Stereoselective Introduction of Fluorine Atom: Synthesis of Racemic Carbocyclic Analogues of 3′-Deoxy-3′-fluororibofuranosides and 3′-Deoxy-3′-fluoroarabinofuranosides

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(Received April 8, 1993)

New carbocyclic analogues of nucleoside analogues substituted at the 3′-position with fluorine atom have been synthesized. Racemic carbocyclic 3′-deoxy-3′-fluoroarabinofuranoside analogue (**3**) has been prepared in several steps beginning with the regio- and stereoselective ring opening of (1α,2α,3α,4α)-4-acetamido-2,3-epoxycyclopentylmethylacetate (**1**). On the other hand, the corresponding carbocyclic analogue of fluororibofuranosyl derivative (**14**) has been obtained by S_N2 displacement of siloxy group at 3′-position with piperidinosulfur trifluoride followed by removal of benzyl protecting group. The obtained sugar moiety **3** and **14** were transformed into the nucleoside derivatives respectively.

A number of fluorinated nucleosides have a broad spectrum of antiviral activity as well as anticancer activity.[1] During the last few years, considerable interest has been focussed on the synthesis of nucleoside analogues substituted with fluorine in the sugar moiety[2] to search for agents effective in the treatment of virus infections, such as 2′-deoxy-2′-fluoro sugars,[3] 3′-deoxy-3′-fluoro analogues,[4] fluoromethyl derivatives,[5] fluorinated 2′,3′-unsaturated nucleosides,[6] fluorinated oxetanosines,[7] fluoroacyclonucleosides,[8] and fluorinated carbocyclic analogues.[9]

However, there have been only limited reports on the synthesis of nucleosides with fluorine atom on 3′-position.[10] Since carbocyclic analogues of nucleosides benefit from greater metabolic stability than furanose counterparts,[11] we decided to synthesize 3′-fluorinated carbocyclic derivatives.[12] We describe here the novel synthesis of racemic carbocyclic analogues of 3′-deoxy-3′-fluororibo- and arabinofuranosides.

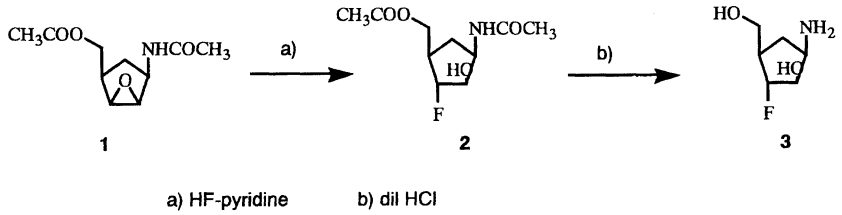
For the synthesis of the 3′-fluorocarbocyclic nucleosides, we first examined the ring-opening reaction of epoxide **1** with hydrogen fluoride-pyridine in regard to the regio- and stereoselectivity. The attack of fluorine atom occurred predominantly at the position farthest from the acetamido group at the ratio of >9 : 1 (**2**), similar to the reaction with buffered sodium azide (Scheme 1).[13] The direction of epoxide ring opening was evident from the ^{1}H NMR spectrum of **2**. On the contrary, the opening of epoxide **1** with KF or KHF_2 at the temperature of more than 200 °C failed to give the desired fluorocyclopentanol. Removal of acetyl protection from **2** with dil HCl gave the fluoro amino diol **3**, which was used for the construction of nucleoside analogues without further purification.

The synthetic plan to reach the *cis*-fluorohydrin **14** required access to the inversion of configuration at C-2 of *trans*-fluorohydrin **2**. For example, the imidazolylsulfonate[14] of *trans*-fluoro alcohol **2** failed to react with $PhCOONH_4$ or CsOAc,[15] and the Mitsunobu reaction[16] (EtOCON=NCOOEt, Ph_3P–HCOOH) of **2** resulted only in recovery of the starting material. After several attempts of stereoconversion of the hydroxyl group, synthesis of the desired *cis*-fluorohydrin was finally accomplished by the displacement of the trimethylsiloxy group at the C-3 of *trans*-diol **12** with fluoride ion.

