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A divergent synthesis of D- and L-carbocyclic 4′-fluoro-2′,3′-dideoxynucleosides as potential antiviral agents

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Abstract

D- and L-Carbocyclic 4′-fluoro-2′,3′-dideoxynucleosides have been synthesized from **2**, which can be conveniently prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol **1** in eight steps. Ruthenium-catalyzed ring-closing metathesis has been employed in the synthesis of D-nucleosides, whereas the L-series have been obtained through an intramolecular nucleophilic substitution reaction. The Mitsunobu condensation was used as a general tool for the synthesis of both purine and pyrimidine nucleosides. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Nucleoside analogues display a wide range of biological activities and have attracted particular attention as antitumor and antiviral agents.[1] In spite of the initial success obtained with several nucleosides, the instability of the glycosidic bond of the classical 4′-oxonucleosides under physiological conditions[2] as well as undesirable side effects and toxicities of certain nucleosides have prompted the search for other antiviral or antitumor agents with improved biological and chemical properties. Consequently, extensive modifications have been made to both the heterocyclic base as well as the sugar moiety,[3] and the latter has been extensively substituted by acyclic[4] and carbocyclic moieties.[5] Among several approaches to modify the structure of nucleosides, carbocyclic nucleosides have attracted great interest because the replacement of the furanose ring oxygen offers greater metabolic stability to the endogenous phosphorylases which cleave the glycosidic linkage.[6] Another interesting feature of carbocyclic nucleosides is that a number of carbocyclic adenosine analogues are assumed to exert their antiviral action through the inhibition of *S*-adenosylhomocysteine hydrolase, and this mechanism might be exploited in a combination therapy in association with nucleosides acting with

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different mechanisms.[7] The recent approval of abacavir (Fig. 1) by the Food and Drug Administration for the treatment of HIV shows the therapeutic significance of carbocyclic nucleosides.[8]

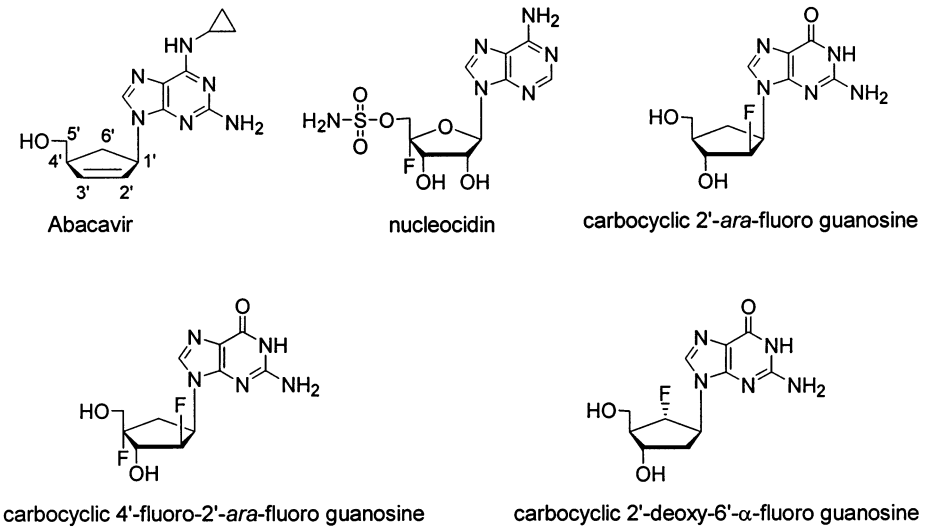
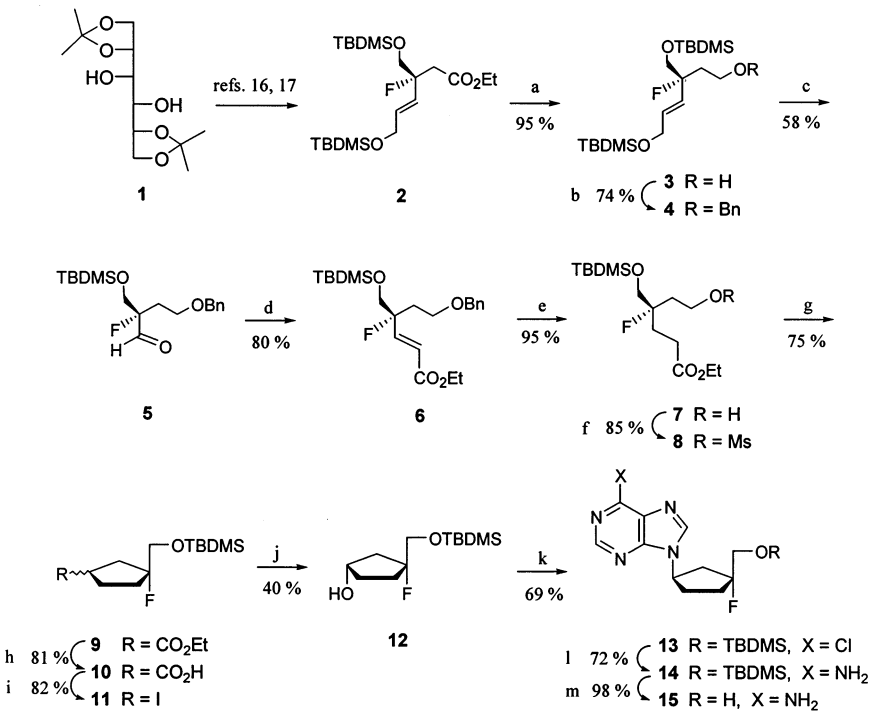


Figure 1.

However, since the conformation of the five-membered ring is believed to play a critical role in modulation of biological activity, the structural change following the removal of the oxygen is significant and generally results in decreased biological activity. Introduction of a small and highly electronegative fluoride atom to a nucleoside structure has been employed to confer biologically active conformations to the carbocyclic nucleosides.[9] The isosteric relationship between oxygen and a fluoromethylene group[10] has prompted various syntheses of fluoro-substituted carbocyclic nucleosides. Several fluoride-containing carbocyclic nucleosides at 2′, 3′, and 6′ positions have been reported.[11] Thus, 2′-*ara*-fluoro and 6′-α-fluoro substituent have been shown to confer potent antiherpes activity to some purine analogues[12] (Fig. 1). In contrast, substitution at the 4′-position of carbocyclic nucleosides has been largely ignored despite the presence of a 4′-fluoro substituent in the naturally occurring furanose antibiotic nucleocidin (Fig. 1). To our knowledge, carbocyclic 4′-fluoro-2′-deoxyguanosine from aristeromycin,[13] and carbocyclic 4′-α-fluoro-2′-*ara*-fluoro guanosine[14] (Fig. 1), which showed potent anti HSV-1 and anti HSV-2 activity, are the only examples of 4′-fluoro-substituted carbocyclic nucleosides. The importance of carbocyclic nucleosides as antiviral agents, as well as the potential importance of fluorine substitution, prompted us to combine these two features into novel carbocyclic 4′-fluoro-2′,3′-dideoxy nucleosides.[15,16]

Previously, we have reported preliminary synthetic results of 4′-substituted carbocyclic nucleosides as a communication.[16b] Herein we report an efficient and general approach to the asymmetric synthesis of D- and L-carbocyclic 4′-fluoro-2′,3′-dideoxy nucleosides by using the common intermediate **2** (Scheme 1)[17] obtained by [3,3]-sigmatropic rearrangement of a fluoro allylic alcohol. Starting from this common intermediate, we developed a divergent synthetic pathway leading to both D- and L-nucleosides. The synthesis of the L-isomer was accomplished by way of classical five-membered ring cyclization method, whereas a more convenient ring-closing metathesis route was employed for the synthesis of the D-isomer. In both cases, the Mitsunobu condensation between an α-cyclopentanol and heterocyclic bases was generally used.



