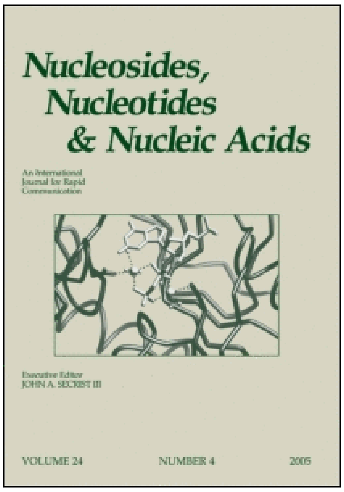


**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# CONVENIENT SYNTHESIS OF FLUORINATED NUCLEOSIDES WITH PERFLUOROALKANESULFONYL FLUORIDES

Satoshi Takamatsu[a]; Satoshi Katayama[a]; Naoko Hirose[a]; Etienne De Cock; Geert Schelkens; Marc Demillequand; Jozef Brepoels; Kunisuke Izawa[a]
[a] AminoScience Laboratories, Kawasaki-ku, Kawasaki, Japan

**To cite this Article** Takamatsu, Satoshi , Katayama, Satoshi , Hirose, Naoko , De Cock, Etienne , Schelkens, Geert , Demillequand, Marc , Brepoels, Jozef and Izawa, Kunisuke(2002) 'CONVENIENT SYNTHESIS OF FLUORINATED NUCLEOSIDES WITH PERFLUOROALKANESULFONYL FLUORIDES', Nucleosides, Nucleotides and Nucleic Acids, 21: 11, 849 — 861

**To link to this Article: DOI:** 10.1081/NCN-120016572
**URL:** http://dx.doi.org/10.1081/NCN-120016572

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 21, Nos. 11 & 12, pp. 849–861, 2002

# CONVENIENT SYNTHESIS OF FLUORINATED NUCLEOSIDES WITH PERFLUOROALKANESULFONYL FLUORIDES

**Satoshi Takamatsu,[1],* Satoshi Katayama,[1] Naoko Hirose,[1]
Etienne De Cock,[2] Geert Schelkens,[2] Marc Demillequand,[2]
Jozef Brepoels,[2] and Kunisuke Izawa[1]**

[1]AminoScience Laboratories, Ajinomoto Co., Inc., 1-1, Suzuki-cho,
Kawasaki-ku, Kawasaki 210-8681, Japan
[2]n.v. OmniChem, Cooppallaan 91, B-9200 Wetteren, Belgium

## ABSTRACT

Perfluoroalkanesulfonyl fluorides are effective dehydroxy-fluorination agents for the hydroxyl group at the sugar moiety of nucleoside derivatives and give the corresponding fluorinated nucleosides in good yield with an inversion of configuration in a single step.

## INTRODUCTION

Fluorinated organic compounds have attracted much attention because of their unique physiological activities.[1] Fluorinated nucleosides and their derivatives are an important class of non-natural compounds that have been used in a wide variety of biological applications.[2] They are usually synthesized by selective fluorination of preformed *non*-fluorinated nucleosides or by glycosylation of heterocyclic bases with fluoro-sugar derivatives.[3] However, since it is well known that the glycosylation of 2′-deoxysugar suffers from a

---

*Corresponding author. Fax: 81 3 5250 8273; E-mail: satoshi_takamatsu@ajinomoto.com

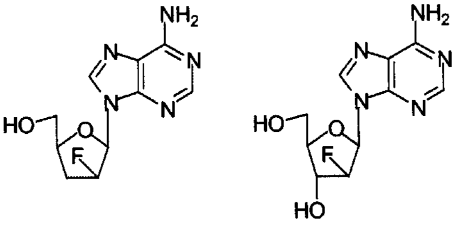
DOI: 10.1081/NCN-120016572
1525-7770 (Print); 1532-2335 (Online)
www.dekker.com

low chemical efficiency, convenient methods for the direct fluorination of nucleosides are needed.

Various methods have been developed to substitute the hydroxyl group of nucleosides with fluorine atoms.[4] These dehydroxy-fluorination processes can be classified into two types: i.e., one involves the formation of activated ester and subsequent fluorination by nucleophilic substitution, and the other involves the single-step dehydroxy-fluorination of alcohol. In the former case, although many methods are available to prepare activated ester and generate a nucleophilic fluoride anion, at least two steps are needed to substitute the hydroxyl group of the nucleoside with fluorine. In the latter case, the fluorination agent acts as both an activating agent and a fluoride source. Consequently, procedures using diethylaminosulfur trifluoride (DAST),[5] Olah's reagent,[6] and fluoroalkylamine reagent (FAR)[7] have been developed for fluorination in a single step at a laboratory scale.