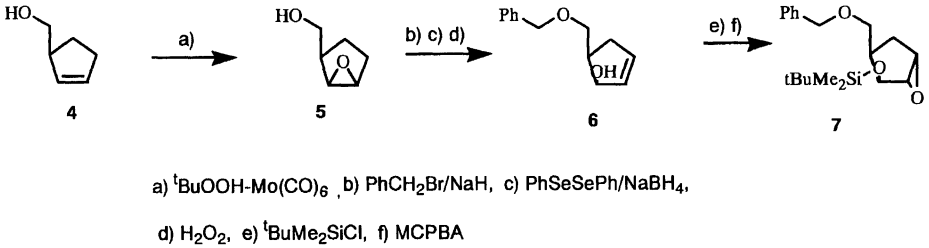
Oxidation of 2-cyclopentene-1-methanol **4**[17] with *t*-butyl hydroperoxide under $Mo(CO)_6$[18] catalysis furnished the *cis*-epoxide **5** as a >9 : 1 ratio of stereoisomers. The same stereoselectivity was obtained by the reaction with $VO(acac)_2$[18] as a catalyst (Scheme 2). However, in the case of epoxidation carried out with *m*-chloroperbenzoic acid, the ratio was decreased to 4 : 1. Benzylation with the free hydroxyl group followed by ring opening with phenyl selenide ion and oxidation with 30% hydrogen peroxide gave the allylic alcohol **6** and the regio isomer in the ratio 6 : 4.

The stereochemistry of *cis*-diol derivatives was determined as follows (Scheme 3). Removal of benzyl protection of compound **6** followed by selective tritylation of diol furnished the mono-ol **8**. Protection of **8** with ^{t}BuMe$_2$SiCl gave the protected cyclopentene **10**, which underwent epoxidation reaction with *m*-chloroperbenzoic acid under the control of steric effect to afford the epoxide **11a** and **11b** in the ratio 3—4 : 1. On the other hand, epoxidation of allylic alcohol **8** with ^{t}BuOOH–$VO(acac)_2$ under the chelation control gave the *cis*-epoxy alcohol **9**. The ^{1}H NMR spectrum of the desilylated product of **11b** was consistent with that of **9**. Similarly, the compound **6** was protected with ^{t}BuMe$_2$Si group and oxidized with *m*-chloroperbenzoic acid to give **7** selectively.

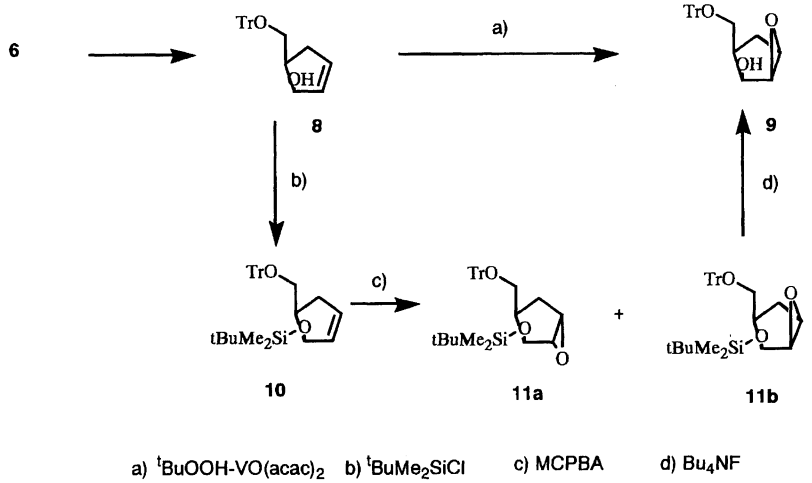
Reaction of the protected *trans*-epoxy alcohol (**7**) with azide ion followed by protection with benzyl group regioselectively furnished the required azido alcohol derivative **12**, which might be proceeded by a participation of bulky neighboring *t*-butyldimethylsiloxy group (Scheme 4). Stereoselective synthesis to the desired *cis*-fluorohydrin was accomplished by the S_N2 displacement of the trimethylsiloxy group with fluoride ion. Treatment of (trimethylsiloxy)cyclopentane derived from **12** with piperidinosulfur trifluoride (PST) gave a mixture



Scheme 1.



Scheme 2.



Scheme 3.

of the fluorinated compounds **13** and **15** in the ratio 1 : 1, resulting in replacement of the hydroxyl group by a fluorine atom with inversion of configuration and partial migration of the hydride. The azide compound was reduced and deprotected with hydrogen in the presence of Pd–C to give the amino diol **14**.

Each fluorocyclopentanediol (**3** and **14**) were subsequently transformed into the nucleoside analogues. The amine **3** was condensed with 5-amino-4,6-dichloropyrimidine and the resulting pyrimidine closed with triethyl orthoformate (Scheme 5) to the 6-chloropurine.[13] Finally, reaction of the obtained chloropurine with ammonia gave **16a**. Similarly, the isomeric amine (**14**) was converted to the corresponding fluorinated carbocyclic adenosine **16b**.

