride (DAST), but the yields of the fluorinated compounds were only 10% in both cases.

In this paper, we report a practical synthesis of FddA through a 6-chlorinated purine 3′-deoxynucleoside. This method does not require deoxygenation after fluorination. This is the first report regarding the C2′-β fluorination of purine 3′-deoxynucleoside in good yield. In addition to our previous communication,[27] we describe fluorination not only with DAST but also with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$), which is more suitable for large-scale synthesis from a handling safety standpoint. We also report the details of the synthesis of the 6-chlorinated purine 3′-deoxynucleoside. The details of the influence of the sugar ring conformation and 6-chloro group on the rate of the nucleophilic displacement reaction versus elimination are also discussed.

Results and Discussion

6-Chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (**9**)[28] was readily obtained from commercially available inosine (**5**) in 50% overall yield, without using an expensive reagent (Scheme 1). Thus, after treatment with trimethyl orthoacetate in acetic acid, **5** was deoxygenated and brominated simultaneously at the 3′-position with acetyl bromide by a modified Reese method.[29] Although reduction of the acetyl-brominated compound (**6**) by palladium-catalyzed hydrogenation predominantly gave a dideoxy compound,[30] the C3′-β bromine of **6** was selectively reduced by radical reduction.[31] Therefore, **6** was treated with 3 equiv of tributyltin hydride and a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) in toluene to obtain 2′,5′-di-*O*-acetyl-3′-deoxyinosine (**7**). Whereas the reaction yield of radical debromination was 92%, separation and purification of the product were rather difficult because of residual tin reagent. After separation and purification by recrystallization, the isolated yield of **7** was 67%. The 6-oxo group of **7** was substituted with chlorine by reaction with Vilsmeier reagent or phosphorus oxychloride. As reported,[28] cleavage of the glycoside bond under standard conditions during chlorination lead to a low yield of the product. However, by monitoring the reaction carefully and cooling the mixture immediately at the end of the reaction, cleavage of the glycoside bond was decreased to a negligible level. After deprotection of the 2′- and 5′-*O*-acetyl groups with sodium methoxide in methanol, 6-chloropurine 3′-deoxyriboside (**9**) was crystallized. This process was shown to be suitable for large-scale production on a 3000-L scale. The details of this synthesis will be reported elsewhere.

In our previous report,[27] 5′-*O*-tritylated compound (**10**) was obtained as an oil after column separation. To improve this process, the 5′-hydroxyl group in **9** was selectively protected with 1.1 equiv of trityl chloride (TrCl) in the presence of 2,4,6-collidine in acetonitrile (CH_3CN) at 45 °C. After quenching with methanol, the resulting solution was subjected to the usual workup to give 5′-*O*-tritylated compound **10** as an oil. Several different solvents were tested and eventually **10** was found to be crystallized only from benzotrifluoride (α,α,α-trifluorotoluene). After crystallization, pure **10** was ob-

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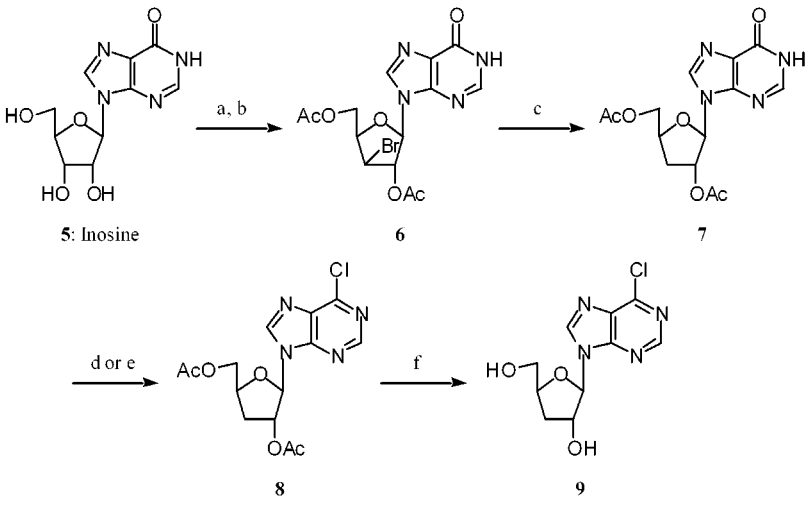
Scheme 1[a]



[a] Reagents: (a) $MeC(OMe)_3$, AcOH, 50 °C; (b) AcBr, CH_3CN, 10 °C, 80.0%; (c) Bu_3SnH, AIBN, toluene, 67.0%; (d) $SOCl_2$, DMF, CH_2Cl_2, reflux, 94.1%; (e) $POCl_3$, *N*,*N*-dimethylaniline, Et_4NCl, CH_3CN, reflux, 99.0%; (f) NaOMe, MeOH, r.t., 94.1%.

tained in 85% yield. The pivotal substrate **10** was further studied for fluorination.

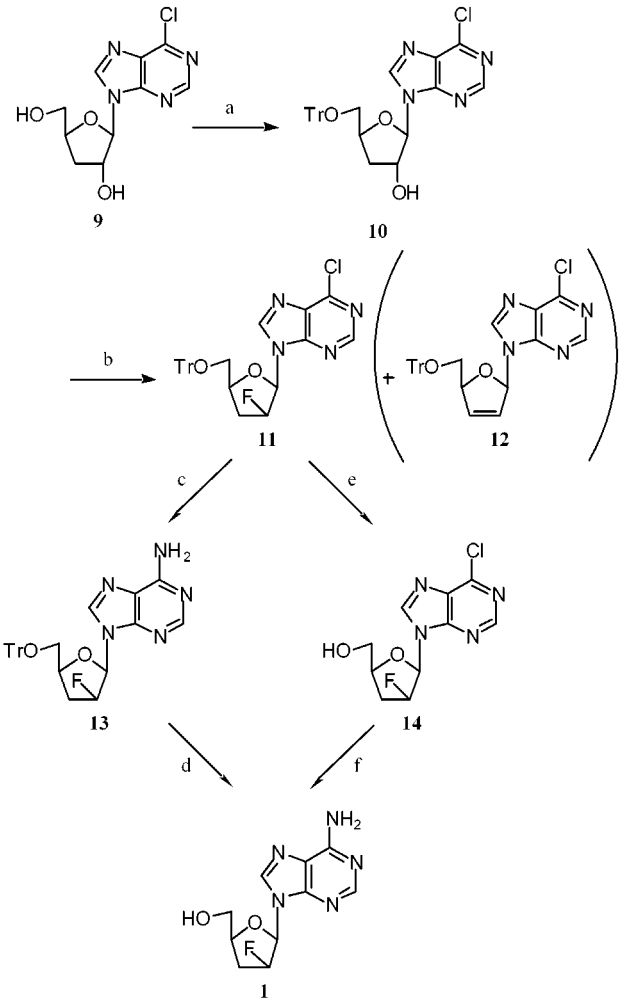
First, we studied diethylaminosulfur trifluoride (DAST)[32] as a fluorinating agent. In the laboratory, DAST is useful for replacing a hydroxyl group with fluorine with an inversion of configuration. However, it has been reported[19] that the C2′-β fluorination of 3′,5′-di-*O*-protected nucleoside with DAST is sometimes low yield because nucleic base migration occurs due to participation of the nucleophilic purine N3 during the reaction. Therefore, we prepared 6-chlorinated compound **10**, which might reduce the nucleophilicity of the nucleic base by substitution of the 6-position of the base with an electron-withdrawing chlorine.