In the course of our studies[8] on the industrial synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA),[9] we became interested in the direct introduction of a fluorine atom to the C2′-β position of the sugar moiety of purine nucleoside. However, this fluorination has proven to be a challenge in nucleoside chemistry. Watanabe, Pankiewicz and their co-workers have also reported[10] problems in the preparation of such C2′-β fluorinated nucleosides to obtain F-ara-A (**2**) by direct fluorination. We have shown that this challenging fluorination at the C2′-β position of the purine nucleoside can be improved by the introduction of a 6-chloro group.[8]

Our interest further led us to investigate the use of DAST and triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$)[11] as a fluorinating agent for the C2′-β position. Although the results of dehydroxy-fluorination were excellent in both cases, in the case of DAST, the reagents are unstable. Furthermore, due to its toxicity and explosive nature, it is not available in large quantities, which prevents this method from being industrially useful. In the case of $Et_3N{\cdot}3HF$, dehydroxy-fluorination requires activation of the hydroxyl group as trifluoromethanesulfonate with expensive triflic anhydride. Thus, two uneconomical steps are necessary. Consequently, an industrially advantageous and safe method for dehydroxy-fluorination is desired.



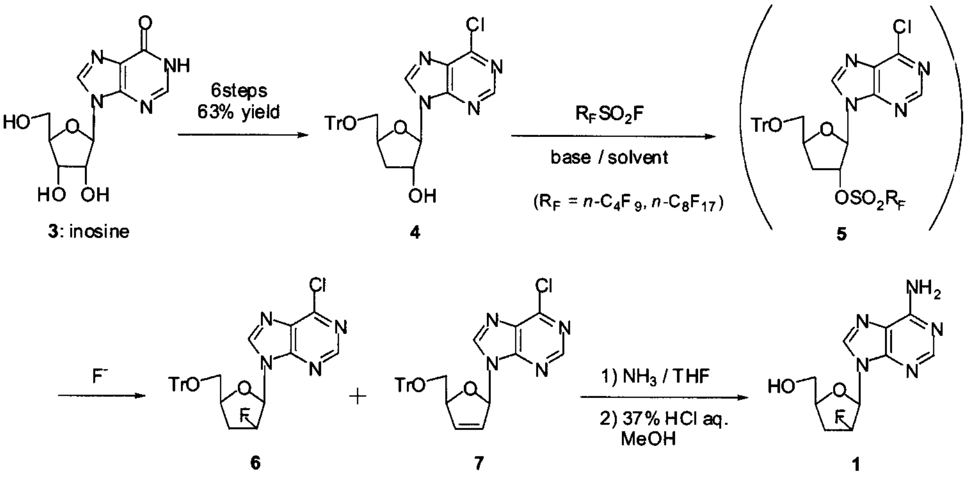
**1**: FddA **2**: F-ara-A

*Figure 1.* C2′-β fluorinated anti-viral nucleosides.

## RESULTS AND DISCUSSION

Among the reagents that can achieve dehydroxy-fluorination in a single step, perfluoroalkanesulfonyl fluorides, such as perfluoro-1-butanesulfonyl fluoride (nonafluoro-1-butanesulfonyl fluoride, $C_4F_9SO_2F$, NfF)[12] and perfluoro-1-octanesulfonyl fluoride ($C_8F_{17}SO_2F$, OctF),[13] appear to be the reagents of choice, since they are only mildly corrosive and are readily available commercially.[14] These reagents are stable at room temperature and less moisture-sensitive, and are thus not difficult to handle at an industrial scale. Perfluoroalkanesulfonyl fluoride can transform an alcohol into its perfluoroalkanesulfonate[15] in the presence of a base. This reagent also provides a fluoride anion for nucleophilic displacement of the sulfonate to give fluorination in a single step. Vorbrüggen et al. reported[16] a conversion of aliphatic alcohols to the corresponding fluorides by treating the alcohols with NfF. Since these reagents have been used for the fluorination of rather simple substrates,[17] we were interested in using them to convert the hydroxyl group of nucleosides to give the corresponding fluorides in a single step.

Thus, 6-chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (**4**) was synthesized from inosine (**3**),[8c,d,18] the 2′-hydroxyl group of which must be converted to C2′-β fluoride to obtain the anti-HIV nucleoside FddA (**1**) (Sch. 1). Vorbrüggen et al. reported that the combination of NfF with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in non-polar solvents efficiently converts primary and secondary alcohols into their corresponding fluorides. In our first experiment, we noticed that NfF reacted slowly with the hydroxyl group in **4** in the presence of triethylamine, even at 50°C (Table 1, run 1). Using pyridine as a base, the reaction did not proceed



*Scheme 1.* Fluorination with perfluoroalkanesulfonyl fluorides and synthesis of FddA.