Likewise, refluxing a mixture of **3** (or **14**) and 2-amino-4,6-dichloropyrimidine produced the substituted pyrimidine. Diazo coupling followed by reduction using zinc-acetic acid, and ring construction with triethyl orthoformate gave the aminochloropurine. Finally, the reaction of the obtained chloropurine with 1 M HCl furnished **17a** (or **17b**) (1 M=1 mol dm^{-3}).

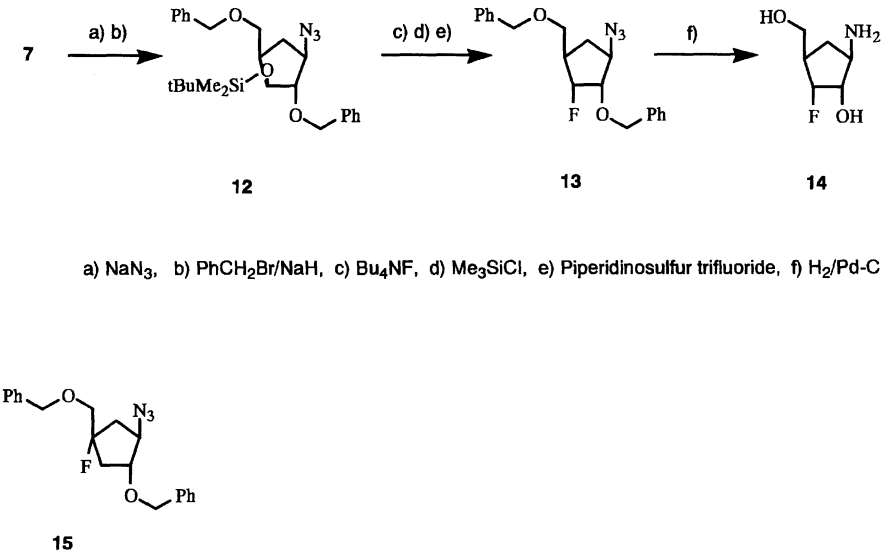
Carbocyclic analogues of 3′-deoxy-3′-fluoropyrimidine nucleosides were also synthesized using standard procedures. As shown in Scheme 5, the amine **3** and **14** were readily converted into the uridine derivatives respectively (**19a** and **20a** from **3**, **19b** and **20b** from **14**).

The biological data including antiviral activity of these compounds will be disclosed elsewhere.

Experimental

Melting points were determined on a Mettler FP80, the IR spectra were taken on a JASCO IR-810 spectrophotometer. ^{1}H and ^{19}F NMR spectra were determined with a JEOL JNM-FX-90Q and GX 400 spectrometer. Proton chemical shifts are expressed in ppm downfield from internal tetramethylsilane using the δ scale. For ^{19}F NMR, the peak positions were determined by reference to $CFCl_3$. Purification of products were carried out with column chromatography on a silica gel (Merck 0.063—0.200 mm or 0.040—0.063 mm).

(±)-(1α, 2β, 3α, 4α)-4-Acetamido-2-fluoro-3-hydroxycyclopentylmethyl Acetate (2). To a solution



Scheme 4.

of (1α,2α,3α,4α)-4-acetamido-2,3-epoxycyclopentylmethyl acetate (7.0 g, 32.0 mmol) in dichloromethane (100 ml), hydrogen fluoride–pyridine (70%) (18 ml) was added dropwise at 0 °C. After 2 h, the reaction mixture was poured into sat aq potassium carbonate solution and the solution was extracted with dichloromethane. Purification with column chromatography gave **2** (5.87 g, 77% yield). ^{1}H NMR ($CDCl_3$) δ=1.4—1.6 (1H, m, H-6), 2.00 (3H, s), 2.07 (3H, s), 2.3—2.4 (1H, m, H-6), 2.4—2.5 (1H, m, H-1), 4.07 (2H, d, J=6.8 Hz), 4.1—4.3 (4H, m, H-1, H-3), 4.65 (1H, d, J=50.4 Hz, H-2), 6.45 (1H, d, J=7.2 Hz, NH); ^{19}F NMR ($CDCl_3$) δ=−179.9 (ddd, J=11.7, 29.2, 50.4 Hz). Found: m/z 234.1185. Calcd for $C_{10}H_{16}FNO_4$: M, 234.1142.

