Regio- and Stereoselective Synthesis of Carbocyclic 2′,3′-Dideoxy-3′-fluoro Nucleosides as Potential Antiviral Agents

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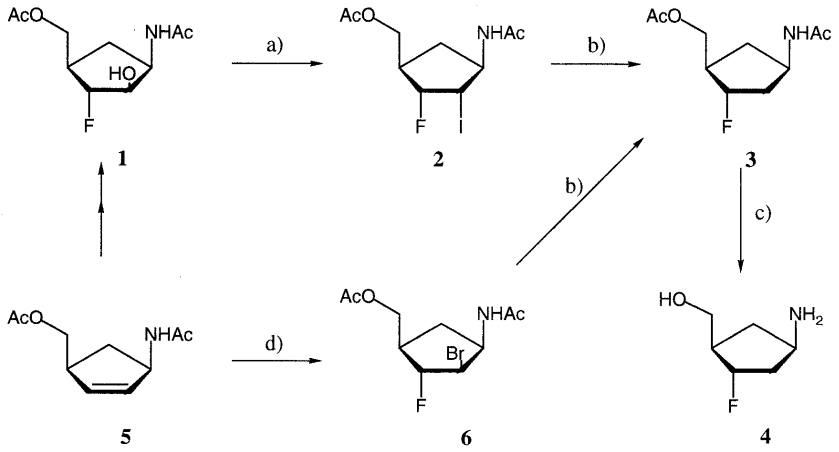
The synthesis and antiviral activity of racemic carbocyclic 2′,3′-dideoxy-3′-fluoro nucleosides are reported. Carbocyclic 2′,3′-dideoxy-3′-fluoro nucleosides were obtained from the 3-fluoro cyclopentane derivative 4, which was prepared by two methods. The *SN*2-displacement of the hydroxyl group of (±)-(1β,2α,3β,4β)-4-acetamido-2-fluoro-3-hydroxycyclopentylmethyl acetate (1) with Ph_3P–I_2 followed by tin hydride reduction afforded the 3-fluoroamino alcohol derivative 3. Alternatively, the protected fluoroamino alcohol 3 was prepared by regio- and stereoselective bromo-fluorination of *cis*-4β-acetamidocyclopent-2-enemethyl acetate (5) with hydrogen fluoride–pyridine/*N*-bromosuccinimide followed by tin hydride reduction to remove the bromine atom. Carbocyclic 2′,3′-dideoxy-3′-fluoroguanosine (14) thus obtained was moderately active against herpes simplex virus *in vitro*.

Keywords bromo-fluorination; carbocyclic nucleoside; fluoronucleoside; tin hydride reduction; antiviral agent; herpes simplex virus

Nucleoside analogues have been extensively investigated in the search for effective antiviral agents. There has been considerable interest in carbocyclic nucleosides, since the replacement of the oxygen atom of the furanose ring with methylene is a drastic change in terms of stereoelectronic effect on the nucleoside molecule and greater metabolic stability.[1] Much effort has been made to synthesize carbocyclic nucleoside analogues and also to modify the cyclopentane ring by introduction of an electronegative fluorine substituent.[2] The synthesis of a carbocyclic analogue of 3′-deoxy-3′-fluorothymidine was an important target, since it is the most potent anti-human immunodeficiency virus (anti-HIV) agent among fluorinated nucleosides so far synthesized.[3] However, only a limited amount of work has been done on the synthesis of 2′,3′-dideoxy-3′-fluoro analogues.[4]

Independently, we have studied the stereo- and regioselective introduction of a fluorine atom onto a carbocyclic sugar moiety. In this report, we describe the synthesis of 2′,3′-dideoxy-3′-fluorocarbocyclic nucleosides using two methods, and we report on the antiviral activity of the products.[5]

Chemistry For the synthesis of 3′-fluoro carbocyclic nucleoside analogues, we required the fluorocyclopentylamine (**4**) (Chart 1). The successful introduction of a fluorine atom into the carbocyclic ring by stereoselective epoxidation of *cis*-4β-acetamidocyclopent-2-enemethyl acetate (**5**)[6] followed by regioselective ring opening with hydrogen fluoride–pyridine to give the protected fluoro alcohol (**1**) with required stereochemistry has been described in an earlier report.[5] However, reduction of the phenylthionocarbonate[7] of the 2′-hydroxyl group with tin hydride gave a complex mixture. After several attempts, replacement of the hydroxyl group by hydrogen atom to afford **3** was achieved by the substitution of the hydroxyl group with iodide using Ph_3P–I_2 to give the *cis*-fluoro