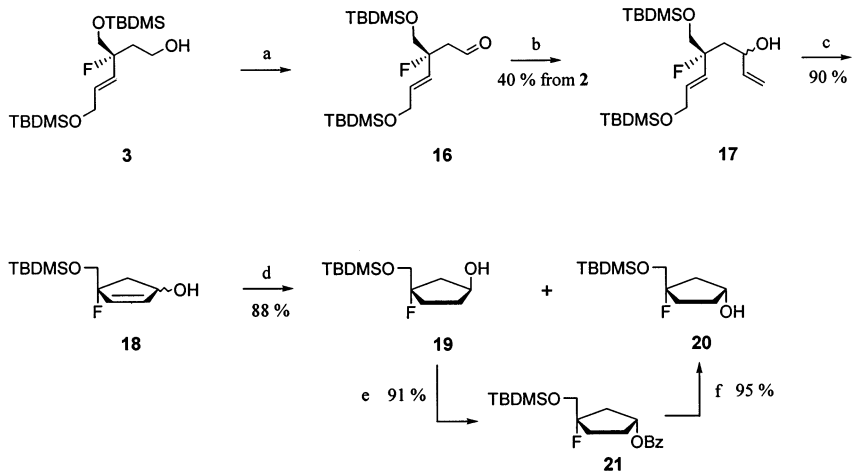
Scheme 1. Synthesis of (1′*R*,4′*R*)-9-[4-fluoro-4-(hydroxymethyl)cyclopentan-1-yl]adenine (**15**). Reagents and conditions: (a) LAH, THF, −40 to −35°C; (b) NaH, BnBr, THF; (c) O_3, MeOH, −78°C, then DMS; (d) $(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, THF, −78°C; (e) H_2, Pd/C, cyclohexane; (f) MsCl, pyridine, CH_2Cl_2, 0°C; (g) NaH, THF, reflux; (h) $NaOH/H_2O$, EtOH, rt; (i) $Pb(OAc)_4$, CCl_4, *hv*, reflux, 15 min; I_2, CCl_4, *hv*, reflux, 2 h; (j) $NaHCO_3$, 15% (v/v) water/HMPA, 100°C; (k) 6-chloropurine, DEAD, PPh_3, THF; (l) NH_3, MeOH, 100°C, steel bomb; (m) TBAF, THF, rt

2. Results and discussion

Even though the critical intermediate **2** was easily obtained, the cyclopentanol derivative **12** could not be prepared straightforwardly because the tertiary fluoride group was very susceptible for β-elimination under basic conditions. Several classical methods such as the Dieckmann condensation[18] of diesters and the intramolecular Horner–Emmons reaction of a β-ketophosphonate[19] were tried, but failed because the highly acidic α proton of the ester **2** was easily abstracted to result in the formation of a diene.[20] As reported previously,[16b] the susceptibility of the protected ester **2** toward elimination made the synthesis of the L-isomer more difficult than expected (Scheme 1). In order to synthesize L-nucleosides, ester **2** was reduced to alcohol **3** in 95% yield by treatment with a solution of lithium aluminum hydride in THF at −40°C followed by an anhydrous work-up. At temperatures higher than −20°C, the eliminated by-product was obtained as an inseparable mixture with **3**. Alcohol **3** was benzylated to a fully protected triol **4**, which was treated with ozone in methanol at −78°C, followed by decomposition of the ozonide by dimethyl sulfide to give the aldehyde **5**. The Horner–Emmons reaction was performed by the treatment of **5** with the sodium salt of triethyl phosphonoacetate in THF. *E*-Alkene **6**, obtained in 80% yield, was quantitatively converted to the intermediate **8** by catalytic hydrogenolysis followed by mesylation of the resulting alcohol **7**. Treatment of **8**

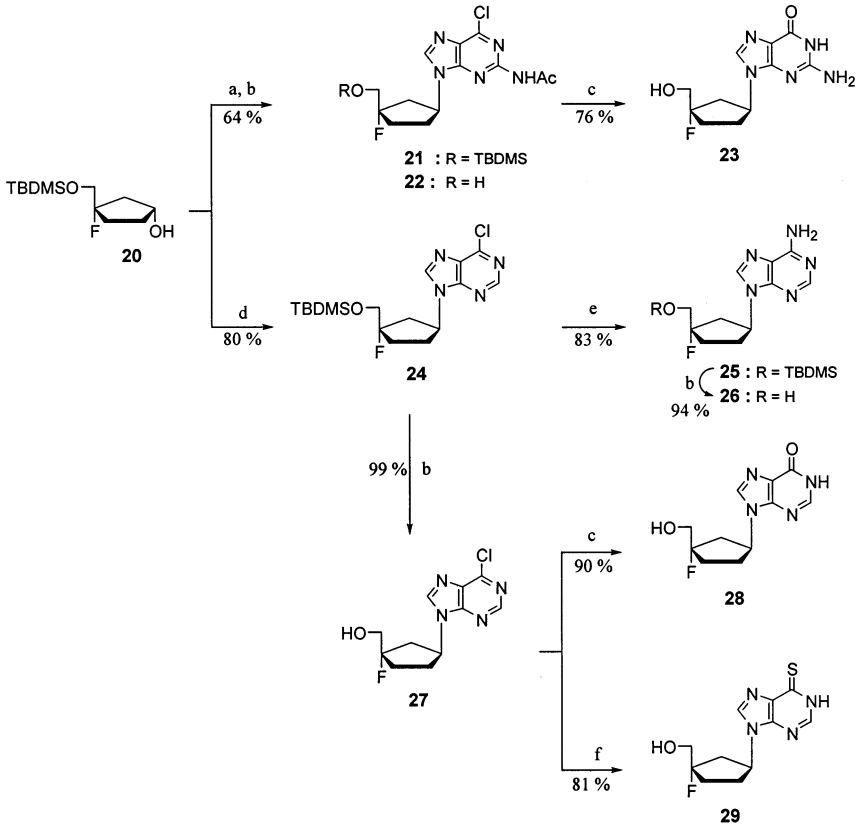
with sodium hydride in THF under reflux generated the enolate that cyclized through an intramolecular nucleophilic substitution reaction to produce epimeric esters **9** in 75% yield. The esters **9** were hydrolyzed to acids **10** by treatment with a solution of sodium hydroxide in 1:1 water/ethanol, followed by careful acidification. Oxidative iododecarboxylation of **10** could be achieved by the method reported by Barton et al.[21] to afford epimeric iodides **11**, which were smoothly hydrolyzed by heating at 100°C in a solution of sodium bicarbonate in 15% water/HMPA. Surprisingly, only the α-alcohol could be isolated from the hydrolysis of the mixture **11** (epimeric ratio ≈ 1:1). Under the reaction conditions, the α-iodide was not hydrolyzed and only longer reaction times or higher temperatures caused its decomposition. A solution of the alcohol **12** was added to a mixture containing 6-chloropurine and the preformed triphenylphosphine/DEAD complex in THF, and the reaction was performed at room temperature in the dark for 6 h. Removal of the solvent and flash chromatography gave **13** in 80% yield. The 6-chloropurine derivative **13** was converted to a protected adenosine analogue **14** by treatment with a saturated solution of ammonia in methanol in a steel bomb at 100°C for 2.5 h. Desilylation of the primary alcohol by treatment with tetrabutylammonium fluoride (TBAF) in THF resulted in the final L-carbocyclic 4′-fluoro-2′,3′-dideoxyadenosine **15** in 98% yield.