(±)-(1α,2β,3α,4α)-4-Amino-2-fluoro-3-hydroxycyclopentanemethanol (3). A mixture of **2** (5.87 g, 26.3 mmol) and 142 ml of 2 M HCl in methanol (142 ml) was boiled under reflux for 1 h. The solvent was removed under reduced pressure and the solution was neutralized with Diaion SA-21A (OH^- form) (300 ml). Evaporation of the solvent gave the amino diol (**3**) (3.6 g, 92% yield), which was used directly in the next stage. ^{19}F NMR ($CDCl_3$) δ=−179.1 (ddd, J=16.1, 27.2, 41.5 Hz). Found: m/z 150.0910. Calcd for $C_6H_{12}FNO_2$: M, 150.0930.

(±)-(1α,2α,3α)-2,3-Epoxycyclopentanemethanol (5). To a suspension of $Mo(CO)_6$ (0.16 g, 0.6 mmol) and ^{t}BuOOH (3.0 g, 30 mmol) in benzene (80 ml), 2-cyclopentene-1-methanol (**4**) (2.0 g, 20.0 mmol) in 20 ml of benzene was added and heated to reflux for 1.5 h. The reaction mixture was poured into the cold sat sodium sulfite and the solution was extracted with ethyl acetate. The crude product was purified by column chromatography to give epoxy alcohol (**5**) (1.6 g, 70% yield). ^{1}H NMR ($CDCl_3$) δ=0.8—1.4 (1H, m), 1.4—2.5 (5H, m), 3.56 (2H, br s), 3.78 (2H, d, J=6.5 Hz).

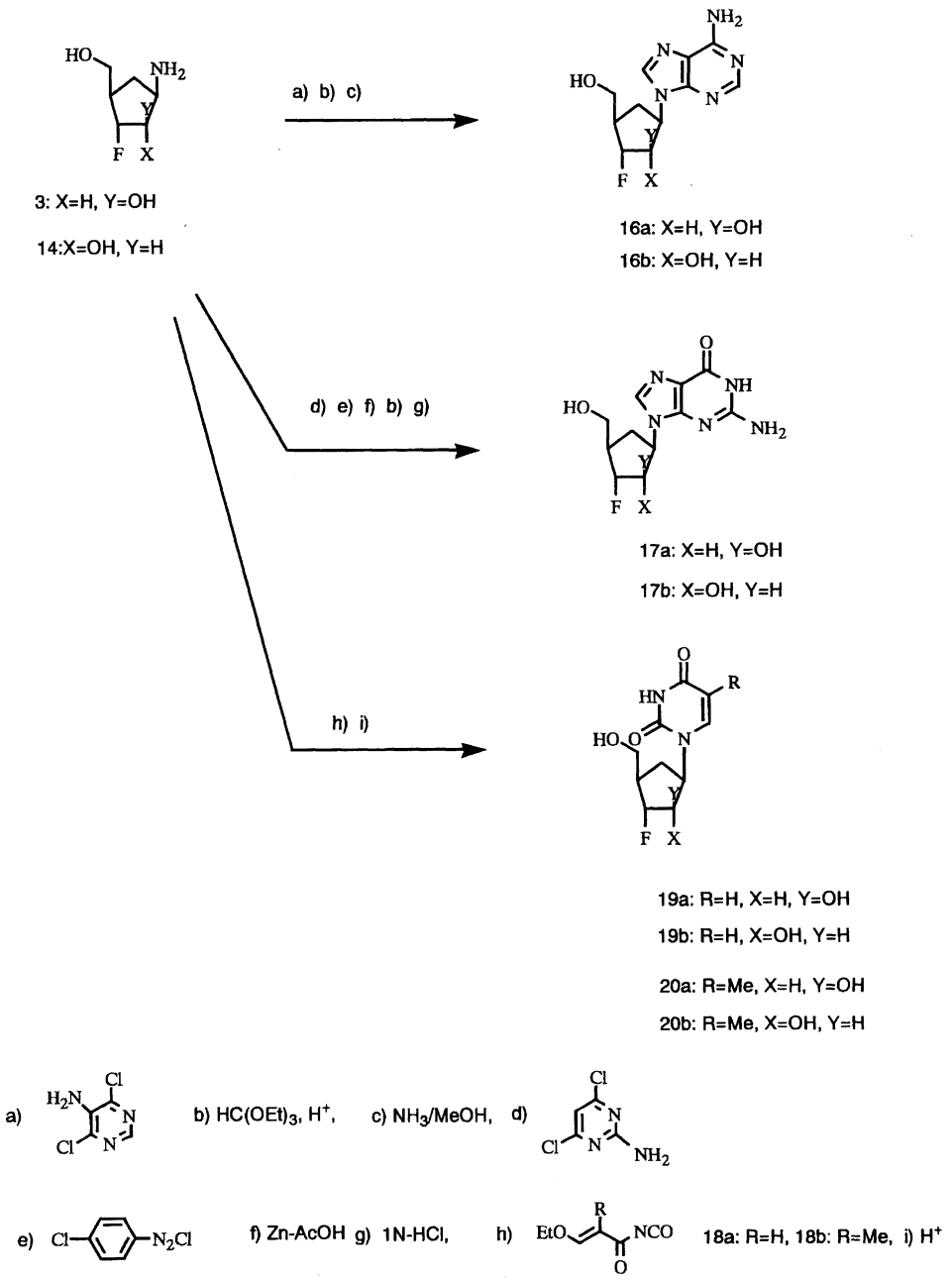
(±)-(1α, 2α)-2-Hydroxy-3-cyclopentenylmethyl Benzyl Ether (6). A solution of epoxy alcohol (**5**) (12.3 g, 0.11 mol) in tetrahydrofuran (40 ml) was added to a suspension of sodium hydride (55%) (5.7 g, 0.13 mmol) in tetrahydrofuran (90 ml) at 0 °C. After 30 min, benzyl bromide (25.9 g, 0.15 mol) was added and the mixture was boiled under reflux for 30 min. Usual workup gave benzyl ether (21.8 g, 99% yield). ^{1}H NMR ($CDCl_3$) δ=0.8—1.5 (5H, m), 2.4—2.7 (4H, m), 3.62 (2H, s), 7.44 (5H, s).