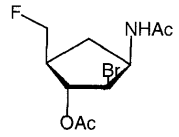
a) Ph_3P–I_2, b) Bu_3SnH, AIBN, c) 2 N HCl, d) HF–Py/NBS

Chart 1

iodide (**2**) in poor yield, followed by reduction with Bu_3SnH/azobisisobutyronitrile (AIBN).[9,10]

A different stereochemistry of the leaving group adjacent to the fluorine atom might be expected to improve the overall yield in the synthesis of the fluorinated deoxycarbocyclic sugar moiety, since the electronic effect of the fluorine atom is expected to affect the substitution reaction. To explore this possibility, we examined bromofluorination[11] of *cis*-4β-acetamidocyclopent-2-enemethyl acetate (**5**) to give the *trans*-bromo-fluoride. Bromofluorination of **5** with hydrogen fluoride–pyridine/*N*-bromosuccinimide was regio- and stereoselective due to the *syn*-directing allylic amide group,[6] giving the expected *trans*-fluoro amide (**6**) and the rearranged fluoroacetate (**7**) in the ratio of 74:26 (65% yield) in tetrahydrofuran as a solvent. When the reaction was carried out in ether as a less polar solvent, the desired *trans*-fluoro amide was obtained exclusively in 77% yield. As expected, the bromine atom was smoothly reduced with Bu_3SnH/AIBN to provide **3** in 88% yield. Finally, deprotection of the acetyl group gave the fluorinated carbocyclic sugar moiety (**4**) in good yield.

The synthetic routes (Chart 2) to the fluorinated uridine, thymidine and cytidine analogues (**8**—**10**) from the fluorocyclopentylamine (**4**) were based on Shealy and O'dell's procedure.[12] Treatment of **4** with 3-ethoxyacryloyl isocyanate in *N*,*N*-dimethylformamide at 0 °C gave an intermediate acryloylurea, which was cyclized under reflux in 2 N hydrochloric acid to afford the fluorinated



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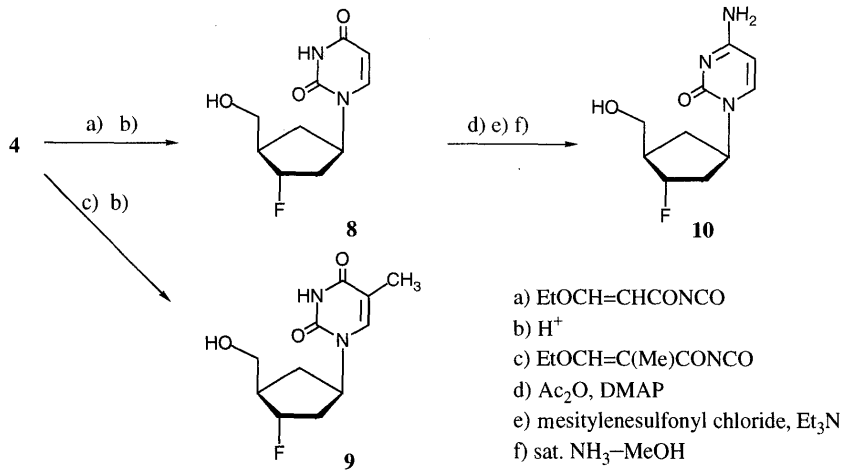
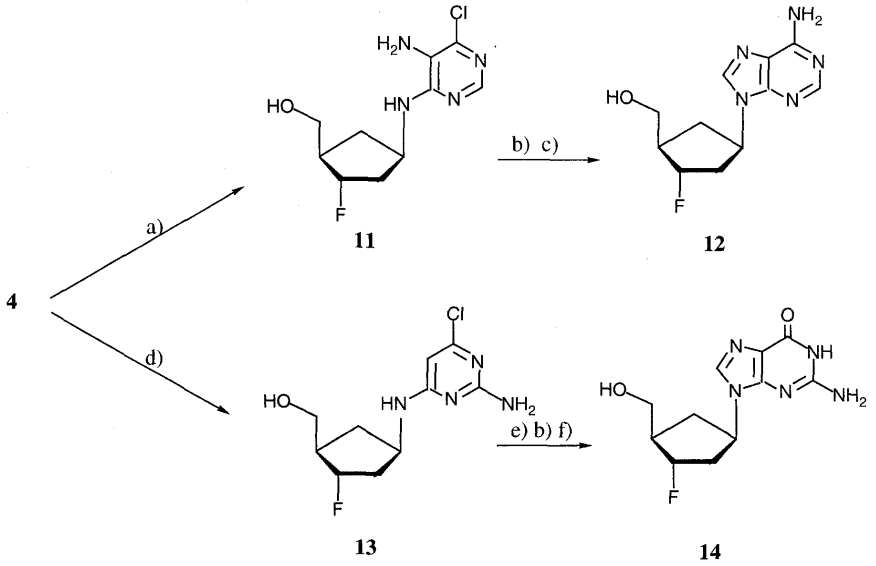