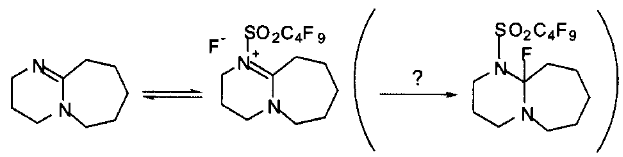
*Table 1.* Conversion of Alcohol of Nucleoside Derivative **4** into Their Corresponding Fluoride **6** with Perfluoroalkanesulfonyl Fluorides

| Run | Reagent[a] (eq.) | Base (eq.) | Solvent | L/Kg[b] | Temp. (°C) | Time (h) | HPLC area%[c] **4** | **5** | **6** | **7** | F/E ratio[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | NfF (1.2) | TEA (2.0) | toluene | 50 | 50 | 48 | 88.5 | 5.0 | 4.0 | 1.3 | (55/45) |
| 2 | NfF (1.2) | DBU (2.0) | toluene | 10 | 20 | 3 | 0.3 | 1.0 | 33.5 | 61.9 | 35/65 |
| 3 | NfF (1.2) | DBU (1.3) | toluene | 50 | 50 | 5 | 8.0 | 14.0 | 42.0 | 34.1 | 55/45 |
| 4 | NfF (1.2) | DBU (1.2)[e] | toluene | 10 | 75 | 1 | 86.5 | 2.9 | 3.3 | 3.6 | (48/52) |
| 5 | OctF (1.2) | DBU (2.0) | toluene | 10 | 20 | 4 | 26.0 | 0.0 | 22.9 | 44.1 | 34/66 |
| 6 | NfF (4.0) | NEP (2.0) | toluene | 10 | 50 | 44 | 1.0 | 0.3 | 64.0 | 29.8 | 68/32 |
| 7 | NfF (2.0) | DMCHA (2.0) | toluene | 10 | 50 | 23 | 0.6 | 1.1 | 67.6[f] | 26.5 | 72/28 |

[a] NfF = perfluoro-1-butanesulfonyl fluoride, OctF = perfluoro-1-octanesulfonyl fluoride.
[b] Quantity of solvent used per kilogram of substrate (solvent (L)/substrate (Kg)).
[c] HPLC area% was calculated by excluding the influence of the solvent peak.
[d] F/E ratio was calculated from the HPLC peak areas of **6** and **7**.
[e] DBU and NfF were mixed before addition.
[f] The yield of **6** was 62.4%.

at all. However, immediately after the addition of DBU to this mixture, the alcohol was converted into fluorinated and eliminated products.

We next sought to improve the ratio of fluorinated product **6** to eliminated product **7**.[8c,d] The area of the HPLC peak in Table 1 was calculated by excluding the influence of the solvent peak. The ratio (F/E) was calculated from the HPLC peak area of both products.[19] In the course of the reaction, we observed the formation of presumed intermediate **5** by HPLC. Among the solvents tested, toluene gave the best results. At 20°C in 10 L/Kg of toluene, we obtained a F/E of 35/65 (run 2). If we reduced the amount of DBU from 2.0 to 1.3 equivalents at 50°C in 50 L/Kg of toluene, the F/E ratio increased to 55/45 (run 3). Remarkably, these reactions go to completion with 1.2 equivalents of NfF. OctF is also available in large quantities. Several test reactions were conducted to compare these reagents. In most cases, both the rate of the reaction and the F/E ratio were worse with OctF (runs 2 and 5). We assume that elimination is enhanced by steric factors. Thus, the perfluorooctanesulfonate leads to more elimination than perfluorobutanesulfonate.



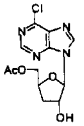
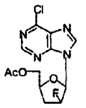
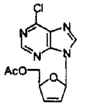
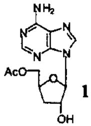
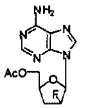
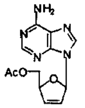
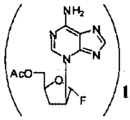
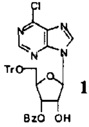
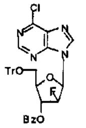
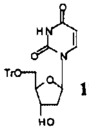
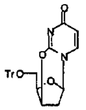
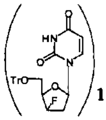
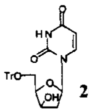
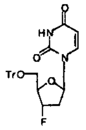
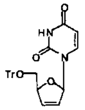
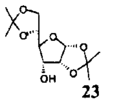
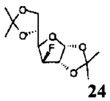
*Scheme 2.* Reaction between NfF and DBU.

The rather high percentage of eliminated product is mainly due to the basicity of DBU. In addition, when DBU and NfF were mixed before addition, the mixture became warm and the reaction did not proceed (run 4). We speculate that these reactions are blocked due to a reaction between the reagent and base (Sch. 2). A similar interaction between NfF and 4-pyrrolidinopyridine has been reported.[16a] Accordingly, we decided to find other moderate bases for this reaction.