Due to the difficulties and low yield encountered in the synthesis of the L-isomer we decided to develop a more efficient method of synthesis for D-isomers, in which the ring-closing metathesis reaction[22] of the 1,6-diene allowed a more facile synthesis of the D-enantiomer (Scheme 2). The common intermediate, alcohol **3**, was oxidized by PCC, and the resulting aldehyde **16** was subjected to carbonyl addition by vinylmagnesium bromide to result in the 1:1 diastereomeric mixture of 1,6-dienes **17**. Due to the instability of intermediates **3** and **16**, the best yield was achieved when they were reacted immediately after filtration without any further purification. Under these conditions, compound **17** was obtained in 40% yield from **3**. A ring-closing metathesis reaction, catalyzed by Grubbs catalyst[23] [benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium], afforded cyclopentenols **18** as a diastereomeric mixture, whose α/β ratio (1:1) was consistent with the diastereomeric ratio of **17**. Even though this reaction proceeded very smoothly and in high (90%) yield, the instability of the cyclopentenols



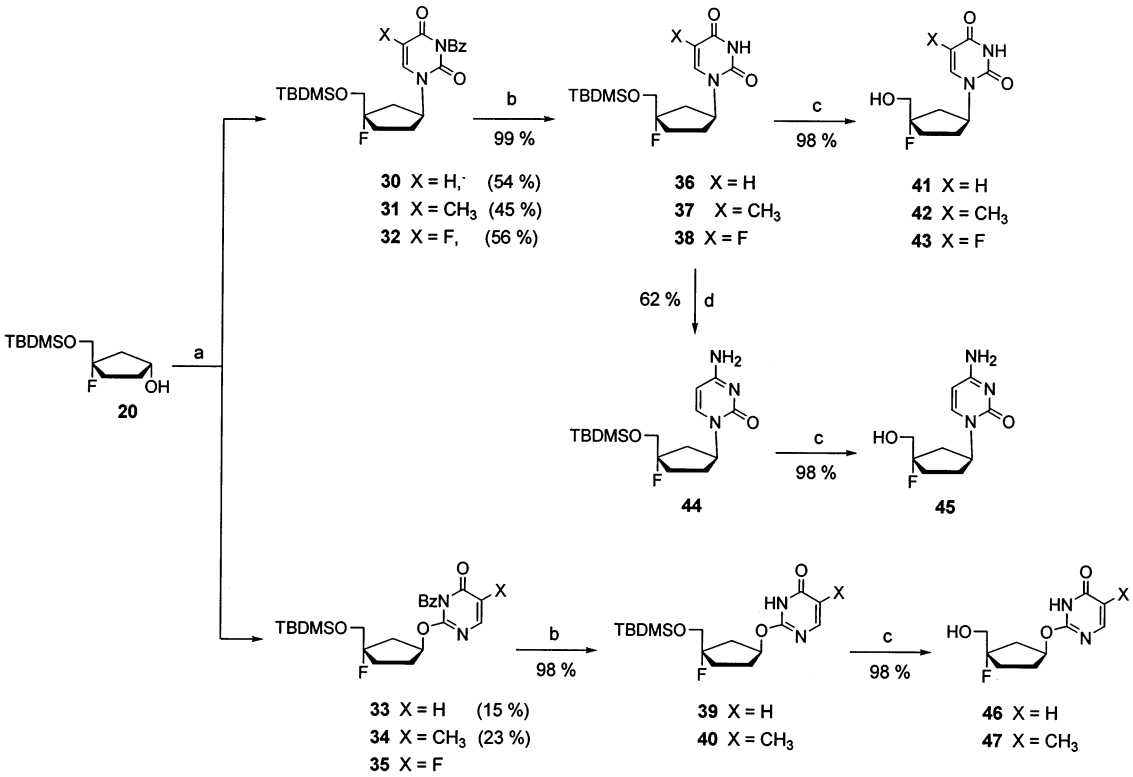
Scheme 2. Synthesis of (1*R*,4*S*)-4-*tert*-butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-ol (**20**). Reagents and conditions: (a) PCC, 4 Å MS, CH_2Cl_2; (b) vinylmagnesium bromide, THF, −78°C; (c) Grubbs catalyst, CH_2Cl_2; (d) H_2, Pd/C, cyclohexane; (e) DEAD, PPh_3, PhCOOH, THF; (f) LAH, THF, −40 to −35°C

18 made it difficult to fully characterize their structures. Therefore, the structure could be confirmed only after saturation of the double bond. Reduction of the double bond in **18** was accomplished by catalytic hydrogenation on 10% Pd/C in cyclohexane to result in two easily separable isomers, **19** and **20**, in 88% yield. The β-alcohol **19**, however, could be converted into the α-epimer **20** by Mitsunobu reaction followed by LAH reduction in 86% overall yield (Scheme 2). The absolute configuration of α-alcohol **20** was confirmed by comparing the spectroscopic data (^{1}H and ^{13}C spectra) as well as optical rotation values with those of its enantiomer (**12**, Scheme 1).[16b] The α-cyclopentanol **20** was condensed with various protected purine and pyrimidine bases under Mitsunobu conditions. The success of Mitsunobu reactions in the syntheses of nucleoside analogues is known to depend on the conditions employed.[24] Therefore, appropriate choice of solvent system, temperature, and procedures are critical for the regioselectivity as well as the yield. In purine synthesis (Scheme 3), THF and a 2:1 mixture of dioxane and DMF were used as solvents for the coupling of the alcohol **20** with 6-chloropurine and N^2-acetylamino-6-chloropurine, respectively. The use of a dioxane–DMF mixture allowed better solubility of the heterocyclic bases and better yields. Slow addition of DEAD to a mixture of alcohol **20**, triphenylphosphine, and the corresponding purine base in anhydrous solvent gave a yellow solution which was stirred for 6–12 hours at room temperature to give protected purine analogues (**21** and **24**) in 65–80% yield. Because of the interference of the reduced form of



Scheme 3. Synthesis of purine nucleosides. Reagents and conditions: (a) DEAD, PPh_3, N^2-acetylamino-6-chloropurine, THF; (b) TBAF, THF; (c) HCO_2H, 90°C, then NH_3, MeOH, rt; (d) DEAD, PPh_3, 6-chloropurine, THF; (e) NH_3, MeOH, 100°C, steel bomb; (f) thiourea, EtOH, reflux

DEAD, 1,2-dicarbethoxyhydrazine, the structure of **21** could not be characterized until it was desilylated to give **22**. The guanosine analogue **23** was prepared from **22** after treating it with formic acid[24a] followed by methanolic ammonia. The 6-chloropurine derivative **24** was converted into three different nucleosides by using conventional nucleoside chemistry. Thus, the adenosine analogue **26** was prepared by amination of the 6-chloropurine analogue **24** followed by desilylation, while treatment of the desilylated 6-chloropurine analogue **27** with either formic acid[24a] or thiourea gave the inosine **28** and the 6-mercaptopurine **29** analogues, respectively (Scheme 4).