Chart 2



a) 5-amino-4,6-dichloropyrimidine, b) $HC(OEt)_3$, H^+,
c) aq. NH_3, d) 2-amino-4,6-dichloropyrimidine,
e) *p*-chlorobenzene diazonium chloride, then Zn-AcOH, f) 2 N HCl

Chart 3

TABLE I. Antiviral and Anticellular Activity of Carbocyclic 2′,3′-Dideoxy-3′-fluoro Nucleosides

Compound	Inhibition % of cytopathic effect of viruses at 20 μg/ml dose[a]				Inhibition % of cytotoxicity at 100 μg/ml dose[a]		
	HSV-1 (KOS)[b]	Influenza A	Adeno 3	VSV	Vero	MDCK	HeLa S_3
8	<10	<10	<10	<10	10—25	<10	<10
9	<10	<10	<10	<10	26—50	10—25	26—50
10	<10	<10	<10	<10	10—25	<10	10—25
12	<10	<10	10—25	<10	26—50	10—25	10—25
14	75—100	<10	<10	<10	10—25	<10	<10

a) Determined by the assay method of Munoz *et al.*[15] using crystal violet for staining viable Vero (HSV-1), MDCK (influenza A), or HeLa S_3 (adeno 3 and VSV) cells or uninfected cells. *b*) The strain is given in parentheses.

uracil (**8**). The corresponding carbocyclic 3′α-fluorothymidine (**9**) was prepared from **4** in a similar manner to that used for the synthesis of **8**. The cytidine analogue was obtained from the fluorinated uridine (**8**) according to the reported procedure.[13]

On the other hand, the amine (**4**) was condensed with 5-amino-4,6-dichloropyrimidine[14] and the resulting pyrimidine (**11**) was treated with triethyl orthoformate in the presence of concentrated hydrochloric acid to give the 6-chloropurine. Reaction of the 6-chloropurine with ammonia gave carbocyclic 2′,3′-dideoxy-3′-fluoroadenosine (**12**) as illustrated in Chart 3.

The amine (**4**) was coupled with 2-amino-4,6-dichloropyrimidine to afford the diamine (**13**). Reaction of **13** with *p*-chlorobenzene diazonium chloride followed by reduction of the intermediate diazo compound gave the triamine, which was cyclized with triethyl orthoformate and then treated with 2 N hydrochloric acid to afford the desired fluoroguanosine (**14**).

Biological Results

The carbocyclic 2′,3′-dideoxy-3′-fluoro nucleosides **8**, **9**, **10**, **12**, and **14** prepared in this study were tested *in vitro* for activity against herpes simplex virus type 1 (HSV-1), influenza virus type A, adenovirus type 3 and vesicular stomatitis virus (VSV). The assay method of Munoz *et al.*[15] using crystal violet for staining viable cells was used to evaluate the activity of these compounds against the cytopathic effect of the viruses. The potency of each compound was evaluated in terms of the efficacy against the viruses at the concentration of 20 μg/ml. The cytotoxicity of each compound was also determined at the concentration of 100 μg/ml. The results obtained are summarized in Table I.

Of the five carbocyclic nucleoside analogues tested, carbocyclic 2′,3′-dideoxy-3′-fluoroguanosine (**14**) showed a marked activity against HSV-1 at 20 μg/ml, and carbocyclic 2′,3′-dideoxy-3′-fluoroadenosine (**12**) was slightly active against adenovirus type 3, but the other compounds **8**, **9**, and **10** showed no activity against any virus at 20 μg/ml. Compound **14** was slightly cytotoxic to Vero cells, but showed no cytotoxicity towards MDCK and HeLa S_3 cells.