Thus, **10** was reacted with 2.6 equiv of DAST (Scheme 2) in the presence of pyridine in dichloromethane at reflux to give a C2′-β fluorinated compound **11** in 43% yield after purification by preparative silica gel plate. The 6-chloro group was shown to be effective for preventing purine base migration and improving the yield of fluorination, compared with the 6-aminated compound. The ^{1}H NMR spectrum of **11** shows a C2′ proton at $\delta = 5.25$ with a large geminal coupling constant ($J_{2',F} = 53.7$ Hz), indicating that the fluorine atom is attached to C2′. This is also supported by vicinal coupling constants of H1′−F ($J_{1',F} = 19.1$ Hz) and H3′−F ($J_{3',F} = 35.0$, 27.5 Hz). Since the ^{1}H NMR spectrum shows long-range coupling between H-8 and the C2′ fluorine ($J_{8,F} = 2.8$ Hz), the fluorine should be in the β configuration. The nuclear Overhauser effect spectroscopy (NOESY) spectrum also supported the structure of **11** (Figure 1). Therefore, **11** was confirmed to have a C2′-β fluorinated structure.

During the reaction of **10** with DAST, almost the same amount of side product was also formed. This side product was separated and shown to be an elimination product (**12**), but was not an isonucleoside as reported by Watanabe.[19−21] The ^{1}H NMR spectrum of **12** shows the existence of a vinyl proton at $\delta = 6.03$ (H-2′) and $\delta = 6.37$ (H-3′) with a vicinal coupling constant ($J_{2',3'} = 5.7$ Hz).

After separation and purification, **11** was added to anhydrous ammonia in tetrahydrofuran (THF) and kept in a sealed tube at 70 °C for 4 days. The aminated compound **13** was then deprotected with aqueous hydrogen chloride in methanol to give the desired FddA (**1**).

Scheme 2[a]



[a] Reagents: (a) TrCl, 2,4,6-collidine, CH_3CN, 45 °C, 85.1%; (b) DAST, pyridine, CH_2Cl_2, 42.6%; (c) NH_3, THF; (d) 37% HCl aq, MeOH, 91.6% from **11**; (e) 37% HCl aq, MeOH, toluene, r.t.; (f) NH_3, MeOH, toluene, 40−60 °C, 72.8% from **11**.

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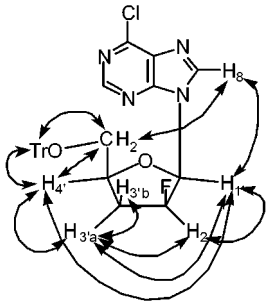
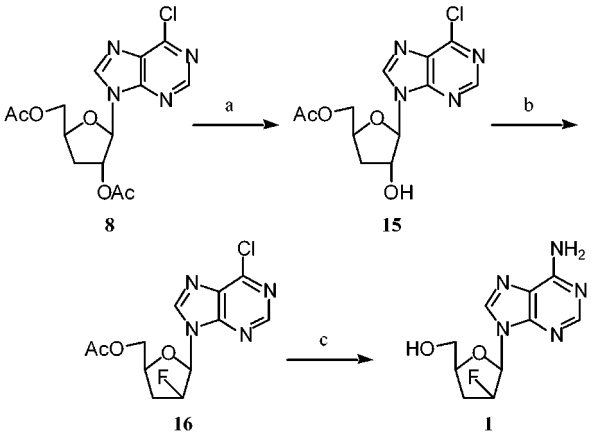


Figure 1. Graphical summary of the NOESY spectrum observed for C2′-*β* fluorinated **11**.

Scheme 3[a]



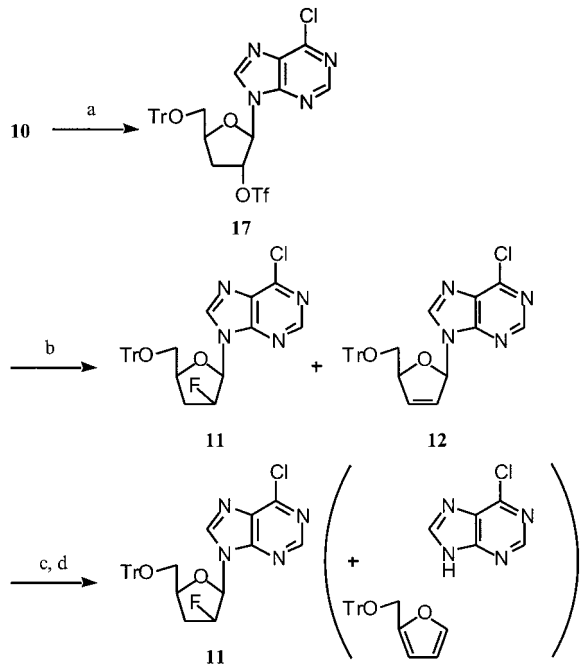
[a] Reagents: (a) Et_3N, MeOH, 33.5%; (b) MOST, pyridine, CH_2Cl_2, 38.8%; (c) NH_3, THF, 88.2% on HPLC analysis.

The desired FddA was also obtained from **11** by an alternative procedure, in which the 5′-*O*-trityl group was first deprotected by aqueous hydrogen chloride followed by amination at the 6 position. In both cases, the spectroscopic properties of **1** were identical in all respects to the published data.[1−3,23]

The 5′-*O*-acetylated compound (**15**) was also synthesized by partial deacetylation of compound **8** (Scheme 3), to investigate if the 5′-hydroxyl protecting group changed the sugar conformation[19−21] and affected the yield of fluorination. Although there is a risk of undesired deprotection during fluorination, fluorination of **15** was performed using morpholinosulfur trifluoride (MOST), which is an alternative to DAST, and the reaction proceeded more mildly. Thus, treatment of the acetylated compound **15** with MOST in the presence of pyridine in dichloromethane at reflux gave a C2′-*β* fluorinated compound (**16**) in 39% yield after purification by silica gel column chromatography. Our results showed that the 5′-hydroxyl protecting group did not influence the sugar conformation and gave a similar yield of fluorination. Treatment of **16** with anhydrous ammonia in THF gave the desired **1** in 88% yield. To the best of our knowledge, this procedure may also be the shortest route to FddA by avoiding sequential deprotection−protection steps from **8** to **10** in Scheme 1.

Although the fluorination yield of 6-chloropurine 3′-deoxyribosides **10** and **15** with dialkylaminosulfur trifluoride (DAST or MOST) were better than that of 3′-deoxy adenosine derivatives, the fluorination conditions were corrosive to glass and a stainless steel reactor in large-scale production. Dialkylaminosulfur trifluoride is also difficult to handle on a commercial scale due to its toxicity. Therefore, we examined an alternative fluorination method for industrial production.

Scheme 4[a]



[a] Reagents: (a) Tf_2O, pyridine, CH_2Cl_2, −10 °C; (b) $Et_3N{\cdot}3HF$, Et_3N, toluene, 40 °C, 64.5% from **10** on HPLC analysis; (c) 80% AcOH, toluene; (d) crystallization, 69.5%.

Chou et al. reported[33] the large-scale synthesis of C-2 (*arabino*) fluorinated sugar derivatives with noncorrosive triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$).[34,35] However, the condensation of fluorinated sugar with purine to synthesize FddA, and its related compounds can still lead to the formation of undesired α-anomer during the reaction. Since the application of $Et_3N{\cdot}3HF$ to fluorinated nucleoside synthesis has not been well studied,[36] we became interested in using $Et_3N{\cdot}3HF$ for the synthesis of FddA (**1**). In our previous paper,[37] we used $Et_3N{\cdot}3HF$ for the fluorination of 3′-*O*-benzoyl-5′-*O*-tritylriboside through 2′-*O*-trifluoromethanesulfonate and 2′-*O*-imidazolesulfonate. We applied our results to the fluorination of 3′-deoxy-5′-*O*-tritylriboside (**10**).