The base must be a good proton acceptor with moderate basicity to avoid elimination and must also have low nucleophilicity. Among the bases we studied, *N*-ethylpiperidine (NEP) gave better results with regard to both the reaction rate and selectivity. At 50°C, with 4 equivalents of NfF and 2 equivalents of NEP as a base, the reaction went to completion after 44 h and the area% of fluorinated product was 64.0% (run 6). *N*,*N*-Dimethylcyclohexylamine (DMCHA) also seems to be a good substitute for DBU. With 2 equivalents of NfF and 2 equivalents of DMCHA as a base, the area% of the fluorinated target reached 67.6% after 23 h (run 7). In this case, after aqueous work-up, HPLC analysis showed that the yield of the fluorinated compound was 62.4% before separation. The yield of **6** from **4** with NfF was much greater than that with DAST (43%).[8c] Both the safety and yield of fluorination, which is the key step in the total synthesis, were greatly improved with NfF.

Although the fluorination process was improved, it still gave a 72:28 mixture of fluorinated compound **6** and eliminated product **7**. For a large-scale procedure, a purification method that did not require column separation was required. One of the advantages of C2′-β fluorinated nucleoside is its stability in acid[9a,b] due to its C2′-β fluoride.[20] In contrast, 2′,3′-dideoxydidehydro nucleoside is acid-labile. In fact, treatment of a mixture of fluorinated nucleoside **6** and 2′,3′-dideoxydidehydro nucleoside **7** with 80% acetic acid in toluene (80% acetic acid/toluene = 1/1) for 3 h at 10°C led to the recovery of **6** without any loss, while **7** was completely decomposed. After phase separation, the resulting crude **6** in the organic phase was subjected to crystallization by the addition of cyclohexane to give pure **6**. The yield of **6** from **4** was 49.8% by fluorination and separation (run 7), which is greater than that we reported previously (45%).[8d] Finally, after separation, compound **6** was treated with ammonia in tetrahydrofuran (THF) followed by acidic hydrolysis of the 5′-*O*-trityl group to give FddA (**1**). Its

*Table 2.* Dehydroxy-fluorination of the Hydroxyl Group in Nucleosides and a Carbohydrate

| Run | Subtrate | NfF[a] (eq.) | DMCHA (eq.) | Solvent | Temp. (°C) | Time (h) | Productive/Yield %[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 |  **8** | 2.0 | 2.0 | BTF | 50 | 20 |  **9** | 48.3 |  **10** | 42.0 | | |
| 2 |  **11** | 4.0 | 4.0 | THF | 50 | 20 |  **12** | 7.6 |  **13** | 33.8 |  **14** | 38.3[c] |
| 3 |  **15** | 2.0 | 2.0 | toluene | 50 | 24 |  **16** | 66.2 | | | | |
| 4 |  **17** | 2.0 | 2.0 | toluene | 50 | 24 |  **18** | quant. |  **19** | 0[c] | | |
| 5 |  **20** | 4.0 | 4.0 | THF | reflux | 48 |  **21** | 20.4 |  **22** | 33.0 | | |
| 6 |  **23** | 2.0 | 2.0 | toluene | 50 | 64 |  **24** | 47.3[d] | | | | |

[a] NfF = perfluoro-1-butanesulfonyl fluoride.

[b] The yield was calculated from the results of HPLC analysis.

[c] HPLC area%.

[d] separated yield.

spectroscopic properties were identical in all respects to the published data.[8a,d,9] This method proceeds without using a corrosive reagent or column separation. Accordingly, the present method is suitable for large-scale synthesis of C2′-β fluorinated nucleoside **1**.

To further demonstrate the applicability of this system, the dehydroxy-fluorination of the hydroxyl group in other nucleosides and a carbohydrate was examined. Table 2 summarizes some of our additional experimental results. Single-step dehydroxy-fluorination of the nucleosides and carbohydrate proceeded smoothly to give the corresponding fluorinated compounds in most cases. The NfF and DMCHA system was used in benzotrifluoride (BTF) to achieve the dehydroxy-fluorination of 6-chlorinated 5′-*O*-acetyl compound **8**[8c,d] and gave the corresponding fluorinated compound **9** and eliminated compound **10** in almost a 1:1 ratio (run 1). In contrast, 6-aminated compound **11** gave 7.6% of fluorinated compound **12**, but more eliminated compound **13** (run 2). In this case, the other main peak attributed to an iso-nucleoside **14**[10] was found, due to the nucleophilicity of the adenine base and consequent intramolecular rearrangement. 6-Chloropurine riboside derivative **15**[8a,b] underwent dehydroxy-fluorination to give fluorinated **16**, which is an intermediate in the synthesis of F-ara-A **2**,[21] in good yield (66.2%, run 3). These single-step dehydroxy-fluorination results (runs 1–3) seem to be as good as those reported previously.[8a,d,22]

When we reacted 5′-*O*-trityl-2′-deoxyuridine **17** with the NfF and DMCHA system, we obtained 2,3′-anhydrouridine **18** almost quantitatively, instead of β-fluorinated compound **19** (run 4).[17] However, 3′-β-hydroxyl compound **20** readily reacted with NfF in the presence of DMCHA to give the corresponding fluoride **21** along with eliminated product **22** (run 5). This system was also used for the dehydroxy-fluorination of a carbohydrate. The α-D-allofuranose **23** gave fluorinated α-D-glucofuranose **24**, which is used for the synthesis of many biologically active compounds,[23] in moderate yield (run 6).