The potency of carbocyclic 2′,3′-dideoxy-3′-fluoroguanosine (**14**) was further tested against herpes simplex virus type 1 and 2 (HSV-1, HSV-2), varicella zoster virus (VZV), and human cytomegalovirus (HCMV) in HEL cells by plaque reduction assays. The results are given in Table II. Adenine arabinoside (Ara-A) and acyclovir (ACV) were used as positive controls in this experiment.

TABLE II. Antiherpes and Anticellular Activity of Carbocyclic 2′,3′-Dideoxy-3′-fluoroguanosine

Virus or cell	ID_{50}[a] (μg/ml)		
	14	Ara A	ACV
HSV-1 (KOS)[b]	2.7	1.6	0.13
HSV-2 (UW268)	10.0	3.2	0.34
VZV (CaQu)	12.1	1.6	2.4
HCMV (AD169)	15.0	6.6	10.0
HEL cells	<15.0	<6.6	440

a) Determined by plaque reduction assays in HEL cells or cell proliferation assays in uninfected cells. *b*) The strain is given in parentheses.

Compound **14** was the most active against HSV-1, with ID_{50} values of 2.7 μg/ml, but was less active against HSV-2, VZV and HCMV, with ID_{50} values of 10.0, 12.1 and 15.0 μg/ml, respectively. The activity against HSV-1 was similar to that of Ara-A, but about 10 times less than that of ACV. The cytotoxicity of **14** towards HEL cells was quite high (< 15.0 μg/ml), and was comparable to that of Ara-A.

Experimental

^{1}H-NMR and ^{19}F-NMR spectra were taken on a JEOL JNM-FX-90Q spectrometer. References were tetramethylsilane for ^{1}H spectra and $CFCl_3$ for ^{19}F spectra. All chemical shifts were recorded downfield from the references. IR spectra were measured on a JASCO IR-810 spectrophotometer. High-resolution mass spectra (high-resolution MS) were recorded on a JEOL SX-102A mass spectrometer. Products were purified by column chromatography on silica gel (Merck, 0.063—0.200 mm or 0.040—0.063 mm).

(±)-(1β,2α,3α,4β)-4-Acetamido-2-fluoro-3-(iodocyclopentyl)methyl Acetate (2) Triphenylphosphine (1.45 g, 1.8 mmol), iodine (0.94 g, 3.7 mmol) and imidazole (0.36 g, 5.5 mmol) were added to a solution of (±)-(1β,2α,3β,4β)-4-acetamido-2-fluoro-3-(hydroxycyclopentyl)methyl acetate (**1**) (0.43 g, 1.6 mmol) in toluene (37 ml), and the mixture was heated under reflux. After 4 h, the mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. Purification by column chromatography gave **2** (oil, 55 mg, 9% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.60 (3H, m), 1.93 (3H, s), 2.03 (3H, s), 4.00—5.50 (5H, m). ^{19}F-NMR ($CDCl_3$): −166.0 ppm (ddd, J = 51.8, 27.3, 6.6 Hz).

(±)-(1β,2α,3β,4β)-4-Acetamido-3-bromo-2-(fluorocyclopentyl)methyl Acetate (6) Hydrogen fluoride–pyridine (70%) (1 ml) was added dropwise to a solution of *N*-bromosuccinimide (218 mg, 1.2 mmol) in ether (1 ml) at 0 °C, and then a solution of *cis*-4β-acetamidocyclopentenemethyl acetate (**5**) (243 mg, 1.2 mmol) in ether (1 ml) was further added dropwise at 0 °C. The mixture was stirred at the same temperature for 30 min and at room temperature for 2 h, then poured into saturated

aqueous sodium hydrogen carbonate solution and extracted with chloroform. The combined extracts were dried with magnesium sulfate, and evaporated to dryness *in vacuo*. Purification by column chromatography (chloroform : methanol = 50 : 1) gave **6** (oil, 280 mg, 77% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.8 (3H, m), 2.03 (3H, s), 2.09 (3H, s), 4.2—5.5 (5H, m), 5.9 (1H, br s). ^{19}F-NMR ($CDCl_3$): −154.0 ppm (ddd, J = 49.6, 13.9, 14.7 Hz). IR ($CDCl_3$): 3040, 1750, 1520 cm^{-1}.