The crude product (21.7 g, 0.11 mmol) in ethanol (15.6 ml) was added dropwise over a period of 45 min to a solution of sodium phenyl selenide in ethanol (131 ml) at room temp, which was prepared by diphenyl diselenide (33.3 g, 0.11 mol) and sodium borohydride (8.07 g, 0.21 mol). The whole was heated under reflux for 1 h. To a cooled solution, 30% hydrogen peroxide (114.5 ml) was poured at 15 °C. Usual workup gave the allylic alcohol (**6**) (86.6 g, 37% yield). ^{1}H NMR ($CDCl_3$) δ=2.0—2.7 (4H, m), 3.6—3.8 (3H, m), 4.60 (2H, s), 4.8—5.0 (1H, m), 5.8—6.2 (2H, m), 7.44 (5H, s).

(±)-(1α,2α,3β,4β)-2-*t*-(Butyldimethylsiloxy)-3,4-epoxycyclopentylmethyl Benzyl Ether (7). A solution of the alcohol (**6**) (6.58 g, 32.3 mmol) was protected with *t*-butyldimethylsilyl group by usual method (9.82 g, 95% yield). ^{1}H NMR ($CDCl_3$) δ=0.18 (6H, s), 1.41 (9H, s), 2.3—2.7 (3H, m), 3.5—4.0 (2H, m), 5.14 (2H, d, J=1.8 Hz), 4.9—5.0 (1H, m), 5.8—6.2 (2H, m), 7.50 (5H, s).

This compound was oxidized with *m*-chloroperbenzoic acid (6.22 g, 34.2 mmol) in dichloromethane. After stirring for 2 h, the reaction mixture was poured into sat sodium hydrogensulfite solution. Purification by column chromatography gave the epoxide (**7**) (7.6 g, 80% yield). ^{1}H NMR ($CDCl_3$) δ=0.19 (3H, s), 0.22 (3H, s), 1.00 (9H, s), 1.3—1.8 (2H, m), 2.0—2.3 (2H, m), 3.4—3.8 (3H, m), 4.46 (1H, distorted d, J=4.0 Hz), 4.62 (2H, d, J=4.3 Hz), 7.55 (5H, s).

(±)-(1α,2α,3β,4α)-4-Azido-3-benzyloxy-2-(*t*-butyldimethylsiloxy)cyclopentylmethyl Benzyl Ether (12). To a solution of the epoxide (**7**) (5.89 g, 17.6 mmol) in H_2O (20 ml) and 2-methoxyethanol (60 ml), ammonium chloride (1.26 g), and sodium azide (6.08 g) were added. After stirring for 18 h at 75 °C, evaporation of the solvents followed by extraction with ether gave the azido alcohol (3.52 g, 90% yield based on the consumed starting material). ^{1}H NMR ($CDCl_3$) δ=0.04 (3H, s), 0.08 (3H, s), 0.98 (9H, s), 1.6—2.4 (4H, m), 3.3—3.8 (3H, m), 3.9—4.1 (2H, m), 4.5—4.6 (2H, m), 7.3—7.5 (5H, m).



Scheme 5.