In summary, we have shown that perfluoroalkanesulfonyl fluorides are convenient and synthetically useful reagents for the conversion of a hydroxyl group to a corresponding fluoride with an inversion of configuration. The combination of NfF with NEP or DMCHA appears to be the reagent of choice, since it gives good results regarding selectivity between fluorination and elimination, and a good rate of reaction. The present method is useful for the synthesis of various fluorinated nucleosides and hydrocarbons, including FddA and F-ara-A.

## EXPERIMENTAL SECTION

All reagents were purchased and used without further purification. 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) 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 $CDCl_3$ (δ 77.0) or DMSO-$d_6$ (δ 39.5) as an internal standard. Infrared (IR) spectra were recorded on a Perkin Elmer PARAGON-1000 FT-IR spectrometer and are reported in wavenumber ($cm^{-1}$). Mass spectra (MS) were obtained with FAB (fast atom bombardment) ionization.

The yields of the products in Table 2 (runs 1–5) were calculated from the results of HPLC analysis by comparison with standard compounds. The products were also separated by preparative silica gel plate and characterized by mass spectra. After the reaction, the total reaction mixture was dissolved in THF and diluted by the mobile phase in HPLC. A solution of the standard compound was also prepared separately. HPLC analysis was used to calculate the yield by comparing the peak area of the reaction mixture with that of the standard. The standard products were prepared previously in our laboratory (**9**,[8d] **12**,[22] and **16**[8b]), according to procedures described in the literature (**10**,[24] **13**,[25] and **18**[26]), or by treating the corresponding nucleosides, which were purchased commercially, with trityl chloride and diisopropylamine in dimethylformamide, followed by silica gel column chromatography separation (**21** and **22**).

**6-Chloro-9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-*threo*-pentofuranosyl]-9*H*-purine (6). Reaction with OctF and DBU.** To a solution of 6-chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (200 mg, 0.390 mmol) in toluene (2.0 mL) was added 1,8-diazabicyclo[5,4,0]undec-7-ene (0.117 mL, 0.780 mmol). To this solution was added perfluoro-1-octanesulfonyl fluoride (0.129 mL, 0.468 mmol) dropwise with stirring. After stirring for 4 h at 20°C, this reaction mixture was cooled to room temperature. HPLC analysis showed that the desired product was obtained in 22.9 area%.

**Reaction with NfF and NEP.** To a solution of 6-chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (500 mg, 0.975 mmol) in toluene (5 mL) was added *N*-ethylpiperidine (0.268 mL, 1.95 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride (0.70 mL, 3.90 mmol) dropwise with stirring. After stirring for 44 h at 50°C, this reaction mixture was cooled to room temperature. HPLC analysis showed that the desired product was obtained in 64.0 area%.

**Reaction with NfF and DMCHA.** To a solution of 6-chloro-9-[3-deoxy-5-*O*-(triphenylmethyl)-β-D-*erythro*-pentofuranosyl]-9*H*-purine (30.0 g, 58.5 mmol) in toluene (300 mL) was added *N,N*-dimethylcyclohexylamine (17.7 mL, 117 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride (23.3 mL, 117 mmol) dropwise with stirring. After stirring for 23 h at 50°C, HPLC analysis showed that the desired product was obtained in 67.6 area%. To the reaction mixture was then added 5% aqueous ammonium chloride (75 mL), and the mixture was separated into layers. The lower layer was extracted with toluene (30 mL) and the combined organic layers were washed with 5% aqueous ammonium chloride (75 mL) and water (75 mL). HPLC analysis showed that the desired product was obtained in 62.4% yield (18.8 g, 36.5 mmol). The toluene solution was used without further purification.

The toluene solution was concentrated under reduced pressure and to the resulting concentrated toluene solution (150 mL) of the mixture of **6** and **7** was added 80% acetic acid (150 mL) at 10°C. After stirring for 3 h at 10°C, the reaction mixture was separated into layers. The organic layer was washed with water (150 mL), and then treated with cyclohexane (150 mL). The resulting crystals were filtered, washed with cyclohexane (150 mL), and dried under reduced pressure to give the pure desired product (15.0 g, 29.1 mmol, 49.8% yield from **4**) as white crystals. Mp 191–192°C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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$^{-1}$; HRMS (FAB+) calcd for $C_{29}H_{25}N_4O_2FCl$ $(M + H)^+$ 515.1650, found 515.1658.