When the reaction was carried out in tetrahydrofuran, **6** was obtained in 48% yield accompanied with the rearranged product (**7**) in 17% yield.[16] **7**: ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (3H, m), 2.03 (3H, s), 2.08 (3H, s), 3.4—3.7 (2H, m), 3.9—4.9 (3H, m), 5.9—6.1 (1H, m). ^{19}F-NMR ($CDCl_3$): −218.5 ppm (ddd, J = 47.4, 28.1, 11.0 Hz).

(±)-(1β,2α,4β)-4-Acetamido-2-(fluorocyclopentyl)methyl Acetate (3) Method A (from Iodide **2**): α,α′-AIBN (1 mg) and tributyltin hydride (0.23 ml, 0.85 mmol) were added to a solution of **2** (55 mg, 0.16 mmol) in benzene (1 ml). The solution was refluxed for 20 min and all the volatile materials were evaporated off under reduced pressure. The residue was purified on a silica gel column to give **3** (powder, 36 mg, 100% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.60 (5H, m), 1.96 (3H, s), 2.08 (3H, s), 4.00—5.40 (4H, m), 5.90 (1H, br s). ^{19}F-NMR ($CDCl_3$): −171.1 ppm (dddd, J = 52.7, 33.2, 28.6, 21.7 Hz). IR ($CHCl_3$): 1743, 1680, 1520 cm^{-1}.

Method B (from Bromide **6**): α,α′-AIBN (5 mg) and tributyltin hydride (1.25 ml, 4.6 mmol) were added to a solution of **6** (178 mg, 0.94 mmol) in benzene (20 ml) and the solution was refluxed for 10 min. All the volatile materials were removed *in vacuo* and the residue was purified by silica gel column chromatography to give **3** (169 mg, 88% yield).

(±)-(1β,2α,4β)-4-Amino-2-fluorocyclopentanemethanol (4)[4a] A suspension of **3** (169 mg, 0.78 mmol) in 2 N hydrochloric acid (4 ml) was heated under reflux for 8 h. Purification with Diaion SA-11A gave **4** (oil, 103 mg, 100% yield). ^{1}H-NMR (D_2O) δ: 0.80—2.40 (5H, m), 3.40—5.20 (4H, m). ^{19}F-NMR (D_2O): −165.1 ppm (dddd, J = 54.0, 36.6, 31.3, 22.7 Hz).

(±)-1-[(1β,3α,4β)-3-Fluoro-4-(hydroxymethyl)cyclopentyl]uracil (8) 3-Ethoxy-2-propenoyl isocyanate (0.4 M benzene solution, 2.5 ml, 1.0 mmol) was added to a solution of **4** (130 mg, 0.98 mmol) in *N*,*N*-dimethylformamide (5 ml) at 0 °C over a period of 5 min. After 10 min, all the volatiles were evaporated off under reduced pressure at 30 °C. The residue was taken up in 2 N hydrochloric acid (10 ml) and heated under reflux for 20 min. After cooling to 0 °C, the solution was neutralized with 2 N sodium hydroxide and the solvent was evaporated off. Purification by silica gel column chromatography afforded **8** (fine powder, 150 mg, 67% yield). ^{1}H-NMR (D_2O) δ: 1.6—3.0 (5H, m), 3.8—4.0 (2H, m), 4.9—5.8 (2H, m), 6.10 (1H, d, J = 7.9 Hz), 8.00 (1H, d, J = 7.9 Hz). ^{19}F-NMR (D_2O): −159.2 (m). High-resolution MS (FAB) m/z: Calcd for $C_{10}H_{13}FN_2O_3$: 229.0989. Found: 229.0995. *Anal.* Calcd for $C_{10}H_{13}FN_2O_3$: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.33; H, 5.75; N, 12.47.