Scheme 4. Synthesis of pyrimidine nucleosides. Reagents and conditions: (a) DEAD, PPh_3, N_3-benzoylpyrimidine, DMF–dioxane (2:1), 0°C; (b) NH_3, MeOH, 0°C; (c) TBAF, THF, rt; (d) 1,2,4-triazole, 4-chlorophenyldichlorophosphate, pyridine, 0°C, then NH_3, MeOH, 100°C, steel bomb

On the other hand, the syntheses of pyrimidine nucleosides were more complex than the purine case due to the formation of O^2-alkylated by-products (**33**, **34** and **35**). The formation of O^2-alkylated compounds was inevitable in the reaction conditions tested, but the ratio of N- to O-alkylation was dramatically improved by changing the solvent from THF to 2:1 mixture of dioxane–DMF; the ratio of **30**:**33** changed from 1.3:1 in THF to 3.6:1 in dioxane–DMF. The structures of O^2-alkylated compounds (**33** and **34**) were confirmed by ^1H and ^{13}C NMR after removing the N_3-benzoyl groups because debenzoylated compounds (**39** and **40**) allowed direct comparison with ^1H and ^{13}C spectra reported for other O^2-alkylated pyrimidine nucleosides;[24c,d] the H-2′ chemical shifts of **39** and **40** (δ 5.51, 5.46, respectively) were appreciably downfield from those of the N_1 Mitsunobu products **36** and **37** (δ 5.02, 5.00, respectively). Furthermore, the C-1′ chemical shifts of **39** and **40** (δ 80.14, 79.84, respectively) were also shifted downfield from those

of the N_1 Mitsunobu products **36** and **37** (δ 59.87, 57.76, respectively). Unfortunately, the O^2-alkylated product of 5-fluorouridine analogue **35** could not be isolated because it easily decomposed during column chromatography on silica gel. The products of the Mitsunobu reaction **30**, **31** and **32** were converted into nucleoside analogues **41**, **42** and **43** via successive treatment with methanolic ammonia and tetrabutylammonium fluoride. The cytidine analogue **45** was synthesized by amination of uridine analogue **36** because it is known that the O-alkylation is the predominant pathway[24c] in the Mitsunobu reaction of protected cytosine with cyclopentanol. The well-known two-step conversion of uridine to cytidine[25] was adopted to give the protected cytidine analogue **44** in 62% yield. The final cytidine analogue **45** was obtained by desilylation.

Anti-HIV activity and cytotoxicity evaluations on the synthesized nucleosides **15**, **23**, **26**, **28**, **29**, **41**, **42**, **43** and **45** were performed in human peripheral blood mononuclear cells (PBMC). The adenine analogue **26** and guanine analogue **23** exhibited weak activity against HIV with EC_{50} values of 27.6 and 32.3 μM, respectively, while no other synthesized nucleosides showed significant anti-HIV activity. The toxicities of these nucleosides were also assessed, and these compounds did not exhibit any significant toxicities at concentration up to 100 μM in CEM, PBM and Vero cells.

In summary, we have developed a synthetic method for stereoselectively introducing a tertiary fluoride group and a de novo synthesis of the key α- and β-cyclopentanol intermediates **12** and **20**. Condensation of these intermediates with protected purine and pyrimidine bases, followed by ammonolysis and deprotection, readily provided optically pure D- and L-carbocyclic 4′-fluoro-2′,3′-dideoxynucleosides. The convenience of our approach lies in the possibility of obtaining a number of different analogues by the reaction of a single intermediate with several heterocyclic bases.

3. Experimental

Melting points were determined on a Mel-temp II apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker 400 AMX spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR with tetramethylsilane as the internal standard. Chemical shifts (δ) are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). UV spectra were recorded on a Beckman DU-650 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Flash column chromatography was performed using silica gel G (TLC grade, >440 mesh). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

*3.1. (−)-(3*R*)-3-*tert*-Butyldimethylsilyloxymethyl-6-*tert*-butyldimethylsilyloxy-3-fluorohex-4-enoic acid ethylester* **2**

This compound was prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol in eight steps. The reaction conditions are described in detail in supplementary material: $[\alpha]_D^{24}$ −1.3 (*c* 1.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 2H), 4.14 (br m, 2H), 4.06 (q, $J=7.1$ Hz, 2H), 3.71 (m, 2H), 2.82

(dd, $J=18.4$, 15.2 Hz, 1H), 2.71 (dd, $J=15.2$, 15.0 Hz, 1H), 1.18 (t, $J=7.1$ Hz, 3H), 0.84 (s, 9H), 0.83 (s, 9H), 0.00 (s, 6H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.88 (d, $J=10.9$ Hz), 131.24 (d, $J=9.6$ Hz), 127.38 (d, $J=19.2$ Hz), 95.64 (d, $J=179.3$ Hz), 67.30 (d, $J=26.5$ Hz), 63.22, 60.84, 40.48 (d, $J=26.0$ Hz), 26.29, 26.18, 18.76, 18.65, 14.57, −5.05, −5.17. Anal. calcd for $C_{21}H_{43}FO_4Si_2$: C, 58.02; H, 9.97. Found: C, 58.30; H, 9.98.

3.2. (+)-(3R)-3-tert-Butyldimethylsilyloxymethyl-6-tert-butyldimethylsilyloxy-3-fluorohex-4-en-1-ol **3**

To a stirred solution of 300 mg (0.69 mmol) of **2** in 50 ml of dry diethylether, 1.04 ml (1.04 mmol) of 1.0 M solution of lithium aluminum hydride was added at −50°C. The reaction mixture was stirred at between −40 and −35°C for 1.5 h, and then quenched with 5 ml of EtOAc. After 30 minutes the reaction mixture was diluted with 50 ml of hexane and allowed to slowly warm to rt. It was filtered through a short TLC grade silica gel pad washing with a 4:1 mixture of hexane and ethyl acetate. Evaporation of the solvents under the reduced pressure gave 270 mg (0.69 mmol) of **3** as a light yellow oil which was used for the next step without further purification: $[\alpha]_D^{25}$ +7.7 (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.89 (dt, $J=15.6$, 4.0 Hz, 1H), 5.77 (ddt, $J=21.6$, 15.6, 1.6 Hz, 1H), 4.21 (dt, $J=4.0$ Hz, 1.6 Hz, 2H), 3.81 (m, 1H), 3.73 (m, 1H), 3.69 (dd, $J=13.2$, 11.1 Hz, 1H), 3.63 (dd, $J=22.7$, 11.1 Hz, 1H), 2.35 (br s, 1H), 2.12 (dddd, $J=17.3$, 14.8, 7.3, 4.9 Hz, 1H), 1.98 (dddd, $J=25.3$, 14.8, 6.7, 4.8 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 130.4 (d, $J=10.1$ Hz), 127.95 (d, $J=19.8$ Hz), 97.21 (d, $J=175.3$ Hz), 68.00 (d, $J=28.4$ Hz), 62.72, 58.18 (d, $J=5.2$ Hz), 38.63 (d, $J=21.4$ Hz), 25.89, 25.76, 18.36, 18.27, −5.44, −5.55; FABMS (*m*/*z*) 393 $(M+H)^+$. Anal. calcd for $C_{19}H_{43}FO_4Si_2$: C, 58.11; H, 10.52. Found: C, 58.07; H, 10.51.

3.3. (+)-(4R)-6-Benzyloxy-1-tert-butyldimethylsilyloxy-4-tert-butyldimethylsilyloxymethyl-4-fluorohex-2-ene **4**

To a stirred, ice cooled suspension of sodium hydride (0.60 g of 60% dispersion in mineral oil, 15.0 mmol) in anhydrous THF (20 ml), was added a solution of **3** (2.37 g, 6.0 mmol) in anhydrous THF (20 ml). The mixture was stirred at rt for 1 h, then tetrabutylammonium iodide (TBAI, 0.22 g, 0.6 mmol) was added and, upon recooling at 0°C, benzyl bromide (1.1 ml, 9.2 mmol) was added. The reaction mixture was stirred at rt overnight, then cooled to 0°C, quenched with water (20 ml), and extracted with ethyl acetate (3×50 ml) to give a crude product which was purified by flash chromatography (49:1 hexanes/ethyl acetate) to yield 2.17 g (4.49 mmol, 74%) of **4** as a colorless oil: $[\alpha]_D^{26}$ +1.1 (*c* 1.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.86 (dt, $J=28.8$, 4.0 Hz, 1H), 5.79 (m, 1H), 4.58 (dd, $J=16.2$, 12.2 Hz, 1H), 4.48 (s, 1H), 4.20 (m, 2H), 3.77–3.50 (m, 2H), 2.27–1.88 (m, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.07 (s, 6H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.06, 130.27 (d, $J=10.0$ Hz), 128.34, 127.98 (d, $J=20.3$ Hz), 127.65, 127.61, 96.58 (d, $J=176.4$ Hz), 73.01, 68.00 (d, $J=28.0$ Hz), 65.78 (d, $J=5.3$ Hz), 62.91, 38.73 (d, $J=22.0$ Hz), 25.91, 25.82, 18.37, 18.27, −5.29, −5.42, −5.54.