**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 (15.0 g, 29.1 mmol) was dissolved in tetrahydrofuran (250 mL). After stirring for 72 h at 70°C under a 7–8 bar ammonia atmosphere, the temperature was allowed to reach room temperature, and the pressure was reduced to ambient pressure. The resulting mixture was concentrated in vacuo to give the desired product quantitatively, which was used without further purification.

To a solution of the resulting 9-[2,3-dideoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-*threo*-pentofuranosyl]adenine in methanol (144 mL) was added 37% aqueous hydrogen chloride (4.8 mL). After being stirred for 4 h at room temperature, to the reaction mixture was again added 37% aqueous hydrogen chloride (2.4 mL). After additional stirring for 4 h at room temperature, the reaction mixture was quenched (pH 4.5) with 25% aqueous ammonia. After concentration in vacuo, the residue was dissolved in water

(58 mL) and ethyl acetate (53 mL). After vigorous stirring, the reaction mixture was acidified (pH 2.0) with 37% aqueous hydrogen chloride and separated into layers. The aqueous layer was washed with ethyl acetate (2 × 14.4 mL), neutralized (pH 7–8) with 25% aqueous ammonia, and slightly concentrated under reduced pressure to remove the trace methanol. The resulting slurry was stirred for 16 h at room temperature and then cooled to 0°C. After stirring for an additional 1 h, the resulting crystals were filtered, washed with cold water, and dried at 50°C under reduced pressure to obtain the desired product (5.34 g, 21.1 mmol, 72.4% yield from **6**) as white crystals. Mp 226–227°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$^{-1}$; HRMS (FAB+) calcd for $C_{10}H_{13}N_5O_2F$ $(M + H)^+$ 254.1053, found 254.1048.

**9-(5-*O*-Acetyl-2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-6-chloro-9*H*-purine (9).** To a solution of 9-(5-*O*-acetyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-6-chloro-9*H*-purine (200 mg, 0.640 mmol) in benzotrifluoride (4.0 mL) was added *N,N*-dimethylcyclohexylamine (0.192 mL, 1.28 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride (0.230 mL, 1.28 mmol) dropwise with stirring. After stirring for 20 h at 50°C, this reaction mixture was cooled to room temperature. HPLC analysis showed that the desired product was obtained in 49.3% yield, and the eliminated product was obtained in 42.0% yield.

**9-(5-*O*-Acetyl-2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (12).** To a solution of 9-(5-*O*-acetyl-3-deoxy-β-D-*erythro*-pentofuranosyl)adenine (100 mg, 0.341 mmol) in tetrahydrofuran (3.4 mL) was added *N,N*-dimethylcyclohexylamine (0.204 mL, 1.36 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride (0.244 mL, 1.36 mmol) dropwise with stirring. After stirring for 20 h at 50°C, this reaction mixture was cooled to room temperature. HPLC analysis showed that the desired product was obtained in 7.6% yield, and the eliminated product was obtained in 33.8% yield.

**9-[3-*O*-Benzoyl-2-deoxy-2-fluoro-5-*O*-(triphenylmethyl)-β-D-arabinofuranosyl]-6-chloro-9*H*-purine (16).** To a solution of 9-[3-*O*-benzoyl-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl]-6-chloro-9*H*-purine (1.00 g, 1.58 mmol) in toluene (10 mL) was added *N,N*-dimethylcyclohexylamine (0.473 mL, 3.16 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride

(0.567 mL, 3.16 mmol) dropwise with stirring. After stirring for 24 h at 50°C, this reaction mixture was cooled to room temperature. To the reaction mixture was added aqueous saturated sodium bicarbonate (10 mL), and then toluene (10 mL) and ethyl acetate (20 mL). After additional stirring, the reaction mixture was separated into layers. The organic layer was washed with 5% aqueous citric acid (10 mL) and aqueous saturated sodium bicarbonate (10 mL). HPLC analysis showed that the desired product was obtained in 66.2% yield.

**2′-Deoxy-5′-*O*-(triphenylmethyl)-*O*$^2$,3′-cyclouridine (18).** To a solution of 5′-*O*-(triphenylmethyl)-2′-deoxyuridine (200 mg, 0.425 mmol) in toluene (2.0 mL) was added *N,N*-dimethylcyclohexylamine (0.127 mL, 0.850 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride (0.153 mL, 0.850 mmol) dropwise with stirring. After stirring for 24 h at 50°C, this reaction mixture was cooled to room temperature. HPLC analysis showed that 2′-deoxy-5′-*O*-(triphenylmethyl)-*O*$^2$,3′-cyclouridine was obtained almost quantitatively.