(±)-1-[(1β,3α,4β)-3-Fluoro-4-(hydroxymethyl)cyclopentyl]thymine (9)[4] 3-Ethoxy-2-methyl-2-propenoyl isocyanate (0.4 M benzene solution, 3.8 ml, 1.5 mmol) was added to a solution of **4** (200 mg, 1.5 mmol) in *N*,*N*-dimethylformamide (7 ml) at 0 °C over a period of 5 min. After 10 min, all the volatiles were evaporated off under reduced pressure at 30 °C and 2 N hydrochloric acid (10 ml) was added. The solution was heated under reflux for 20 min, then cooled to 0 °C, and neutralized with 2 N sodium hydroxide. The solution was evaporated to dryness and purified by silica gel column chromatography to give **9** (powder, 350 mg, 96% yield). ^{1}H-NMR (acetone-d_6) δ: 1.6—2.7 (8H, m+s (δ 1.88)), 3.0—5.6 (4H, m), 7.68 (1H, br s). ^{19}F-NMR (acetone-d_6): −165.2 ppm (m). High-resolution MS (FAB) m/z: Calcd for $C_{11}H_{15}FN_2O_3$: 243.1145. Found: 243.1151. *Anal.* Calcd for $C_{11}H_{15}FN_2O_3$: C, 54.54; H, 6.24; N, 11.56. Found: C, 54.54; H, 6.02; N, 11.43.

(±)-1-[(1β,3α,4β)-3-Fluoro-4-(hydroxymethyl)cyclopentyl]cytosine (10) 4-Dimethylaminopyridine (10 mg, 0.08 mmol) and acetic anhydride (1 ml) were added to a solution of **8** (240 mg, 1.0 mmol) in pyridine (10 ml), and the mixture was stirred at room temperature for 30 min. The solution was poured into 0.5 M potassium dihydrogen phosphate solution (50 ml) and extracted with ethyl acetate (50 ml). The organic layer was dried over magnesium sulfate and concentrated. The residue was dissolved in acetonitrile (10 ml), and 2-mesitylenesulfonyl chloride (670 mg, 3.0 mmol) and triethylamine (0.42 ml, 3.0 mmol) were added to the solution at room temperature. The whole was stirred for 50 min, then evaporated to dryness, and saturated ammonia–methanol (3 ml) was added to the residue at room temperature. After 15 h, the solution was evaporated and 50% methanol–water (20 ml) was added to the residue. The solution was applied to an Amberlite CG-120 (H^+ form) column, which was washed with water, and then eluted with 5% ammonium hydroxide to give **10** (powder, 55 mg, 24% yield). ^{1}H-NMR (CD_3OD) δ: 1.64—2.78 (5H, m), 3.83 (2H, br d), 5.26 (1H, dm, J = 53.22 Hz), 5.38 (1H, m), 6.13 (1H, d, J = 7.5 Hz), 7.95 (1H, d, J = 7.5 Hz). ^{19}F-NMR (CD_3OD): −167.5 ppm (ddt, J = 22.95, 30.76, 53.22 Hz). *Anal.* Calcd for $C_{10}H_{14}FN_3O_2 \cdot 0.5H_2O$: C, 50.84; H, 6.40; N, 17.79. Found: C, 50.59; H, 6.21; N, 17.65.

(±)-9-[(1β,3α,4β)-3-Fluoro-4-(hydroxymethyl)cyclopentyl]-6-aminopurine (12) Method A (from Carbocyclic 3′-Deoxy-3′-fluoroadenosine[5]): *N*,*N*-Dimethylformamide dimethylacetal (2.03 ml, 15.3 mmol) was added to a solution of carbocyclic 3′-deoxy-3′-fluoroadenosine (0.67 g, 2.7 mmol) in *N*,*N*-dimethylformamide (12 ml), and the mixture was stirred for 2 h at room temperature. All the volatiles were evaporated off under reduced pressure and purification by silica gel column chromatography gave the 6-dimethylaminomethyleneiminopurine derivative (0.68 g, 2.24 mmol, 83% yield).

Imidazole (0.233 g, 3.42 mmol) and *tert*-butyldimethylsilyl chloride (0.258 g, 1.71 mmol) were added to a solution of the 6-dimethylaminomethyleneiminopurine derivative (0.53 g, 1.71 mmol) in *N*,*N*-dimethylformamide (3 ml) at 0 °C. The mixture was stirred for 10 h at room temperature, and usual work-up gave 5′-*O*-*tert*-butyldimethylsilyl protected carbocyclic fluoroadenosine (gum, 264 mg, 0.63 mmol, 37% yield) and the starting diol (250 mg, 0.82 mmol, 48% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.00 (6H, s), 0.88 (9H, s), 3.19 (3H, s), 3.24 (3H, s), 3.40—5.31 (7H, m), 7.96 (3H, s), 8.67 (1H, s), 9.07 (1H, s). ^{19}F-NMR ($CDCl_3$): −191.3 ppm (ddd, J = 25.7, 32.6, 56.5 Hz).