The resulting hydroxyl group was protected with benzyl bromide in the presence of sodium hydride in tetrahydrofuran. Usual workup afforded the azidocyclopentane (**12**) (4.0 g, 93% yield). ^{1}H NMR ($CDCl_3$) δ=0.00 (6H, s), 0.84 (9H, s), 1.5—2.6 (3H, m), 3.3—3.8 (4H, m), 4.0—4.2 (1H, m), 4.4—4.6 (4H, m), 7.40 (10H, s).

(±)-(1α,2β,3β,4α)-4-Azido-3-benzyloxy-2-fluorocyclopentylmethyl Benzyl Ether (13). To a solution of **12** (4.05 g, 8.65 mmol) in tetrahydrofuran (10 ml), tetrabutylammonium fluoride (1 M tetrahydrofuran solution, 26 ml, 26 mmol) was added over a period of 40 min at room temp and the mixture was stirred for 2 h. After evaporation of the solvent, sat aq ammonium chloride was added and aqueous layer was extracted with chloroform. Purification with column chromatography gave the deprotected alcohol (2.58 g, 85% yield). ^{1}H NMR ($CDCl_3$) δ=1.6—2.6 (3H, m), 2.9—3.1 (1H, m), 3.6—3.9 (4H, m), 4.1—4.4 (1H, m), 4.56 (2H, s), 4.72 (2H, s), 7.44 (10H, s).

The alcohol (1.84 g, 5.22 mmol) in dichloromethane (15 ml) was then trimethylsilylated with chlorotrimethylsilane (2.0 ml, 16 mmol) in the presence of pyridine (4.2 ml, 52 mmol) at 0 °C. Usual workup afforded the trimethylsilyl ether. To a solution of the above product in dichloromethane (25 ml), piperidinosulfur trifluoride (1.0 ml, 7.8 mmol) was added at 0 °C. After 1 h, triethylamine (1.0 ml, 7.8 mmol) and sat aq potassium carbonate was added and aqueous layer was extracted with dichloromethane. Purification with column chromatography gave the fluorocyclopentane (**13**) (0.30 g, 20% yield) and 1-fluoro isomer (**15**) (0.30 g, 20% yield).

13: ^{1}H NMR ($CDCl_3$) δ=1.3—1.4 (1H, m, H-6), 2.2—2.4 (1H, m, H-6), 2.4—2.6 (1H, m, H-1), 3.31 (1H, dd, J=6.0, 9.8 Hz), 3.48 (1H, dd, J=5.1, 9.8 Hz), 3.68 (1H, ddd, J=4.2, 8.8, 29.0 Hz, H-2), 4.03 (1H, q, J=8.9 Hz, H-4), 4.48 (2H, s), 4.64 (1H, d, J=10.2 Hz), 4.74 (1H, d, J=10.2 Hz), 5.00 (1H, dm, J=53.0 Hz, H-2), 7.39 (10H, s); ^{19}F NMR ($CDCl_3$) δ=−188 (ddd, J=23.5, 28.4, 53.0 Hz); IR (neat film) 2160, 1500, 1460 cm^{-1}; MS 326 (M^+-N_2H), 236.

15: ^{1}H NMR ($CDCl_3$) δ=1.7—1.9 (1H, m, H-6), 2.0—2.1 (1H, m, H-2), 2.3—2.5 (2H, m, H-3, H-6), 3.45 (2H, m), 3.8—3.9 (1H, m, H-2), 4.1—4.2 (1H, m, H-4), 4.58 (4H, s), 7.3—7.5 (10H, m); ^{19}F NMR ($CDCl_3$) δ=−141.5 (m); MS 326 (M^+-N_2H), 236, 215.

(±)-(1α,2β,3β,4α)-4-Amino-2-fluoro-3-hydroxycyclopentanemethanol (14). The dibenzyl ether **13** (300 mg, 0.85 mmol) in ethanol (50 ml) and chloroform (2 ml) was hydrogenated in the presence of 5%Pd–C (0.5 g) to give the amino diol **14**, which was used in the next step without further purification. ^{19}F NMR ($CDCl_3$) δ=−188.1 (ddd, J=24.2, 33.4, 56.4 Hz).

(±)-9-[(1α,2α,3β,4α)-3-Fluoro-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-6-aminopurine (16a). A solution of **3** (0.73 g, 4.9 mmol), 5-amino-4,6-dichloropyrimidine (2.0 g, 12.2 mmol), and triethylamine (3.5 ml, 25 mmol) in 1-butanol (20 ml) was heated at 120 °C for 48 h. All the volatiles were evaporated and a solution of the residue in water was washed with chloroform. An aqueous solution was applied to a column containing 10 ml of Amberlite CG-120 (H^+ form). The column was eluted with 0.3% ammonium hydroxide and product-containing fractions were combined and concentrated to dryness in vacuo; yield 0.97 g (97% yield). ^{19}F NMR (CD_3OD) δ=−179.1 (ddd, J=16.1, 27.2, 41.5 Hz).