3.4. (−)-(4S)-4-O-Benzyloxy-2-tert-butyldimethylsilyloxymethyl-2-fluorohexanal **5**

A solution of **4** (5.80 g, 12.0 mmol) in methanol (150 ml) was treated with ozone at −78°C, until a slight blue color persisted (30–45 min). The solution was then degassed with argon,

allowed to warm to rt and methyl sulfide (2.7 ml, 36.8 mmol) was added. The mixture was stirred at 0°C for 2 h, then methanol was removed under reduced pressure and the residue was treated with water (10 ml), and methylene chloride (3×50 ml) was used to extract the product. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (19:1 hexanes/ethyl acetate) to yield 2.36 g (6.93 mmol, 58%) of **5** as a colorless oil: $[\alpha]_D^{28}$ −15.1 (*c* 2.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.70 (dd, $J=6.2$, 0.6 Hz, 1H), 7.36–7.25 (m, 5H), 4.45 (s, 2H), 3.92 (dd, $J=25.8$, 11.6 Hz, 1H), 3.80 (dd, $J=19.8$, 11.6 Hz, 1H), 3.65 (td, $J=10.0$, 3.8 Hz, 1H), 3.58–3.52 (m, 1H), 2.27–2.11 (m, 1H), 2.05–1.96 (m, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.87 (d, $J=40.1$ Hz), 137.78, 128.37, 127.62, 127.53, 99.81 (d, $J=185.3$ Hz), 72.91, 66.15 (d, $J=22.2$ Hz), 63.95 (d, $J=5.7$ Hz), 33.03 (d, $J=21.4$ Hz), 25.67, 18.22, −5.61; FABMS (*m*/*z*) 341 $(M+H)^+$. Anal. calcd for $C_{18}H_{29}FO_3Si{\cdot}0.24CH_2Cl_2$: C, 60.70; H, 8.23. Found: C, 60.38; H, 8.48.

3.5. (+)-(4R)-Ethyl (E)-6-O-benzyloxy-4-tert-butyldimethylsilyloxymethyl-4-fluoro-2-enoate **6**

To a solution of triethyl phosphonoacetate (1.33 ml, 6.7 mmol) in anhydrous THF (20 ml), was added a 1.0 M solution of NaHMDS in THF (6.7 ml, 6.7 mmol) at −78°C. After the addition the mixture was stirred at −78°C for 1 h. A solution of **5** (2.30 g, 6.75 mmol) in anhydrous THF was added. Stirring was continued at −78°C for 1 h, after which the reaction was quenched with saturated ammonium chloride solution (2 ml), allowed to warm to rt, and extracted with ethyl ether (3×10 ml). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (9:1 hexanes/ethyl acetate) to yield 2.22 g (5.41 mmol, 80%) of **6** as a colorless oil: $[\alpha]_D^{27}$ +2.90 (*c* 3.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38–7.25 (m, 5H), 6.94 (dd, $J=22.4$, 15.8 Hz, 1H), 6.08 (d, $J=15.8$ Hz, 1H), 4.48 (d, $J=13.9$ Hz, 1H), 4.45 (d, $J=13.9$ Hz, 1H), 4.20 (q, $J=7.1$ Hz, 1H), 4.19 (q, $J=7.1$ Hz, 1H), 3.70–3.65 (m, 2H), 3.64–3.51 (m, 2H), 2.26–2.01 (m, 2H), 1.28 (t, $J=7.1$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.95, 146.01 (d, $J=20.0$ Hz), 138.07, 128.33, 127.62, 127.57, 120.88 (d, $J=10.2$ Hz), 96.54 (d, $J=181.0$ Hz), 73.06, 67.31 (d, $J=27.6$ Hz), 65.17 (d, $J=5.1$ Hz), 60.49, 34.89 (d, $J=22.1$ Hz), 25.73, 18.22, −5.50, −5.58; FABMS (*m*/*z*) 411 $(M+H)^+$. Anal. calcd for $C_{22}H_{35}FO_4Si$: C, 64.35; H, 8.59. Found: C, 64.45; H, 8.70.

3.6. (+)-(4S)-Ethyl 4-tert-butyldimethylsilyloxymethyl-4-fluoro-6-hydroxyhexanoate **7**

To a solution of **6** (2.56 g, 6.2 mmol) in cyclohexane (100 ml), Pd/C (10%, 1.33 g, 1.2 mmol) was added. The mixture was thoroughly deoxygenated, then saturated with hydrogen and stirred for 24 h. The charcoal was, then, removed by filtration through a short Celite pad, which was thoroughly washed with hexanes. Evaporation of the solvent gave a crude product which was purified by flash chromatography to yield 1.91 g (5.92 mmol, 95%) of **7** as a colorless oil: $[\alpha]_D^{29}$ +2.2 (*c* 2.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.14 (q, $J=7.1$, 2H), 3.84–3.73 (m, 2H), 3.71–3.61 (m, 2H), 2.49 (bs, 1H), 2.45–2.40 (m, 2H), 1.26 (t, $J=7.1$, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.18, 97.19 (d, $J=172.7$ Hz), 66.32 (d, $J=30.7$ Hz), 60.57, 57.96 (d, $J=7.4$ Hz), 38.05 (d, $J=21.5$ Hz), 30.40 (d, $J=21.8$ Hz), 28.13 (d, $J=5.8$ Hz), 25.71, 18.17, 14.16, −5.55, −5.60; FABMS (*m*/*z*) 323 $(M+H)^+$. Anal. calcd for $C_{15}H_{31}FO_4Si$: C, 55.87; H, 9.69. Found: C, 56.11; H, 9.73.

3.7. (−)-(4S)-Ethyl 4-tert-butyldimethylsilyloxymethyl-4-fluoro-6-hydroxy-6-methanesulfonyloxyhexanoate **8**

To a solution of **7** (200 mg, 0.62 mmol) and pyridine (0.18 ml, 2.23 mmol) in anhydrous methylene chloride (5 ml), mesyl chloride (0.15 ml, 1.94 mmol) was added dropwise at 0°C. The reaction mixture was stirred at rt for 24 h, then quenched with methanol (0.3 ml), concentrated under reduced pressure, and purified by flash chromatography (9:1 hexanes/ethyl acetate) to yield 210 mg (0.52 mmol, 85%) of **8** as a colorless oil: $[\alpha]_D^{27}$ −0.3 (*c* 2.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.39 (t, $J=7.1$ Hz, 2H), 4.14 (q, $J=7.1$, 2H), 3.64 (dd, $J=12.2$, 10.9 Hz, 1H), 3.60 (dd, $J=14.3$, 10.9 Hz, 1H), 3.02 (s, 3H), 2.45–2.39 (m, 2H), 2.18 (td, $J=7.1$, 3.9 Hz, 1H), 2.13 (td, $J=7.1$, 2.3 Hz, 1H), 2.08–1.98 (m, 2H), 1.26 (t, $J=7.1$, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.89, 95.98 (d, $J=175.0$ Hz), 65.75 (d, $J=30.3$ Hz), 65.26 (d, $J=7.8$ Hz), 60.63, 37.48, 34.22 (d, $J=22.5$ Hz), 30.23 (d, $J=22.2$ Hz), 28.10 (d, $J=5.9$ Hz), 25.72, 18.13, 14.15, −5.57, −5.61; FABMS (*m*/*z*) 401 $(M+H)^+$.