The above compound (230 mg, 0.52 mmol) in dichloromethane (5 ml) was allowed to react with phenylchlorothionocarbonate (170 mg, 1.56 mmol). The mixture was stirred for 15 min at room temperature, and usual work-up followed by reduction with tributyltin hydride (1.0 g, 3.45 mmol) in the presence of α,α′-azobisisobutyronitrile (5 mg) gave the deoxy derivative. Deprotection of the 5′-hydroxyl group with tetrabutylammonium fluoride and of the 6-amino group with 28% ammonium hydroxide gave carbocyclic 2′,3′-dideoxy-3′-fluoroadenosine (**12**) (powder, 90 mg, 69% yield). ^{1}H-NMR (D_2O) δ: 1.6—2.0 (5H, m), 3.75 (2H, d, J = 5.4 Hz), 3.8—4.6 (2H, m), 7.19 (1H, s), 7.24 (1H, s). ^{19}F-NMR (D_2O–$CDCl_3$): −165.9 ppm (dddd, J = 52.1, 34.5, 30.5, 18.7 Hz). High-resolution MS (FAB) m/z: Calcd for $C_{11}H_{14}FN_5O$: 252.1261. Found: 252.1253. *Anal.* Calcd for $C_{11}H_{14}FN_5O \cdot 2H_2O$: C, 45.99; H, 5.61; N, 24.38. Found: C, 46.02; H, 5.86; N, 24.46.

Method B (from Compound **4**): Compound **12** was synthesized from **4** according to Dalge and Vince.[6] The cyclopentylamine (**4**) was allowed to react with 5-amino-4,6-dichloropyrimidine in the presence of triethylamine, followed by ring construction with triethyl orthoformate and ammonolysis with saturated ammonia–methanol to give carbocyclic 2′,3′-dideoxy-3′-fluoroadenosine.

(±)-9-[(1β,3α,4β)-3-Fluoro-4-(hydroxymethyl)cyclopentyl]guanine (14) 2-Amino-4,6-dichloropyrimidine (2.49 g, 15.22 mmol) and triethylamine (2.1 ml, 15.2 mmol) were added to a solution of **4** (910 mg, 6.8 mmol) in 1-butanol (30 ml), and the mixture was heated under reflux for 15 h. The solution was cooled to 0 °C and filtered, and the filtrate was evaporated to dryness to give **13**. The residue was dissolved in acetic acid (34 ml)–H_2O (34 ml), and then sodium acetate trihydrate (13.6 g) and 4-chlorobenzenediazonium chloride solution (16 ml, 7.5 mmol) were added. The whole was stirred at 70 °C for 1 h, then the precipitate was collected and dried. To the residue, 50% ethanol–H_2O (100 ml), acetic acid (11 ml), and zinc powder (11 g) were successively added and the mixture was stirred at 70 °C for 1 h. After filtration, the solution was poured onto Amberlite CG-120 (H^+ form), washed with water, and eluted with 5% ammonium hydroxide to give (4α,2β,1α)-4-(2,5-diamino-6-chloro-4-pyrimidinylamino)-2-fluorocyclopentanemethanol (380 mg, 20% yield). IR (film): 3300 cm^{-1}.

Triethyl orthoformate (30 ml) and concentrated hydrochloric acid (1 ml) were added to a solution of this triaminopyrimidine (190 mg, 0.69 mmol) in *N*,*N*-dimethylformamide (20 ml), and the mixture was stirred for 48 h. After evaporation of all the volatiles, 2 N hydrochloric acid (20 ml) was added to the residue and the mixture was heated under reflux for 4 h. The solution was applied to a column of Amberlite CG-120 (H^+ form) and eluted with 5% ammonium hydroxide to give **14** (powder, 101 mg, 55% yield). ^{1}H-NMR (CD_3OD) δ: 1.91—2.89 (5H, m), 3.87 (2H, br d), 5.02—5.68 (2H, m), 8.09 (1H, s). ^{19}F-NMR (CD_3OD):

−167.5 ppm (m). High-resolution MS (FAB) *m/z*: Calcd for $C_{11}H_{15}FN_5O_2$: 268.1210. Found: 268.1208. *Anal.* Calcd for $C_{11}H_{15}FN_5O_2 \cdot 3.5H_2O$: C, 39.88; H, 6.69; N, 21.13. Found: C, 40.12; H, 6.56; N, 20.94.

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