Thus, **10** was fluorinated with $Et_3N{\cdot}3HF$ in two steps, as shown in Scheme 4. Prior to the reaction with $Et_3N{\cdot}3HF$, the 2′-hydroxyl group of **10** was converted to trifluoromethanesulfonate (**17**). The conditions for the reaction of $Et_3N{\cdot}3HF$ with the triflate **17** were examined as shown in Table 1. The normarized HPLC peak area ratio in Table 1 was calculated to exclude an influence of solvent peak from the data comparison. The reaction proceeded slowly at room temperature (runs 1−3, 7−9). The results at 70 °C were not as good as expected (runs 4−6), because depurination of starting material and products occur at the temperature. The reaction had to

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Table 1. Fluorination of 17 with $Et_3N·3HF$

run	solvent	$Et_3N·3HF$/equiv	Et_3N/equiv	temp/°C	time/days	HPLC peak area ratio[a] 17	11	12	yield/%[b] 11
1	CH_3CN	6.0	-	r.t.	4.9	37.3	23.6	38.7	16.2
2	AcOEt	6.0	-	r.t.	4.9	43.8	24.6	31.6	20.5
3	toluene	6.0	-	r.t.	4.9	82.4	13.8	3.8	11.7
4	CH_3CN	6.0	-	70	0.3	4.3	85.8	9.9	20.3
5	AcOEt	6.0	-	70	0.3	0.4	57.8	41.7	38.4
6	toluene	6.0	-	70	0.9	0.0	70.4	29.6	34.9
7	CH_3CN	6.0	3.0	r.t.	4.9	0.6	34.2	65.2	28.6
8	AcOEt	6.0	3.0	r.t.	4.9	0.0	38.6	61.3	34.5
9	toluene	6.0	3.0	r.t.	4.9	8.1	64.4	27.5	57.8
10	toluene	6.0	3.0	40	3.0	0.0	64.7	35.3	60.3
11	toluene	4.0	2.0	40	1.8	0.5	66.1	33.4	64.5

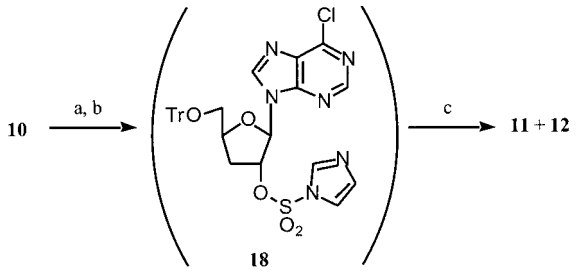
[a] The HPLC peak area ratio is normalized to exclude a solvent peak. [b] The yield includes triflation and is calculated from the results of HPLC analysis.

be carried out in nonpolar solvent to avoid the formation of elimination product **12**. Compared to acetonitrile (CH_3CN) and ethyl acetate (AcOEt), toluene gave the best ratio of fluorinated compound **11** to elimination product **12** (runs 1−3, 7−9). The addition of half an equivalent of triethylamine (Et_3N) to $Et_3N·3HF$ enhanced the nucleophilicity of the reagent[38] and improved the results (run 9). To shorten the reaction time, the reaction temperature was moderately increased to 40 °C (runs 10 and 11). At 40 °C, 4 equiv of $Et_3N·3HF$ were enough to finish the reaction (runs 11). The reaction took approximately 40−48 h (run 11).

Therefore, **17** was reacted with 4 equiv of $Et_3N·3HF$ in toluene in the presence of 2 equiv of Et_3N at 40 °C. HPLC analysis showed that the yield of fluorinated compound **11** was 65% including trifluoromethanesulfonation. Eliminated product **12** was also formed in around 33% yield. Since $Et_3N·3HF$ is noncorrosive,[17,34] the borosilicate glassware was not corroded at all even after a few days under these reaction conditions. The yield of **11** (65%) from **10** in the reaction with $Et_3N·3HF$ was much greater than that in the reaction with DAST (43%). The safety and yield of the fluorination process, which is the key step of the total synthesis, were greatly improved by the use of triethylamine trihydrofluoride.

Although the fluorination process was improved, the fluorination still gave a 2:1 mixture of fluorinated compound **11** and eliminated product **12**. For the large-scale procedure, a purification method without using column separation was required. One of the advantages of C2′-*β* fluorinated nucleoside **1** is its stability in acid[1,2] due to its C2′-*β* fluoride.[39] In contrast, 2′,3′-dideoxydidehydro nucleoside is acid-labile. Hence, if we treat a mixture of **11** and **12** with an appropriate acid, there is a possibility of decomposing only the acid-labile 2′,3′-dideoxy-didehydro nucleoside (**12**), while retaining the acid-stable C2′-*β* fluorinated nucleoside (**11**). In fact, treatment of the mixture of **11** and **12** with 80% acetic acid in toluene for 6 h at 10 °C led to the recovery of **11** without any loss (Scheme 4). On the other hand, elimination product **12** was completely decomposed. The increased HPLC peak of 6-chloropurine showed that **12** underwent depurination during acid treatment. The resulting crude **11** was subjected to crystallization from the toluene−tetrahydrofuran−cyclohexane mixture to give pure **11**. After amination and deprotection, the overall yield of FddA (**1**) from inosine was 17%. This method proceeds without using a corrosive reagent or column separation. Accordingly, the present method is suitable for large-scale synthesis of **1**.

Scheme 5[a]



[a] Reagents: (a) SO_2Cl_2, pyridine, CH_2Cl_2, −35 °C; (b) imidazole, r.t.; (c) $Et_3N·3HF$, Et_3N, toluene, 40 °C, 41.9% from **10** on HPLC analysis.

The imidazolesulfonate (**18**), obtained from **10**, was also reacted with 6 equiv of $Et_3N·3HF$ in toluene at 50 °C for 2 days. After conventional workup, HPLC analysis indicated that the fluorinated compound **11** was obtained in 42% yield in two steps. In the reaction with imidazolesulfonate **18**, the addition of half an equivalent of Et_3N to $Et_3N·3HF$ was not effective at increasing the yield of fluorinated compound **11**. We tried to fluorinate the compound with other leaving groups, but without success. The ^1H NMR spectra show that **10**, **15**, and **17** all have a C3′-endo conformation (Figure 2), as indicated by the rather small vicinal coupling constant between the C1′ and C2′ protons ($J_{1',2'}$ = 2.2, 2.3, and 1.2 Hz, respectively).

In the course of their studies on 2′-deoxy-2′-fluoro-arabinofuranosyl purine nucleoside synthesis, Watanabe, Pankiewicz, and their co-workers have shown[19−21] that if a sugar moiety of a purine nucleoside takes a C3′-endo conformation, nucleophilic substitution of the C2′-α leaving group does not give a C2′-*β* fluorinated nucleoside. This is probably because the hydrogen on C3′ and the leaving group on C2′ are in almost a trans diaxial configuration, which favors *β*-elimination instead of nucleophilic substitution. Indeed, when N^1,$O^{3'}$,$O^{5'}$-tribenzylinosine was treated with DAST, C2′-*β* fluorinated arabino nucleoside was not obtained, while elimination product was obtained exclusively.[19] The conformation of the reaction intermediate of N^1,$O^{3'}$,$O^{5'}$-tribenzylinosine is assumed to be C3′-endo by analogy to its 2′-*O*-triflate ($J_{1',2'}$ = 2.5 Hz). This argument is also supported by a

(38) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527−6530.
(39) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. *J. Org. Chem.* **1998**, *63*, 2161−2167.