A solution of the above product in triethyl orthoformate (25 ml) and conc hydrochloric acid (0.6 ml) was heated at reflux and then all the volatiles were evaporated to dryness to afford the chloropurine. ^{1}H NMR (acetone-d_6) δ=2.0—2.2 (2H, m), 2.3—4.0 (6H, m), 4.5—5.5 (2H, m), 8.59 (1H, s), 8.73 (1H, s); ^{19}F NMR (acetone-d_6) δ=−175.3 (ddd, J=12.3, 26.4, 50.8 Hz).

A solution of the above compound (125 mg, 0.47 mmol) in methanolic ammonia (10 ml, saturated at 0 °C) was heated in autoclave at 100 °C for 18 h. The solvent was removed by evaporation, and then the residue was stirred in 1 M hydrochloric acid (5 ml) for 3 h at room temp. After removal of the solvent by evaporation, the residue was chromatographed (C-18 silica gel) to give **16a** (73 mg, 63% yield). ^{1}H NMR (DMSO-d_6) δ=2.0—2.1 (1H, m), 2.3—2.4 (1H, m), 3.4—3.7 (3H, m), 4.20 (1H, m, H-2′), 4.83 (1H, d, J=49.7 Hz, H-3′), 4.8—5.0 (1H, m, H-1′), 7.20 (2H, s, N<u>H</u>$_2$), 8.12 (1H, s, H-2), 8.32 (1H, s, H-8); ^{19}F NMR (DMSO-d_6) δ=−175.0 (ddd, J=12.1, 32.0, 49.7 Hz); mp 200—210 °C (decomp). Found: m/z 268.1167. Calcd for $C_{11}H_{14}FN_5O_2$: M, 268.1210.

(±)-9-[(1α, 2β, 3β, 4α)-3-Fluoro-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-6-aminopurine (16b). The title compound was obtained in 61% yield from **14**. ^{1}H NMR (DMSO-d_6) δ=1.7—1.9 (1H, m, H-6′), 2.2—2.4 (2H, m, H-6′, 2′-O<u>H</u>), 3.4—3.6 (2H, m), 4.60 (1H, dd, J=3.7, 30.0 Hz, H-2′), 4.72 (1H, s, H-4′), 4.80 (1H, dd, J=3.7, 54.2 Hz, H-3′), 4.95 (1H, s, O<u>H</u>), 7.20 (2H, s, N<u>H</u>$_2$), 8.11 (1H, s, H-8), 8.20 (1H, s, H-2); ^{19}F NMR (DMSO-d_6) δ=−185.9 (ddd, J=28.0, 30.0, 54.2 Hz); mp 196.2—199.2 °C (decomp). MS 267 (M^+), 236, 216. Found: m/z 268.1214. Calcd for $C_{11}H_{14}FN_5O_2$: M, 268.1210.

(±)-2-Amino-1,9-dihydro-9-[(1α,2α,3β,4α)-3-fluoro-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-6*H*-purin-6-one (17a). A mixture of **3** (412 mg, 2.76 mmol), 2-amino-4,6-dichloropyrimidine (906 mg, 5.52 mmol), and triethylamine (0.79 ml, 5.52 mmol) in 1-butanol (15 ml) was refluxed for 15 h. The mixture was evaporated to dryness under reduced pressure. To the residue suspended in acetic acid (14 ml) and H_2O (14 ml), sodium acetate·$3H_2O$ (5.52 g) and 4-chlorobenzenediazonium chloride (3.2 mmol) were added and this mixture was stirred for 15 h at room temp. The resulting yellow solid was obtained by filtration, washed with cold H_2O, and dried.

A mixture of the above residue, Zn (2.2 g), and glacial acetic acid (2.2 ml) in ethanol (15 ml) and H_2O (15 ml) were heated at 70 °C for 1 h. The reaction mixture was filtrated and the filtrate was evaporated under reduced pressure. The residue was applied to the column of Amberlite CG-120 (H^+ form) and eluted with 5% aqueous ammonia to give the diamine intermediate.