3.8. Ethyl (1R, 3R)-3-tert-butyldimethylsilyloxymethyl-3-fluorocyclopentancarboxylate **9** and ethyl (1S,3R)-3-tert-butyldimethylsilyloxymethyl-3-fluorocyclopent-1-yl carboxylate **9**

To a suspension of sodium hydride (175 mg of 60% dispersion in mineral oil, 4.37 mmol) in anhydrous THF (20 ml), a solution of **8** (350 mg, 0.87 mmol) in anhydrous THF (20 ml) was added. The reaction was refluxed overnight, then cooled to 0°C and quenched with saturated ammonium chloride solution (20 ml). Water (5 ml) was added to dissolve precipitated salt, and the mixture was extracted with ethyl acetate (3×40 ml). The combined organic layer was washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product which was purified by flash chromatography (49:1 hexanes/ethyl acetate) to yield α- and β-**9** as colorless oil (combined yield: 200 mg, 0.66 mmol, 75%): **For major isomer**, $[\alpha]_D^{27}$ −1.2 (*c* 1.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.13 (q, $J=7.1$, 2H), 3.74 (dd, $J=14.5$, 11.0 Hz, 1H), 3.70 (dd, $J=15.2$, 11.0 Hz, 1H), 3.11–3.02 (m, 1H), 2.21–1.82 (m, 6H), 1.26 (t, $J=7.1$, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 175.65, 106.24 (d, $J=176.1$ Hz), 66.24 (d, $J=29.5$ Hz), 60.50, 42.28, 38.14 (d, $J=23.6$ Hz), 33.82 (d, $J=23.2$ Hz), 28.08, 25.81, 18.28, 14.20 −5.45; FABMS (*m*/*z*) 305 $(M+H)^+$. Anal. calcd for $C_{15}H_{29}FO_3Si$: C, 59.17; H, 9.60. Found: C, 59.46; H, 9.59. **For minor isomer**, $[\alpha]_D^{27}$ +5.7 (*c* 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.15 (q, $J=7.1$, 2H), 3.67 (d, $J=15.0$ Hz, 2H), 2.83–2.74 (m, 1H), 2.20 (dd, $J=26.3$, 8.6 Hz, 1H), 2.14–2.06 (m, 1H), 2.03–1.91 (m, 2H), 1.85–1.69 (m, 2H), 1.26 (t, $J=7.1$, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 174.88, 105.18 (d, $J=178.0$ Hz), 66.09 (d, $J=32.5$ Hz), 60.54, 43.26, 37.63 (d, $J=24.4$ Hz), 34.61 (d, $J=24.0$ Hz), 28.13, 25.81, 18.25, 14.21 −5.47; FABMS (*m*/*z*) 305 $(M+H)^+$. Anal. calcd for $C_{15}H_{29}FO_3Si$: C, 59.17; H, 9.60. Found: C, 59.35; H, 9.53.

3.9. (4R)-3-tert-Butyldimethylsilyloxymethyl-3-fluorocyclopentancarboxylic acid **10**

To a solution of **9** (0.90 g, 2.95 mmol) in ethanol (50 ml), a solution of sodium hydroxide (0.41 g in 50 ml, 10.25 mmol) was added. The mixture was stirred at rt for 5 h, then concentrated under reduced pressure to about 50 ml, cooled to 0°C, quenched with glacial acetic acid (1.2 ml, 20.96 mmol), and rapidly extracted with ethyl acetate (3×200 ml). The combined extracts were washed with water (20 ml) and brine (20 ml), then dried over $MgSO_4$ and concentrated in vacuo. The crude product thus obtained was rapidly purified by flash chro-

matography (1:1 hexanes/ethyl acetate) to yield 0.66 g (2.39 mmol, 81%) of the epimeric mixture **10** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 10.52 (bs, 1H), 3.78–3.63 (m, 4H), 3.16–3.08 (m, 1H), 2.91–2.82 (m, 1H), 2.27–1.83 (m, 12H), 0.90 (s, 18H), 0.07 (s, 12H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 181.59, 106.12 (d, $J=176.3$ Hz), 66.06 (d, $J=30.0$ Hz), 42.08, 38.04 (d, $J=23.7$ Hz), 33.81 (d, $J=23.1$ Hz), 27.96, 25.79, 18.25, −5.47; δ (minor isomer) 180.93, 105.19 (d, $J=177.0$ Hz), 65.91 (d, $J=32.7$ Hz), 42.87, 37.43 (d, $J=24.4$ Hz), 34.16 (d, $J=24.0$ Hz), 28.00, 25.79, 18.26, −5.47; HR-FABMS (m/z) obsd 277.1603, calcd for $C_{13}H_{26}FO_3Si$ 277.1635 $(M+H)^+$. Anal. calcd for $C_{13}H_{25}FO_3Si{\cdot}0.11C_6H_{14}$: C, 56.82; H, 9.21. Found: C, 57.17; H, 9.22.

*3.10. (4*R*)-1-*tert-*Butyldimethylsilyloxymethyl-1-fluoro-3-iodopentane* **11**

A mixture of **10** (0.66 g, 2.39 mmol) and lead tetraacetate (3.18 g, 7.17 mmol) in carbon tetrachloride (20 ml) was stirred under reflux while illuminated with a 250 W tungsten lamp for 15 min. Then, while maintaining the same conditions of reflux and illumination, a solution of iodine (1.83 g, 7.20 mmol) in carbon tetrachloride (60 ml) was added in small portions until no more discoloration was observed. The reaction was continued for one more hour, then allowed to cool to rt. The lead salts were filtered off and the filtrate was decolorized by shaking with a 2% solution of sodium thiosulfate. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo to a crude product which was purified by flash chromatography (hexanes) to yield 0.70 g (1.95 mmol, 82%) of the epimeric mixture **11** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.44–4.36 (m, 1H), 4.10–4.02 (m, 1H), 3.75 (dd, $J=14.3$, 10.9 Hz, 1H), 3.71 (dd, $J=15.2$, 10.9 Hz, 1H), 3.63 (d, $J=14.0$ Hz, 2H), 2.67–1.72 (m, 12H), 0.91 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H) 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 105.44 (d, $J=178.0$ Hz), 104.24 (d, $J=179.9$ Hz), 66.53 (d, $J=31.8$ Hz), 66.19 (d, $J=35.0$ Hz), 48.56 (d, $J=23.9$ Hz), 47.79 (d, $J=24.4$ Hz), 38.81, 38.42, 35.11 (d, $J=24.4$ Hz), 34.35 (d, $J=24.0$ Hz), 25.82, 25.78, 21.74, 19.39, 18.29, 18.21, −5.43, −5.49; FABMS (m/z) 359 $(M+H)^+$. Anal. calcd for $C_{12}H_{24}FIOSi{\cdot}0.02C_6H_{14}$: C, 40.43; H, 6.80. Found: C, 40.76; H, 6.87.