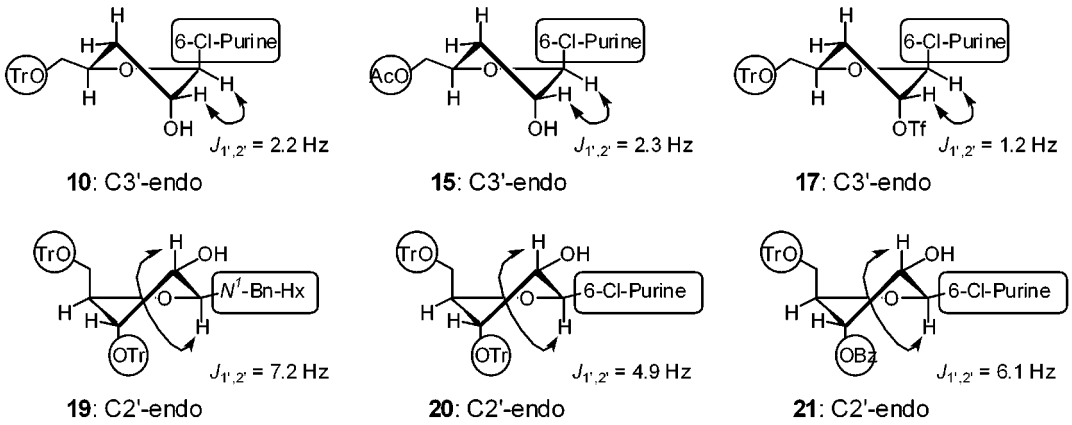


Figure 2. The 3′-deoxynucleosides **10**, **15**, and **17** each have a C3′-endo conformation as indicated by the rather small vicinal coupling constant between the C1′ and C2′ protons, while in the case of **19**, **20**, and **21**, the two bulky C3′ and C5′ hydroxyl groups shift the conformation toward C2′-endo, as indicated by the rather large vicinal coupling constant.

report that the fluorination of 5′-*O*-trityl-3′-deoxyadenosine ($J_{1',2'}$ = 1.1 Hz)[25] with DAST resulted in a poor yield.

On the other hand, when 3′,5′-di-*O*-trityl-1-benzylinosine (**19**, $J_{1',2'}$ = 7.2 Hz) was treated with DAST, C2′-β fluorinated arabino nucleoside was obtained in 63% yield,[19] since the two bulky trityl groups at the C3′- and C5′-hydroxyl groups shift the conformation toward C2′-endo (Figure 2), which favors nucleophilic substitution. Nevertheless, when 3′,5′-di-*O*-trityl-inosine ($J_{1',2'}$ = 7.1 Hz) was treated with DAST, despite its C2′-endo conformation, C2′-β fluorinated arabino nucleoside was obtained in only 30% yield.[19] This might be explained by participation of the hypoxanthine N3 in the sugar moiety transformation, which results in undesired base migration. To decrease the influence of the participation of N3, in previous studies we synthesized 6-chlorinated purine ribosides such as 3′,5′-di-*O*-trityl-6-chloropurine riboside (**20**, $J_{1',2'}$ = 4.9 Hz)[22] and 3′-*O*-benzoyl-5′-*O*-trityl-6-chloropurine riboside (**21**, $J_{1',2'}$ = 6.1 Hz),[23] and successfully fluorinated these with DAST in good yield (87% and 78%, respectively).

Our present results are quite novel, since this is the first example in which purine 3′-deoxynucleosides (**10**, **15**, and **17**) gave a good C2′-β fluorination yield (up to 65%). These 6-chloropurine 3′-deoxynucleosides were confirmed to have a C3′-endo conformation favoring β-elimination. We assume that an electron-withdrawing 6-chloro group might not only suppress nucleic base migration by reducing the nucleophilicity of the nucleic base, but may also suppress the formation of elimination product by reducing the participation of N3 in C3′-β hydrogen removal.

Conclusion

The pivotal substrate **10**, which was obtained from inosine by a five-step reaction, was treated with DAST to afford C2′-β fluorinated nucleoside **11**. Further amination and deprotection of **11** gave FddA in good yield. Another 3′-deoxynucleoside **15** also gave the desired C2′-β fluorinated derivative **16** under similar treatment with MOST. To the best of our knowledge, this method is one of the shortest synthetic route to FddA.

2′-Hydroxyl-activated 3′-deoxynucleoside **17** was also subjected to the nucleophilic reaction with $Et_3N{\cdot}3HF$, to give the desired C2′-β fluorinated nucleoside **11** along with elimination product **12**. The safety and yield of the fluorination process were greatly improved by the use of $Et_3N{\cdot}3HF$. The 2:1 mixture of **11** and **12** was treated with acetic acid to decompose the acid-sensitive impurity **12**, while acid-stable C2′-β fluorinated **11** remained and was easily recrystallized to give pure nucleoside **11**.

Our 6-chloropurine 3′-deoxynucleosides gave a good fluorination yield despite a C3′-endo conformation. We assume that the electron-withdrawing 6-chloro group of the purine moiety might not only suppress base migration, but may also suppress the formation of elimination product.

Experimental Section

All reagents were purchased and used without further purification. Preparative layer chromatography (PLC) was conducted on preparative silica gel plate (layer thickness 2.0 mm). All high-performance liquid chromatography (HPLC) analyses were carried out with a GL Science ODS-2 column. All proton NMR spectra were measured in $CDCl_3$ or DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00), $CDCl_3$ (δ 7.26), or DMSO-d_6 (δ 2.50) as an internal standard. Data are reported as follows: chemical shift (integrated intensity or assignment, multiplicity, coupling constants in hertz, assignment). All carbon NMR spectra were measured in $CDCl_3$ or DMSO-d_6 solvent, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00), $CDCl_3$ (δ 77.0), or DMSO-d_6 (δ 39.5) as an internal standard. Mass spectra (MS) were obtained with FAB (fast atom bombardment) ionization.

9-(2,5-Di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)-1,9-dihydro-6*H*-purine-6-one (6). To a suspension of inosine (20.0 g, 74.6 mmol) in acetic acid (100 mL) was added trimethyl orthoacetate (11.7 g, 97.4 mmol). After being stirred for 5 h at 50 °C, the reaction mixture was concentrated under reduced pressure. To this concentrate was added acetic acid (20 mL), and the reaction mixture was concentrated again under reduced pressure. To this concentrate was added acetonitrile (100 mL), and the reaction mixture was cooled to 5 °C. To this solution was slowly added acetyl bromide (22.0 mL, 298 mmol) over 2 h. After additional stirring for 4 h at 10 °C, the reaction mixture was neutralized with aqueous sodium carbonate and separated into layers. The aqueous layer was extracted with acetonitrile (50 mL), and the combined organic layers were dried over sodium sulfate, concentrated in vacuo, and purified by silica gel column chromatography ($CHCl_3$/MeOH = 5/1) to give the desired product (24.8 g, 59.7 mmol, 80.0% yield) as crystals. An analytical sample was obtained by recrystallization from acetonitrile: mp 171−172 °C; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.34 (1H, s, H-2), 8.24 (1H, s, H-8), 6.20 (1H, bs, H-1′), 5.74 (1H, bs, H-2′), 4.4−4.6 (4H, m, H-3′, H-4′, H-5′ab), 2.20 (3H, s, 5′O-Ac), 2.14 (3H, s, 2′O-Ac); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (1H, s, H-2), 8.10 (1H, s, H-8), 6.16 (1H, m, H-1′), 5.82 (1H, m, H-2′), 4.92 (1H, m, H-3′), 4.57 (1H, m, H-4′), 4.36 (2H, m, H-5′), 2.11 (3H, s, 5′O-Ac), 2.06 (3H, s, 2′O-Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 158.8, 148.4, 146.0, 138.4, 124.2, 87.9, 83.0, 78.6, 64.7, 20.7; IR (KBr) 1750, 1698, 1376, 1226, 1044 cm^{-1}; UV (MeOH) λ_{max} 206, 245 nm; HRMS (FAB+) calcd for $C_{14}H_{16}N_4O_6Br$ $(M + H)^+$ 415.0253, found 415.0248.