A solution of this diamine (300 mg, 1.03 mmol), triethyl orthoformate (15 ml) and concd HCl (0.5 ml) in *N*,*N*-dimethylformamide (2 ml) was stirred at room temp for 15 h, and then evaporated to dryness. The residue was dissolved in 2 M HCl (20 ml) and a mixture was heated under reflux for 3 h. The reaction mixture was treated with Amberlite CG-120 (H^+ form) and eluted with 5% aqueous ammonia to afford **17a** (126 mg, 43% yield). ^{1}H NMR (CD_3OD) δ=1.22—1.83, (1H, m), 2.05—2.95 (3H, m), 3.88 (2H, m), 4.35—5.25 (3H, m), 9.11 (1H, s); ^{19}F NMR (CD_3OD) δ=−174.2 (ddd, J=11.4, 32.6, 52.0 Hz). Found: m/z 284.1137. Calcd for $C_{11}H_{14}FN_5O_3$: M, 284.1159.

(±)-2-Amino-1,9-dihydro-9-[(1α,2β,3β,4α)-3-fluoro-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-6*H*-purin-6-one (17b). The title compound was prepared in 37% yield from **14**. ^{1}H NMR (CD_3OD) δ=1.20—1.78, (1H, m), 1.98—2.01 (3H, m), 3.88 (2H, m), 4.72—5.50 (3H, m), 8.00 (1H, m); ^{19}F NMR (CD_3OD) δ=−189.0 ppm (m). Found: m/z 284.1181. Calcd for $C_{11}H_{14}FN_5O_3$: M, 284.1159.

(±)-1-[(1α,2α,3β,4α)-3-Fluoro-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (19a). To a solution of the fluoro amine **3** (300 mg, 2.0 mmol) in *N*,*N*-dimethylformamide (10 ml) at −25 °C was added dropwise during 5 min a solution of 3-ethoxy-2-propenoyl isocyanate (**18a**) (0.4 M benzene solution, 5.0 ml, 2.0 mmol). After 10 min, the mixture was allowed to warm to room temp and then the solvents were evaporated under reduced pressure at 30 °C to give acylurea as an intermediate.

A solution of this acylurea in 2 M HCl (10 ml) was heated under reflux for 20 min and cooled to 0 °C. The mixture was neutralized with 2 M NaOH and the water was evaporated under reduced pressure. The residue was purified by column chromatography to give **19a** (340 mg, 90% yield). ^{1}H NMR (CD_3OD) δ=1.9—2.8, (3H, m), 3.6—4.0 (2H, m), 4.3—5.4 (3H, m), 5.85 (1H, d, J=8.6 Hz), 7.98 (1H, d, J=8.6 Hz); ^{19}F NMR (CD_3OD) δ=−175.3 (ddd, J=12.7, 28.3, 51.0 Hz). Found: m/z 245.0931. Calcd for $C_{10}H_{13}FN_2O_4$: M, 245.0938.

(±)-1-[(1α,2β,3β,4α)-3-Fluoro-2-hydroxy-4-(hy-

droxymethyl)cyclopentyl]- 2, 4(1*H*, 3*H*)- pyrimidinedione (19b). The title compound was obtained in 67% yield from **14**. ^{1}H NMR (D_2O) δ=1.48—1.80, (1H, m), 2.32—2.82 (2H, m), 3.86 (2H, m), 4.80—5.44 (3H, m), 6.30 (1H, d, J=7.5 Hz), 7.94 (1H, d, J=7.5 Hz). Found: m/z 245.0923. Calcd for $C_{10}H_{13}FN_2O_4$: M, 245.0938.

(±)- 1- [(1α, 2α, 3β, 4α)- 3- Fluoro- 2- hydroxy- 4- (hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)- pyrimidinedione (20a). The thymidine derivative was prepared similar to the method of the synthesis **19a** with **18b** instead of **18a** (82% yield). ^{1}H NMR (CD_3OD) δ=1.8—2.8 (totally 6H, m+s (δ=2.02 (3H, s)), 3.7—4.0 (3H, m), 4.2—4.6 (2H, m), 7.80 (1H, br s); ^{19}F NMR (CD_3OD) δ= −175.0 (ddd, J=12.7, 28.3, 51.0 Hz). Found: m/z 259.1080. Calcd for $C_{11}H_{15}FN_2O_4$: M, 259.1094.

(±)- 1- [(1α, 2β, 3β, 4α)- 3- Fluoro- 2- hydroxy- 4- (hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)- pyrimidinedione (20b). The title compound was obtained in 100% yield from **14**. ^{1}H NMR (acetone-d_6) δ= 1.4—2.8 (totally 6H, m+s (δ=1.90, s)), 3.5—5.2 (5H, m), 7.70 (1H, br s); ^{19}F NMR (acetone-d_6) δ= −186.9 (ddd, J=23.9, 29.8, 53.7 Hz). Found: m/z 259.1105. Calcd for $C_{11}H_{15}FN_2O_4$: M, 259.1094.

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