**2′,3′-Dideoxy-3′-fluoro-5′-*O*-(triphenylmethyl)uridine (21).** To a solution of 1-[2-deoxy-5-*O*-(triphenylmethyl)-β-D-xylofuranosyl]uracil (200 mg, 0.425 mmol) in tetrahydrofuran (2.0 mL) was added *N,N*-dimethylcyclohexylamine (0.255 mL, 1.70 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride (0.305 mL, 1.70 mmol) dropwise with stirring. After stirring for 48 h at reflux, this reaction mixture was cooled to room temperature. HPLC analysis showed that the desired product was obtained in 20.4% yield, and the eliminated product was obtained in 33.0% yield.

**3-Deoxy-3-fluoro-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (24).** To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (5.00 g, 19.2 mmol) in toluene (50 mL) was added *N,N*-dimethylcyclohexylamine (5.76 mL, 38.4 mmol). To this solution was added perfluoro-1-butanesulfonyl fluoride (6.90 mL, 38.4 mmol) dropwise with stirring. After stirring for 64 h at 50°C, this reaction mixture was cooled to room temperature. To the reaction mixture was added aqueous saturated ammonium chloride (50 mL), and the mixture was then separated into layers. The aqueous layer was extracted with toluene (50 mL) and the combined organic layers were washed with aqueous saturated ammonium chloride (× 2). The organic layer was concentrated in vacuo and the residual oil was purified by silica gel column chromatography to give the desired product (2.38 g, 9.07 mmol, 47.3% yield) as an oil.

## ACKNOWLEDGMENT

The authors thank Prof. Tokumi Maruyama of Tokushima Bunri University for his scientific discussions and help in preparing the manuscript.

# REFERENCES

1. For reviews on biologically active organofluorine compounds see: (a) Welch, J.T. Tetrahedron **1987**, *43*, 3123–3197; (b) Liebman, J.F.; Greenberg, A.; Dolbier Jr., W.R. *Fluorine-containing Molecules, Structure, Reactivity, Synthesis and Application*; VCH: New York, 1988; (c) Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley: New York, 1991; (d) Patani, G.A.; LaVoie, E.J. Chem. Rev. **1996**, *96*, 3147–3176.
2. For reviews on biologically active fluorinated nucleosides see: (a) Huryn, D.M.; Okabe, M. Chem. Rev. **1992**, *92*, 1745–1768; (b) *Nucleosides Nucleotides as Antitumor and Antiviral Agents*; Chu, C.K., Baker, D.C., Ed.; Plenum Press: New York, 1993; (c) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.R.; Earl, R.; Guedj, R. Tetrahedron **1994**, *50*, 10,611–10,670; (d) *Anti-AIDS Drugs Development: Challenges, Strategies and Prospects*; Baba, M., Moham, P., Ed.; Harwood Academic: Switerland, 1995.
3. Novo, B.; Resnati, G. Stereocontrolled Synthesis of Fluorinated Carbohydrates. In *Enantiocontrolled Synthesis of Fluoro-organic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V.A., Ed.; John Wiley: New York, 1999; 349–390.
4. For recent reviews on fluorination of organic compounds see: (a) Wilkinson, J.A. Chem. Rev. **1992**, *92*, 505–519; (b) Resnati, G. Tetrahedron **1993**, *49*, 9385–9445; (c) Mascaretti, O.A. Aldrichim. Acta **1993**, *26*, 47–58; (d) *Fluororganic Chemistry: Synthetic Challenges and Biomedicinal Rewards*. Tetrahedron Symposia in Print No. 58, Tetrahedron **1996**, *52*, 1–330; (e) Fluorine Chemistry. Chem. Rev. **1996**, *96*, 1555–1824.
5. Middleton, W.J. J. Org. Chem. **1975**, *40*, 574–578.
6. Olah, G.A.; Welch, J.T.; Vanker, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. J. Org. Chem. **1979**, *44*, 3872–3881.
7. (a) Yarovenko, N.N.; Raksha, M.A. Zh. Obshch. Khim. **1959**, *29*, 2159–2163; (b) Takaoka, A.; Iwakiri, H.; Ishikawa, N. Bull. Chem. Soc. Jpn. **1979**, *52*, 3377–3380.
8. (a) Maruyama, T.; Takamatsu, S.; Kozai, S.; Satoh, Y.; Izawa, K. Chem. Pharm. Bull. **1999**, *47*, 966–970; (b) Takamatsu, S.; Maruyama, T.; Katayama, S.; Hirose, N.; Izawa, K. Tetrahedron Lett. **2001**, *42*, 2321–2324; (c) Takamatsu, S.; Maruyama, T.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. Tetrahedron Lett. **2001**, *42*, 2325–2328; (d) Takamatsu, S.; Maruyama, T.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. J. Org. Chem. **2001**, *66*, 7469–7477.
9. (a) Marquez, V.E.; Tseng, C.K.-H.; Kelley, J.A.; Mitsuya, H.; Broder, S.; Roth, J.S.; Driscoll, J.S. Biochem. Pharmacol. **1987**, *36*, 2719–2722; (b) Marquez, V.E.; Tseng, C.K.-H.; Mitsuya, H.; Aoki, S.; Kelley, J.A.; Ford, Jr., H.; Roth, J.S.; Broder, S.; Johns, D.G.; Driscoll, J.S. J. Med. Chem. **1990**, *33*, 978–985; (c) Ruxrungtham, K.; Boone, E.; Ford, Jr., H.; Driscoll, J.S.; Davey, Jr., R.T.; Lane, H.C. Antimicrob. Agents Chemother. **1996**, *40*, 2369–2374 and references cited therein; (d) Graul, A.; Silvestre, J. Drugs of the Future **1998**, *23*, 1176–1189 and references cited therein.