2′,5′-Di-*O*-acetyl-3′-deoxyinosine (7). To a solution of 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)-1,9-dihydro-6*H*-purin-6-one (4.31 g, 10.4 mmol) in toluene (77 mL) were added tributyltin hydride (8.63 mL, 31.1 mmol) and 2,2′-azobisisobutyronitrile (147 mg, 0.893 mmol). After being stirred for 2 h at 90 °C, the reaction mixture was immediately cooled to 0 °C and poured into petroleum ether (41 mL). HPLC analysis showed that the desired product was obtained in 92.2% yield (3.22 g, 9.57 mmol). The resulting precipitate was filtered and recrystallized sequentially from ethanol (54 mL) and acetonitrile/water (5/1, 42 mL). The resulting crystals were filtered and dried at 40 °C under reduced pressure to give an analytical sample of the desired product (2.34 g, 6.97 mmol, 67.0% yield) as white crystals: mp 242−244 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, s, H-2), 8.07 (1H, s, H-8), 6.04 (1H, d, J = 1.1 Hz, H-1′), 5.59 (1H, bd, J = 5.9 Hz, H-2′), 4.60 (1H, m, H-4′), 4.39 (1H, dd, J = 12.3, 2.9 Hz, H-5′a), 4.22 (1H, dd, J = 12.3, 5.2 Hz, H-5′b), 2.50 (1H, ddd, J = 14.0, 10.5, 5.9 Hz, H-3′a), 2.16 (1H, ddd, J = 14.0, 5.8, 1.1 Hz, H-3′b), 2.09 (3H, s, 5′O-Ac), 2.04 (3H, s, 2′O-Ac); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (1H, s, H-2), 8.10 (1H, s H-8), 6.11 (1H, d, J = 1.4 Hz, H-1′), 5.61 (1H, bd, J = 6.3 Hz, H-2′), 4.52 (1H, m, H-4′), 4.29 (1H, dd, J = 12.0, 2.9 Hz, H-5′a), 4.16 (1H, dd, J = 12.0, 5.8 Hz, H-5′b), 2.60 (1H, ddd, J = 14.1, 10.3, 6.3 Hz, H-3′a), 2.22 (1H, ddd, J = 14.1, 5.9, 1.1 Hz, H-3′b), 2.10 (3H, s, 5′O-Ac), 1.99 (3H, s, 2′O-Ac); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.3, 170.1, 156.7, 147.9, 146.2, 138.9, 124.6, 88.6, 78.2, 77.7, 64.6, 32.6, 20.9, 20.7; IR (KBr) 1746, 1724, 1707, 1419, 1344, 1230, 1205, 1122, 1101 cm^{-1}; UV (MeOH) λ_{max} 203, 245 nm; HRMS (FAB+) calcd for $C_{14}H_{17}N_4O_6$ $(M + H)^+$ 337.1148, found 337.1153.

6-Chloro-9-(2,5-di-*O*-acetyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (8). Reaction with Vilsmeier Reagent. To a suspension of 2′,5′-di-*O*-acetyl-3′-deoxyinosine (2.89 g, 8.60 mmol) in dichloromethane (40 mL) were added dimethylformamide (1.92 mL, 24.8 mmol) and thionyl chloride (1.81 mL, 24.8 mmol). After being stirred for 6 h at reflux, the reaction mixture was cooled to 10 °C and poured into ice−water (500 mL). The reaction mixture was separated into layers, and the organic layer was washed with aqueous saturated sodium hydrogencarbonate (× 2). The organic layer was concentrated in vacuo to give the desired product (2.87 g, 8.09 mmol, 94.1% yield) as a colorless foam.

Reaction with $POCl_3$ and Phase-Transfer Catalyst. To a suspension of 2′,5′-di-*O*-acetyl-3′-deoxyinosine (1.00 g, 2.97 mmol) in acetonitrile (4.5 mL) were added *N*,*N*-dimethylaniline (0.81 mL, 6.4 mmol), tetraethylammonium chloride (736 mg, 4.44 mmol), and phosphorus oxychloride (0.62 mL, 6.7 mmol). After being stirred for 2 h at reflux, the reaction mixture was cooled to room temperature and poured into dichloromethane/ice−water. The reaction mixture was separated into layers, and the organic layer was washed with aqueous saturated sodium hydrogencarbonate and water. The organic layer was dried over sodium sulfate and concentrated in vacuo to give the desired product (1.04 g, 2.94 mmol, 99.0% yield) as a colorless foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (1H, s, H-2), 8.32 (1H, s, H-8), 6.15 (1H, d, J = 1.3 Hz, H-1′), 5.74 (1H, d, J = 5.8 Hz, H-2′), 4.63−4.74 (1H, m, H-4′), 4.46 (1H, dd, J = 12.3, 2.8 Hz, H-5′a), 4.30 (1H, dd, J = 12.3, 5.1 Hz, H-5′b), 2.65 (1H, ddd, J = 14.1, 10.6, 6.0 Hz, H-3′a), 2.27 (1H, ddd, J = 14.1, 5.6, 1.3 Hz, H-3′b), 2.17 (3H, s, 5′O-Ac), 2.08 (3H, s, 2′O-Ac); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (2H, s, H-2, H-8), 6.31 (1H, s, H-1′), 5.76 (1H, s, H-2′), 4.55−4.64 (1H, m, H-4′), 4.32 (1H, dd, J = 12.1, 2.8 Hz, H-5′a), 4.22 (1H, dd, J = 12.1, 5.8 Hz, H-5′b), 2.67 (1H, ddd, J = 14.2, 10.3, 6.1 Hz, H-3′a), 2.01−2.32 (1H, m, H-3′b), 2.13 (3H, s, 5′O-Ac), 1.97 (3H, s, 2′O-Ac); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.3, 170.1, 152.0, 151.3, 149.6, 146.0, 131.5, 89.2, 78.6, 77.4, 64.5, 32.4, 20.9, 20.6; IR (neat) 1745, 1674, 1592, 1562, 1387, 1339, 1232, 1094, 1053 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}N_4O_5Cl$ $(M + H)^+$ 355.0809, found 355.0816.

6-Chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (9). To a solution of 6-chloro-9-(2,5-di-*O*-acetyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (20.8 g, 58.6 mmol) in methanol (62.3 mL) was added 28% sodium methoxide in methanol (2.89 mL, 14.2 mmol) at 10 °C. After being stirred for 3 h at room temperature, this reaction mixture was cooled to 5 °C. HPLC analysis showed that the desired product was obtained in quantitative yield. Evaporation of the solvent gave precipitate which was crystallized from methanol/water to give the desired product (14.9 g, 55.2 mmol, 94.1% yield) as white crystals. An analytical sample was obtained by recrystallization from methanol/water: mp 180−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (1H, s, H-2), 8.33 (1H, s, H-8), 5.83 (1H, d, J = 4.6 Hz, H-1′), 4.92 (1H, ddd, J = 7.2, 6.5, 4.6 Hz, H-2′), 4.53−4.59 (1H, m, H-4′), 3.98 (1H, dd, J = 12.5, 2.1 Hz, H5′-a), 3.60 (1H, dd, J = 12.5, 2.6 Hz, H5′-b), 2.53 (1H, ddd, J = 12.9, 7.2, 5.7 Hz, H3′-a), 2.18 (1H, ddd, J = 12.9, 8.0, 6.5 Hz, H3′-b); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97 (1H, s, H-2), 8.82 (1H, s, H-8), 6.06 (1H, d, J = 1.4 Hz, H-1′), 5.80 (1H, s, J = 3.9 Hz, 2′-OH), 5.12 (1H, dd, J = 5.3, 5.2 Hz, 5′-OH), 4.62−4.68 (1H, m, H-2′), 4.42−4.50 (1H, m, H-4′), 3.78 (1H, ddd, J = 12.1, 5.3, 3.2 Hz, H-5′a), 3.59 (1H, ddd, J = 12.1, 5.2, 3.8 Hz, H-5′b), 2.28 (1H, ddd, J = 13.3, 9.6, 5.3 Hz, H-3′a), 1.93 (1H, ddd, J = 13.3, 6.0, 2.2 Hz, H-3′b); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.8, 151.3, 149.3, 145.4, 131.5, 91.6, 81.9, 75.2, 62.1, 33.6; IR (KBr) 3331, 1596, 1562, 1442, 1405, 1391, 1337, 1207, 1129, 1079, 1068 cm^{-1}; UV (MeOH) λ_{max} 204, 265 nm; HRMS (FAB+) calcd for $C_{10}H_{12}N_4O_3Cl$ $(M + H)^+$ 271.0598, found 271.0584.