*3.11. (+)-(1*S,*3*R*)-3-*tert-*Butyldimethylsilyloxymethyl-3-fluorocyclopentan-1-ol* **12**

A mixture of **11** (690 mg, 1.93 mmol) and sodium bicarbonate (0.33 g, 3.93 mmol) in 15% (v/v) water/HMPA was heated at 100°C overnight. The mixture was then cooled to 0°C, diluted with water (20 ml), and extracted with ether (3×40 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure to a crude product which was purified by flash chromatography (6:1 hexanes/ethyl acetate) to yield 190 mg (0.76 mmol, 40%) of the only diastereomer **12** as a colorless oil: $[\alpha]_D^{27}$ +2.2 (*c* 3.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.33 (m, 1H), 3.69 (dd, 1H, $J=15.6$, 10.7 Hz), 3.65 (dd, 1H, $J=16.4$, 10.7 Hz), 2.14–1.74 (m, 6H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 106.17 (d, $J=175.0$ Hz), 73.28, 66.19 (d, $J=32.0$ Hz), 43.68 (d, $J=21.5$ Hz), 34.51, 32.66 (d, $J=24.1$ Hz), 25.78, 18.23, −5.48. HR-FABMS (m/z) obsd 249.1699, calcd for $C_{12}H_{26}FO_2Si$ 249.1686 $(M+H)^+$. Anal. calcd for $C_{12}H_{25}FO_2Si$: C, 58.02; H, 10.14. Found: C, 57.80; H, 9.96.

*3.12. (−)-9-[(1*R,*4*R*)-4-*tert-*Butyldimethylsilyloxymethyl-4-fluorocyclopentyl]-6-chloropurine* **13**

A suspension of triphenylphosphine (590 mg, 2.25 mmol) and 6-chloropurine (348 mg, 2.25 mmol) in anhydrous THF (10 ml) was treated with DEAD (355 μl, 2.25 mmol) at rt in the dark

for 1 h. A solution of **12** (140 mg, 0.56 mmol) in anhydrous THF was, then, added and the mixture was stirred in the dark at rt for 6 h. Evaporation of solvent gave a crude product which was purified by flash chromatography (4:1 hexanes/ethyl acetate) to yield 149 mg (0.39 mmol, 69%) of **13** as a white solid: mp 74–76°C; $[\alpha]_D^{28}$ −12.8 (*c* 1.17, $CHCl_3$); UV ($CHCl_3$) λ_{max} 265.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 8.18 (s, 1H), 5.28–5.20 (m, 1H), 3.83 (dd, J=17.4, 10.6 Hz, 1H), 3.80 (dd, J=19.2, 10.6 Hz, 1H), 2.67–2.52 (m, 3H), 2.47–2.32 (m, 1H), 2.26–2.17 (m, 1H), 2.13–1.99 (m, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.64, 151.62, 151.16, 143.91, 132.25, 104.32 (d, J=176.4 Hz), 65.58 (d, J=32.7 Hz), 55.68, 40.41 (d, J=23.7 Hz), 32.88 (d, J=23.4 Hz), 30.86, 25.79, 18.27, −5.45; FABMS (m/z) 385 $(M+H)^+$. Anal. calcd for $C_{17}H_{26}ClFN_4OSi$: C, 53.04; H, 6.81; N, 14.55; Cl, 9.21. Found: C, 53.28; H, 6.79; N, 14.35; Cl, 9.35.

*3.13. (–)-9-[(1*R,*4*R*)-4-*tert-*Butyldimethylsilyloxymethyl-4-fluorocyclopentyl]adenine* **14**

Compound **13** (140 mg, 0.36 mmol) was dissolved in 15 ml of a stock solution of ammonia in methanol, and then stirred at 100°C in a steel bomb for 2.5 h. Evaporation under reduced pressure afforded an off-white solid, which was purified by flash chromatography (49:1 chloroform/methanol) to yield 96 mg (0.26 mmol, 72%) of **14** as a white solid: mp 152–154°C; $[\alpha]_D^{26}$ −17.9 (*c* 2.17, $CHCl_3$); UV ($CHCl_3$) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H), 7.86 (s, 1H), 5.70 (br s, 2H), 5.21–5.12 (m, 1H), 3.83 (dd, J=17.6, 10.6 Hz, 1H), 3.69 (dd, J=19.2, 10.6 Hz, 1H), 2.66–1.96 (m, 6H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.45, 152.64, 150.02, 139.02, 120.19, 104.46 (d, J=176.6 Hz), 65.79 (d, J=32.4 Hz), 54.85, 40.57 (d, J=23.7 Hz), 32.92 (d, J=23.4 Hz), 31.06, 25.80, 18.28, −5.45; FABMS (m/z) 366 $(M+H)^+$. Anal. calcd for $C_{17}H_{28}FN_5OSi$: C, 55.86; H, 7.72; N, 19.16. Found: C, 55.68; H, 7.65; N, 19.07.

*3.14. (–)-9-[(1*R,*4*R*)-4-Fluoro-4-hydroxymethylcyclopentyl]adenine* **15**

A 1.0 M solution of TBAF in THF (1 ml) was stirred with **14** (78.0 mg, 0.21 mmol) at rt for 30 min. Evaporation of the solvent under reduced pressure gave an oil that was purified by flash chromatography (1:19 methanol/chloroform) to yield 52.6 mg (0.197 mmol, 92%) of **15** as a white solid: mp 167–168°C; $[\alpha]_D^{29}$ −12.7 (*c* 0.37, MeOH); UV (MeOH) λ_{max} 260.0 (ε 20 890, pH 2), 261.5 (ε 19 800, pH 7), 261.5 (ε 17 980, pH 11); ^{1}H NMR (CD_3OD): δ 8.12 (s, 1H), 8.08 (s, 1H), 5.08 (m, 1H), 3.69 (dd, 1H, J=16.2, 12.1 Hz), 3.65 (dd, 1H, J=17.4, 12.1 Hz), 2.43–2.34 (m, 3H,), 2.33–2.15 (m, 1H,), 2.13–2.04 (m, 1H,), 2.00–1.86 (m, 1H,). ^{13}C NMR (CD_3OD): δ 157.3, 153.5, 150.7, 141.2, 120.5, 105.9 (d, J=176.6 Hz), 66.7 (d, J=27.4 Hz), 56.1, 41.6 (d, J=24.1 Hz), 33.7 (d, J=23.8 Hz), 31.5. HR-FABMS, (m/z) obsd 252.1268; Calcd for $C_{11}H_{15}FON_5$, m/z 252.1261 (MH^+). Anal. calcd for $C_{11}H_{14}FON_5$: C, 52.58; H, 5.62; N, 27.87. Found: C, 52.74; H, 5.73; N, 27.72.

*3.15. (3*R*)-3-*tert-*Butyldimethylsilyloxymethyl-6-*tert-*butyldimethylsilyloxy-3-fluorohex-4-en-1-al* **16**

The primary alcohol (270 mg, 0.69 mmol) **3** obtained above was dissolved in dry methylene chloride (50 ml). To this colorless solution was added pyridinium chlorochromate (223 mg, 1.03 mmol) and 223 mg of 4 Å molecular sieves. The resulting dark brown mixture was vigorously stirred at rt for 2 h and then filtered through a short TLC grade silica gel pad washing with

methylene chloride. Evaporation under the reduced pressure gave 270 mg (0.69 mmol) of the crude aldehyde **16** as a pale yellow oil which was used for the next step without further purification: ^{1}H NMR (C_6D_6) δ 9.63 (q, J=2.3 Hz, 1H), 5.85 (m, 2H), 3.94 (br, s, 2H), 3.60 (dd, J=14.4, 11.2 Hz, 1H), 3.49 (dd, J=25.8, 11.2 Hz, 1H), 2.60 (ddd, J=16.8, 16.2, 2.3 Hz, 1H), 2.50 (ddd, J=21.9, 16.2, 2.3 Hz, 1H), 0.94 (s, 9H), 0.89 (s, 9H), −0.02 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (C_6D_6) δ 196.56 (d, J=7.3 Hz), 130.41 (d, J=9.7 Hz), 125.69 (d, J=19.7 Hz), 94.52 (d, J=177.2 Hz), 66.65 (d, J=26.1 Hz), 61.25, 47.59 (d, J=21.5 Hz), 24.67, 24.54, 17.11, 17.04, −6.82, −6.94.