10. (a) Pankiewicz, K.W.; Krzeminski, J.; Ciszewski, L.A.; Ren, W.-Y.; Watanabe, K.A. J. Org. Chem. **1992**, *57*, 553–559; (b) Pankiewicz, K.W.; Krzeminski, J.; Watanabe, K.A. J. Org. Chem. **1992**, *57*, 7315–7321; (c) Pankiewicz, K.W.; Watanabe, K.A. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C.K., Baker, D.C., Eds.; Plenum Press: New York, 1993; 55–71; (d) Pankiewicz, K.W.; Watanabe, K.A. J. Fluorine Chem. **1993**, *64*, 15–36.
11. Franz, R. J. Fluorine Chem. **1980**, *15*, 423–434.
12. (a) Beyl, V.; Niederprüm, H.; Voss, P. Justus Liebigs Ann. Chem. **1970**, *731*, 58–66; (b) Zimmer, R.; Webel, M.; Reißig, H.-U. J. Prakt. Chem. **1998**, *340*, 274–277.
13. Harzdorf, C.; Meussdoerffer, J.N.; Niederprüm, H.; Wechsberg, M. Justus Liebigs Ann. Chem. **1973**, 33–39.
14. NfF is produced in large quantities by anodic fluorination of sulfolene. See also reference 12a.
15. (a) Hansen, R.L. J. Org. Chem. **1965**, *30*, 4322–4324; (b) Subramanian, L.R.; Bentz, H.; Hanack, M. Synthesis **1973**, 293–294; (c) Stang, P.J.; Hanack, M.; Subramanian, L.R. Synthesis **1982**, 85–126.
16. (a) Bennua-Skalmowski, B.; Krolikiewicz, K.; Vorbrüggen, H. Bull. Soc. Chim. Belg. **1994**, *103*, 453–461; (b) Bennua-Skalmowski, B.; Vorbrüggen, H. Tetrahedron Lett. **1995**, *36*, 2611–2614.
17. NfF was applied to the formation of 2,3′-anhydrothymidine: Bennua-Skalmowski, B.; Vorbrüggen, H. Nucleosides & Nucleotides **1996**, *15*, 739–742.
18. Takamatsu, S.; Maruyama, T.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. Tetrahedron Lett. **2001**, *42*, 7605–7608.
19. The normalized HPLC peak area ratio (F/E) was calculated for data comparison. The ratio (F/E) is an index of fluorination reaction priority.
20. McAtee, J.J.; Schinazi, R.F.; Liotta, D.C. J. Org. Chem. **1998**, *63*, 2161–2167.
21. Maruyama, T.; Sato, Y.; Oto, Y.; Takahashi, Y.; Snoeck, R.; Andrei, G.; Witvrouw, M.; De Clercq, E. Chem. Pharm. Bull. **1996**, *44*, 2331–2334.
22. Shiragami, H.; Tanaka, Y.; Uchida, Y.; Iwagami, H.; Izawa, K.; Yukawa, T. Nucleosides & Nucleotides **1992**, *11*, 391–400.
23. (a) Sleath, P.R.; Handlon, A.L.; Oppenheimer, N.J. J. Org. Chem. **1991**, *56*, 3608–3613; (b) Yoshimura, Y.; Endo, M.; Sakata, S. Tetrahedron Lett. **1999**, *40*, 1937–1940.
24. Brossette, T.; Klein, E.; Creminon, C.; Grassi, J.; Mioskowski, C.; Lebeau, L. Tetrahedron **2001**, *57*, 8129–8143.
25. Amino, Y.; Iwagami, H. Chem. Pharm. Bull. **1991**, *39*, 622–625.
26. Colla, L.; Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, H. Eur. J. Med. Chem. Chim. Ther. **1985**, *20*, 295–301.

Received April 23, 2002
Accepted August 30, 2002