6-Chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (10). To a solution of 6-chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (20.0 g, 98.9% purity, 73.1 mmol) in acetonitrile (140 mL) were added 2,4,6-collidine (11.6 mL, 87.8 mmol) and trityl chloride (22.4 g, 80.4 mmol). After being stirred for 3 h at 45 °C, methanol (1.48 mL) was added to the reaction mixture. After additional stirring for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (200 mL) and water (100 mL), acidified (pH 3.0) with 6 N hydrogen chloride, and separated into layers. The organic layer was again mixed with water (100 mL), acidified (pH 3.0) with 6 N hydrogen chloride, and separated into layers. The organic layer was mixed with water (100 mL), neutralized (pH 7.0) with saturated aqueous sodium hydrogencarbonate, and separated into layers. The organic layer was dried over sodium sulfate and concentrated. The residue was concentrated with benzotrifluoride (220 mL) and then crystallized from benzotrifluoride (180 mL). The resulting crystals were filtered and dried at 40 °C under reduced pressure to give the desired product (31.9 g, 62.2 mmol, 85.1% yield) as white crystals: mp 205−206 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (1H, s, H-2), 8.40 (1H, s H-8), 7.21−7.41 (15H, m, 5′O-Tr), 6.04 (1H, d, J = 2.2 Hz, H-1′), 4.85−4.91 (1H, m, H-2′), 4.68−4.78 (1H, m, H-4′), 3.44 (1H, dd, J = 10.6, 3.1 Hz, H-5′a), 3.33 (1H, dd, J = 10.6, 4.6 Hz, H-5′b), 2.30 (1H, ddd, J = 13,3. 7.7, 5.6 Hz, H-3′a), 2.17 (1H, ddd, J = 13.3, 6.5, 3.9 Hz, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 151.2, 150.4, 146.7, 143.3, 132.4, 128.5, 127.8, 127.2, 93.1, 87.0, 80.7, 76.0, 64.7, 33.9; IR (KBr): 3354, 3059, 1592, 1562, 1491, 1449, 1400, 1338, 1206, 1130, 1078, 1018 cm^{-1}; UV (MeOH) λ_{max}: 207, 265 nm; HRMS (FAB+) calcd for $C_{29}H_{26}N_4O_3Cl$ $(M + H)^+$ 513.1693, found 513.1717. Anal. Calcd for $C_{29}H_{25}N_4O_3Cl$: C, 67.90; H, 4.91; N, 10.92. Found: C, 67.92; H, 4.95; N, 10.76.

6-Chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-*threo*-pentofuranosyl]-9*H*-purine (11) and 6-Chloro-9-[2,3-dideoxy-2,3-didehydro-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (12). Reaction with DAST. To a solution of 6-chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (104 mg, 0.202

mmol) in dichloromethane (10 mL) was added pyridine (0.120 mL, 1.48 mmol) at 0 °C. At this temperature, to this solution was added diethylaminosulfur trifluoride (70.0 μL, 0.530 mmol) dropwise with vigorous stirring. After stirring for 4 h at reflux, this reaction mixture was recooled to room temperature and then poured into aqueous saturated sodium hydrogencarbonate (20 mL) and dichloromethane (10 mL) with vigorous stirring. After additional stirring for 20 min, the reaction mixture was separated into layers. The organic layer was concentrated azeotropically with toluene under reduced pressure. The residue was purified by preparative silica gel plate (hexane/ethyl acetate = 1/1) to give the desired product (44.3 mg, yield 42.6%) as a white solid. An analytical sample was obtained by recrystallization from hexane/ethyl acetate: mp 191−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (1H, s, H-2), 8.34 (1H, d, J = 2.8 Hz, H-8), 7.22−7.52 (15H, m, 5′O-Tr), 6.41 (1H, dd, J = 19.1, 3.1 Hz, H-1′), 5.25 (1H, dddd, J = 53.7, 5.2, 3.1, 2.0 Hz, H-2′), 4.42−4.50 (1H, m, H-4′), 3.48 (1H, dd, J = 9.9, 6.6 Hz, H-5′a), 3.30 (1H, dd, J = 9.9, 3.8 Hz, H-5′b), 2.57 (1H, dddd, J = 35.0, 14.8, 9.0, 5.6 Hz, H-3′a), 2.36 (1H, dddd, J = 27.5, 15.1, 5.1, 1.7 Hz, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 151.2 (d, J = 16.8 Hz), 144.7 (d, J = 5.8 Hz), 143.6, 128.6, 127.9, 127.2, 90.6 (d, J = 188.9 Hz), 86.9, 85.0 (d, J = 16.4 Hz), 76.8, 65.7, 33.8 (d, J = 20.5 Hz); IR (KBr): 1593, 1567, 1492, 1220, 1206, 1079 cm^{-1}; UV (MeOH) λ_{max}: 206, 264 nm; HRMS (FAB+) calcd for $C_{29}H_{25}N_4O_2FCl$ (M + H)$^+$ 515.1650, found 515.1658; Anal. Calcd for $C_{29}H_{24}N_4O_2FCl$: C, 67.64; H, 4.70; N, 10.88; Cl, 6.88. Found: C, 67.34; H, 4.81; N, 10.61; Cl, 6.98.

The side product **12** was also purified by preparative silica gel plate (hexane/ethyl acetate = 1/1). An analytical sample was obtained by recrystallization from hexane/ethyl acetate: mp 156 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (1H, s, H-2), 8.15 (1H, s H-8), 7.14−7.41 (15H, m, 5′O-Tr), 7.09 (1H, bs, H-1′), 6.37 (1H, bd, J = 5.7 Hz, H-3′), 6.03 (1H, bd, J = 5.7 Hz, H-2′), 5.10 (1H, bs, H-4′), 3.40 (1H, dd, J = 10.2, 5.5 Hz, H-5′a), 3.27 (1H, dd, J = 10.2, 3.9 Hz, H-5′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 151.1, 150.5, 143.3, 143.0, 134.9, 131.6, 128.2, 127.5, 126.9, 124.3, 88.8, 86.6, 86.4, 65.0; IR (KBr): 3058, 1591, 1558, 1335, 1195, 1075 cm^{-1}; UV (MeOH) λ_{max}: 212, 265 nm; HRMS (FAB+) calcd for $C_{29}H_{24}N_4O_2Cl$ (M + H)$^+$ 495.1588, found 495.1583. Anal. Calcd for $C_{29}H_{23}N_4O_2Cl$: C, 70.37; H, 4.68; N, 11.32. Found: C, 70.20; H, 4.81; N, 11.19.

9-[2,3-Dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-*β*-D-*threo*-pentofuranosyl]adenine (13) and 9-(2,3-dideoxy-2-fluoro-*β*-D-*threo*-pentofuranosyl)adenine (1, FddA). 6-Chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-*β*-D-*threo*-pentofuranosyl]-9*H*-purine (17.7 g, 34.4 mmol) was dissolved in tetrahydrofuran (270 mL). After stirring for 4 days at 70 °C under a 5.6−6.0 bar ammonia atmosphere, the pressure was reduced to ambient pressure, and the temperature was allowed to fall to room temperature. The resulting mixture was concentrated in vacuo to give the desired product. An analytical sample was obtained by recrystallization from ethyl acetate/methanol: mp 235−236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s, H-2), 8.06 (1H, d, J = 3.0 Hz, H-8), 7.20−7.52 (15H, m, 5′O-Tr), 6.33 (1H, dd, J = 19.9, 2.9 Hz, H-1′), 6.18 (2H, bs, 6-NH_2), 5.20 (1H, dm, J = 53.8 Hz, H-2′), 4.35−4.45 (1H, m, H-4′), 3.46 (1H, dd, J = 10.0, 6.5 Hz, H-5′a), 3.27 (1H, dd, J = 10.0, 4.1 Hz, H-5′b), 2.50 (1H, dddd, J = 35.5, 14.9, 9.0, 5.4 Hz, H-3′a), 2.31 (1H, dddd, J = 27.5, 14.9, 4.8, 1.4 Hz, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 152.9, 149.6, 143.6, 140.1 (d, J = 6.9 Hz), 128.6, 127.9, 127.1, 119.0, 90.6 (d, J = 188.6 Hz), 86.7, 84.7 (d, J = 16.7 Hz), 76.2, 65.8, 33.9 (d, J = 20.6 Hz); IR (KBr): 3151, 1649, 1599, 1578, 1403, 1063 cm^{-1}; UV (MeOH) λ_{max}: 208, 259 nm; HRMS (FAB+) calcd for $C_{29}H_{27}N_5O_2F$ (M + H)$^+$ 496.2149, found 496.2141.

To a solution of the resulting 9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-*β*-D-*threo*-pentofuranosyl]adenine in methanol (173 mL) was added 37% aqueous hydrogen chloride (11.6 mL, 139 mmol). After being stirred for 1 h at room temperature, the reaction mixture was quenched (pH 4.5) with 25% aqueous ammonia. After concentration in vacuo at 18 °C, the residue was dissolved in water (52 mL) and ethyl acetate (52 mL). After vigorous stirring, the reaction mixture was acidified (pH 1.8) with 37% aqueous hydrogen chloride and separated into layers. The aqueous layer was washed with ethyl acetate (2 × 17 mL), neutralized (pH 7.5) with 25% aqueous ammonia, and cooled to 6 °C. After stirring for 1 h, the resulting crystals were filtered, washed with water, and dried at 50 °C under reduced pressure to obtain the desired product (7.97 g, 31.5 mmol, 91.6% yield) as white crystals: mp 226−227 °C (lit.[2] 227 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (1H, d, J = 2.3 Hz, H-8), 8.16 (1H, s, H-2), 7.33 (2H, bs, 6-NH_2), 6.32 (1H, dd, J = 16.1, 3.9 Hz, H-1′), 5.43 (1H, dm, J = 54.4 Hz, H-2′), 5.07 (1H, t, J = 5.9 Hz, 5′-OH), 4.13−4.23 (1H, m, H-4′), 3.54−3.69 (2H, m, H-5′ab), 2.47−2.68 (1H, m, H-3′a), 2.17−2.36 (1H, m, H-3′b); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.2, 152.9, 149.3, 139.7 (d, J = 4.7 Hz), 118.4, 91.5 (d, J = 185.9 Hz), 83.8 (d, J = 16.1 Hz), 77.9, 63.1, 32.6 (d, J = 19.3 Hz); IR (KBr): 3328, 3208, 3136, 1661, 1076, 1061 cm^{-1}; UV (MeOH) λ_{max}: 259, 204 nm; HRMS (FAB+) calcd for $C_{10}H_{13}N_5O_2F$ (M + H)$^+$ 254.1053, found 254.1048. Anal. Calcd for $C_{10}H_{12}N_5O_2F$: C, 47.43; H, 4.78; N, 27.66; F, 7.50. Found: C, 47.45; H, 4.84; N, 27.46; F, 7.13.

6-Chloro-9-(2,3-dideoxy-2-fluoro-*β*-D-*threo*-pentofuranosyl)-9*H*-purine (14) and 9-(2,3-Dideoxy-2-fluoro-*β*-D-*threo*-pentofuranosyl)adenine (1, FddA). To a suspension of 6-chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-*β*-D-*threo*-pentofuranosyl]-9*H*-purine (3.65 g, 7.09 mmol) in methanol (18 mL) and toluene (18 mL) was added 0.5 equiv of 37% aqueous hydrogen chloride (0.30 mL, 3.5 mmol). After being stirred for 4 h at room temperature, the reaction mixture was treated with 2 equiv of poly (4-vinylpyridine) and filtered. The filtrate was concentrated under reduced pressure. An analytical sample was obtained by recrystallization from dichloromethane/methanol: mp 154−155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89 (1H, d, J = 1.4 Hz, H-8), 8.84 (1H, s, H-2), 6.52 (1H, dd, J = 14.1, 4.0 Hz, H-1′), 5.55 (1H, ddd, J = 54.2, 9.9, 4.3 Hz, H-2′), 5.11 (3H, t, J = 5.8 Hz, 5′OH), 4.20−4.31 (1H, m, H-4′), 3.59−3.75 (2H, m, H-5′ab), 2.50−2.72 (1H, m H-3′a), 2.22−2.42 (1H, m, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 151.3, 149.3, 145.8 (d, J = 3.4 Hz), 130.7, 91.4 (d, J = 186.9 Hz), 84.2 (d, J = 16.2 Hz), 78.5, 62.6, 32.0 (d, J = 19.3 Hz); IR (KBr) 3397, 1592, 1564, 1494, 1452, 1343, 1214, 1144, 1059 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{11}N_4O_2FCl$ (M + H)$^+$ 273.0555, found 273.0555. The resulting residue was dissolved in methanol (200 mL) and toluene (200 mL). After stirring for 5 days at 40−60 °C under a 3−5 bar ammonia atmosphere, the pressure was reduced to ambient pressure, and the temperature was allowed to fall to room temperature. The resulting mixture was concentrated in vacuo, and the residue was triturated with 80% aqueous acetone. The resulting crystals were filtered to give the desired product (1.60 g, 81.7% purity, 72.8% yield) as pale yellow crystals. An analytical sample was obtained by recrystallization from acetone/water and ethanol/water.

9-(5-*O*-Acetyl-3-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-chloro-9*H*-purine (15). To a solution of 6-chloro-9-(2,5-di-*O*-acetyl-3-deoxy-*β*-D-*erythro*-pentofuranosyl)-9*H*-purine (5.00 g, 14.1 mmol) in methanol (25 mL) was added triethylamine (2.00 mL, 14.3 mmol). After additional stirring for 66 h, the reaction mixture was neutralized (pH 7.0) with 1 N hydrogen chloride. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate = 1/3) to give the desired product (1.48 g, 4.73 mmol, 33.5% yield). An analytical sample was obtained by recrystallization from hexane/ethyl acetate: mp 161−164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (1H, s, H-2), 8.43 (1H, s, H-8), 6.04 (1H, d, J = 2.3 Hz, H-1′), 4.84−4.90 (1H, m, H-2′), 4.77−4.84 (1H, m, H-4′), 4.42 (1H, dd, J = 12.4, 3.0 Hz, H-5′a), 4.31 (1H, dd, J = 12.4, 4.4 Hz, H-5′b), 2.18−2.31 (2H, m, H-3′ab), 2.07 (3H, s 5′O-Ac); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.4, 151.9, 151.4, 149.4, 145.6, 131.6, 91.7, 78.5, 74.5, 65.0, 34.6, 20.7; IR (KBr): 3230, 1752, 1593, 1569, 1241, 1134 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}N_4O_4Cl$ (M + H)$^+$ 313.0704, found 313.0690. Anal. Calcd for $C_{12}H_{13}N_4O_4Cl$: C, 46.09; H, 4.19; N, 17.92. Found: C, 46.13; H, 4.24; N, 17.96.

9-(5-*O*-Acetyl-2,3-dideoxy-2-fluoro-*β*-D-*threo*-pentofuranosyl)-6-chloro-9*H*-purine (16) and 9-(2,3-Dideoxy-2-

fluoro-β-D-*threo*-pentofuranosyl)adenine (1, FddA). To a solution of 9-(5-*O*-acetyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-6-chloro-9*H*-purine (100 mg, 0.320 mmol) in dichloromethane (3.2 mL) was added pyridine (0.16 mL, 1.9 mmol) at 5 °C. At this temperature, to this solution was added morpholinosulfur trifluoride (98 μL, 0.80 mmol) dropwise with vigorous stirring. After stirring for 3 h at reflux, the reaction mixture was recooled to room temperature and then poured into aqueous saturated sodium hydrogencarbonate (20 mL) and dichloromethane (20 mL) with vigorous stirring. After additional stirring for 30 min, the reaction mixture was separated into layers. The organic layer was washed with 0.5 N hydrogen chloride (20 mL) and saturated aqueous sodium hydrogencarbonate (20 mL), dried over sodium sulfite, and concentrated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 10/1) to give the desired product (38.9 mg, 0.124 mmol, 38.8% yield) as a foam. An analytical sample was obtained by recrystallization from hexane/ethyl acetate.Mp 201 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (1H, s, H-2), 8.45 (1H, d, J = 2.7 Hz, H-8), 6.43 (1H, dd, J = 18.9, 3.1 Hz, H-1′), 5.32 (1H, dddd, J = 53.4, 5.1, 3.1, 1.8 Hz, H-2′), 4.50−4.59 (1H, m, H-4′), 4.43 (1H, dd, J = 11.9, 6.4 Hz, H-5′a), 4.32 (1H, dd, J = 11.9, 3.7 Hz, H-5′b), 2.68 (1H, dddd, J = 36.0, 15.2, 8.8, 5.2 Hz, H-3′a), 2.43 (1H, dddd, J = 25.7, 15.2, 4.5, 1.7 Hz, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 152.1, 151.4, 144.6 (d, J = 5.6 Hz), 90.5 (d, J = 189.2 Hz), 85.4 (d, J = 16.7 Hz), 75.7, 65.3, 33.7 (d, J = 20.7 Hz), 20.9; IR (KBr): 1731, 1595, 1565, 1271, 1222 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{13}N_4O_3ClF$ $(M + H)^+$ 315.0660, found 315.0651; Anal. Calcd for $C_{12}H_{12}N_4O_3ClF$: C, 45.80; H, 3.84; N, 17.80. Found: C, 46.05; H, 3.90; N, 17.79. The resulting 9-(5-*O*-acetyl-2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-6-chloro-9*H*-purine (32.4 mg, 0.103 mmol) was dissolved in tetrahydrofuran (0.5 mL). After stirring for 4 days at 60 °C under a 2.8 bar ammonia atmosphere, the pressure was reduced to ambient pressure, and the temperature was allowed to fall to room temperature. HPLC analysis showed that the desired product was obtained in 88.2% yield (23.0 mg, 0.0908 mmol).

6-Chloro-9-[3-deoxy-2-*O*-[(trifluoromethyl)sulfonyl]-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (17). To a solution of 6-chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-erythro-pentofuranosyl]-9*H*-purine (40.0 g, 78.0 mmol) in dichloromethane (400 mL) were added pyridine (18.9 mL, 234 mmol) and trifluoromethanesulfonic anhydride (14.4 mL, 85.8 mmol) at −10 °C. After being stirred for 4 h at −10 °C, the reaction mixture was treated with ice (220 g) and water (100 g), acidified (pH 3.0) with 2 M sulfuric acid, and separated into layers. The organic layer was washed with water (320 mL) and aqueous sodium hydrogencarbonate (320 mL) and concentrated in vacuo. The residue was concentrated azeotropically with toluene to give the desired product quantitatively as a foam which was used without further purification. An analytical sample was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1): mp 108−112 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (1H, s, H-2), 8.30 (1H, s H-8), 7.21−7.40 (15H, m, 5′O-Tr), 6.32 (1H, d, J = 1.2 Hz, H-1′), 6.18 (1H, bd, J = 5.2 Hz, H-2′), 4.62−4.73 (1H, m, H-4′), 3.50 (1H, dd, J = 10.8, 3.1 Hz, H-5′a), 3.40 (1H, dd, J = 10.8, 4.5 Hz, H-5′b), 2.87 (1H, ddd, J = 15.0. 9.7, 5.4 Hz, H-3′a), 2.44 (1H, ddd, J = 14.7, 5.6, 1.4 Hz, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 151.4, 150.4, 143.7, 143.0, 132.2, 128.4, 127.8, 127.2, 118.3 (q, J = 318.1 Hz), 89.6, 88.9, 87.1, 80.2, 63.5, 33.1; IR (KBr): 1593, 1564, 1419, 1248, 1211, 1143, 1081 cm^{-1}; HRMS (FAB+) calcd for $C_{30}H_{25}N_4O_5ClF_3S$ $(M + H)^+$ 645.1186, found 645.1179; Anal. Calcd for $C_{30}H_{24}N_4O_5ClF_3S$: C, 55.86; H, 3.75; N, 8.69. Found: C, 55.40; H, 4.04; N, 8.46.

6-Chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-*threo*-pentofuranosyl]-9*H*-purine (11). Reaction with $Et_3N{\cdot}3HF$. To a solution of 6-chloro-9-[3-deoxy-2-*O*-[(trifluoromethyl)sulfonyl]-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (50.3 g, 78.0 mmol) in toluene (2000 mL) were added triethylamine trihydrofluoride (50.3 g, 50.9 mL, 312 mmol) and triethylamine (15.8 g, 21.8 mL, 156 mmol) at 32 °C. After being stirred for 43 h at 40 °C, the reaction mixture was treated with water (400 mL) and separated into layers. The organic layer was washed with water (2 × 400 mL), aqueous sodium hydrogencarbonate (400 mL), and aqueous sodium carbonate (2 × 400 mL). After concentration, HPLC analysis showed that 25.9 g of desired product was obtained (64.5% yield in two steps). The side product **12** was also obtained in 32.6% yield.

Purification and Separation of 6-Chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-*threo*-pentofuranosyl]-9*H*-purine (11). To part of the resulting concentrated toluene solution (260 mL) of the mixture of 6-chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-*threo*-pentofuranosyl]-9*H*-purine (15.7 g, 30.5 mmol) and **12** was added 80% acetic acid (120 mL). After vigorous stirring for 6 h at 10 °C, the reaction mixture was separated into layers. The aqueous layer was extracted with toluene (24 mL), and the combined organic layers were washed with water (2 × 24 mL). The organic layers were treated with tetrahydrofuran (48 mL) and 80% acetic acid (3 mL) and again separated into layers. The organic layer was concentrated to 50 mL under reduced pressure at 20 °C and treated with cyclohexane (72 mL). The resulting crystals were filtered, washed with cyclohexane (2 × 24 mL), and dried under reduced pressure to give the pure desired product (10.9 g, 21.2 mmol, 69.5% yield) as white crystals.

6-Chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-*threo*-pentofuranosyl]-9*H*-purine (11). Reaction with $Et_3N{\cdot}3HF$ through 6-Chloro-9-[3-deoxy-2-*O*-(sulfurylimidazolyl)-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (18). To a solution of 6-chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (590 mg, 1.15 mmol) in dichloromethane (11 mL) were added pyridine (0.17 mL, 2.05 mmol) and sulfuryl chloride (0.11 mL, 1.37 mmol) at −35 °C. After being stirred for 30 min at −35 °C, the reaction mixture was treated with imidazole (360 mg, 5.13 mmol) and stirred for 16 h at room temperature. To this reaction mixture was added imidazole (800 mg, 1.14 mmol), and the result was stirred for 4.5 h at room temperature. The reaction mixture was treated with water and separated into layers. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over sodium sulfate, concentrated in vacuo, and purified by silica gel column chromatography to give the desired product (790 mg) as an oil.

To a solution of 6-chloro-9-[3-deoxy-2-*O*-(sulfurylimidazolyl)-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (110 mg, 0.18 mmol) in toluene (1.8 mL) was added triethylamine trihydrofluoride (0.18 mL, 1.1 mmol) at 50 °C. After being stirred for 2 days at 50 °C, the reaction mixture was cooled to room temperature and treated with ethyl acetate and aqueous sodium hydrogencarbonate. The reaction mixture was separated into layers and dried over sodium sulfate. After concentration, HPLC analysis showed that 38.0 mg of the desired product was obtained (41.9% yield in two steps).

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1** and **6**−**17** and NOESY data for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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