*3.16. (5*R,*3*R*)/(5*R,*3*S*)-5*-tert-*Butyldimethylsilyloxymethyl-8*-tert-*butyldimethylsilyloxy-5-fluoro-3-hydroxyocta-1,6-diene* **17**

To a stirred solution of the aldehyde **16** (270 mg, 0.69 mmol) in dry THF at −78°C, was slowly added a 1.0 M solution of vinylmagnesium bromide solution in THF (0.95 ml, 0.95 mmol). After 1.5 h, water (5 ml) was added, and the reaction mixture was slowly warmed to rt. The aqueous phase was extracted with diethyl ether (3×10 ml), and the combined organic layer was dried over $MgSO_4$, filtered, and evaporated to give a yellow crude product which was purified by column chromatography on silica gel (15:1 hexane/diethyl ether) to give 115 mg (0.275 mmol, 40% yield from compound **3**) of the desired 1,6-diene **17**: ^{1}H NMR ($CDCl_3$) δ 5.83–5.66 (m, 6H), 5.10 (dt, J=17.2, 1.5 Hz, 2H), 4.95 (dtt, J=10.4, 3.8, 1.5 Hz, 2H), 4.22–4.17 (m, 2H), 4.15–4.13 (br m, 4H), 3.65 (dd, J=21.0, 11.1 Hz, 1H), 3.62 (dd, J=15.3, 10.8 Hz, 1H), 3.59 (dd, J=16.8, 11.1 Hz, 1H), 3.54 (dd, J=19.5, 10.8 Hz, 1H), 1.94–1.78 (m, 4H), 0.84 (s, 9H), 0.83 (s, 9H), 0.82 (s, 9H), 0.81 (s, 9H), 0.004 (s, 6H), −0.0053 (s, 6H), −0.0106 (s, 6H), −0.0151 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.41, 143.37, 131.47 (d, J=10.2 Hz), 131.37 (d, J=10.2 Hz), 130.58 (d, J=19.9 Hz), 130.19 (d, J=20.0 Hz), 114.67, 114.40, 99.12 (d, J=177.1 Hz), 98.02 (d, J=176.9 Hz), 70.18, 70.12, 69.84 (d, J=28.3 Hz), 69.36 (d, J=27.4 Hz), 64.49, 64.42, 44.37, 44.16, 26.86, 26.79, 19.64, 19.60, −4.79, −4.85; HR-FABMS (m/z) obsd 419.2793, calcd for $C_{21}H_{44}FO_3Si_2$ 419.2813 $(M+H)^+$. Anal. calcd for $C_{21}H_{43}FO_3Si_2$: C, 60.24; H, 10.35. Found: C, 60.38; H, 10.37.

*3.17. (1*S,*4*S*)-4*-tert-*Butyldimethylsilyloxymethyl-4-fluorocyclopent-3-en-1-ol* **18**

Grubbs catalyst (20 mg, 0.024 mmol) dissolved in dry methylene chloride (35 ml) in a dry two-necked flask equipped with an N_2 inlet. To this solution a solution of 100 mg (0.24 mmol) of the 1,6-diene **17** in dry methylene chloride (15 ml) was slowly added over 10 minutes under an N_2 atmosphere. The wine-red solution was stirred for 30 more minutes, and the resulting dark brown solution was evaporated and purified by column chromatography on silica gel (6:1:0.01 hexane/diethyl ether/triethyl amine) to give 53 mg (0.215 mmol, 90% yield) of the cyclopentenol **18** as a 1:1 mixture of diastereomers, which was immediately used in the next step. Due to the instability of this compound, the structure of this compound was characterized only by NMR spectra: ^{1}H NMR (CD_3OD) δ 6.04 (dt, J=5.7, 2.2 Hz, 1H), 5.99 (dt, J=5.7, 1.9 Hz, 1H), 5.86 (dt, J=5.7, 1.5 Hz, 1H), 5.82 (dt, J=5.5, 1.6 Hz, 1H), 4.83 (br s, 1H), 4.53 (br m, 1H), 3.74 (dd, J=18.0, 11.4 Hz, 1H), 3.71 (dd, J=19.8, 11.4 Hz, 1H), 3.63 (dd, J=14.4, 10.9 Hz, 1H), 3.55 (dd, J=17.8, 10.9 Hz, 1H), 2.52 (dt, J=14.0, 7.4 Hz, 1H), 2.26 (ddd, J=21.7, 14.7, 6.8 Hz, 1H), 1.75 (ddd, J=20.6, 14.7, 3.7 Hz, 1H), 1.69 (ddd, J=25.7, 14.0, 4.6 Hz, 1H), 0.83 (s, 9H), 0.81 (s, 9H), 0.00 (s, 6H), 0.00 (s, 6H), −0.019 (s, 3H), −0.027 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.81 (d, J=8.8 Hz), 141.39 (d, J=9.2 Hz), 134.29 (d, J=23.4 Hz), 133.98 (d, J=18.3 Hz),

108.25 (d, $J=174.4$ Hz), 106.17 (d, $J=180.0$ Hz), 76.22, 75.32, 69.14 (d, $J=30.8$ Hz), 68.57 (d, $J=34.6$ Hz), 44.35 (d, $J=18.7$ Hz), 43.72 (d, $J=25.2$ Hz), 26.73, 26.67, 19.64, 19.54, −4.87, −4.90, −4.93, −4.99.

*3.18. For the 1:1 mixture of diastereomers (−)-(1*S,*3*S*)-3-*tert*-butyldimethylsilyloxymethyl-3-fluorocyclopentan-1-ol **19** and (+)-(1*R,*3*S*)-3-*tert*-butyldimethylsilyloxymethyl-3-fluoro-cyclopentan-1-ol **20***

A solution of **18** (1.35 g, 5.48 mmol) in cyclohexane (50 ml) was treated with Pd/C (135 mg, 10% w/w). The mixture was thoroughly deoxygenated, and then saturated with hydrogen. After stirring for 2 h at rt the reaction mixture was filtered through a Celite pad and evaporated to give a 1:1 mixture of diastereomeric cyclopentanols which was separated by column chromatography on silica gel (10:1 hexanes/ethyl acetate). 621 mg (2.50 mmol, 46% yield) of β-alcohol **19** and 570 mg (2.30 mmol, 42% yield) of α-alcohol **20** were obtained as colorless oil: For **19**, $[\alpha]_D^{25}$ −0.95 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.44 (br d, 1H, H-1), 3.69 (d, $J=12.7$ Hz, 2H, H-6), 2.55–1.66 (m, 6H, H-2, H-4, H-5), 0.91 (s, 9H, Si-C(CH_3)$_3$), 0.09 (s, 6H, Si-CH_3); ^{13}C NMR ($CDCl_3$) δ 104.9 (d, $J=80.5$ Hz), 73.18, 67.20 (d, $J=34.8$ Hz), 45.53 (d, $J=22.5$ Hz), 34.75, 32.61 (d, $J=23.9$ Hz), 26.15, 18.72, −5.09; FABMS (*m*/*z*) obsd 249. Anal. calcd for $C_{12}H_{25}FO_2Si$: C, 58.02; H, 10.14. Found: C, 58.20; H, 9.98. For **20**, $[\alpha]_D^{24}$ −2.3 (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.33 (br s, 1H, H-1), 3.68 (dd, $J=15.4$, 10.2 Hz, 1H, H-6), 3.66 (dd, $J=16.2$, 10.2 Hz, 1H, H-6), 2.14–1.79 (m, 6H, H-2, H-4, H-5), 0.89 (s, 9H, Si-C(CH_3)$_3$), 0.06 (s, 6H, Si-CH_3); ^{13}C NMR ($CDCl_3$) δ 106.12 (d, $J=175.1$ Hz), 73.23, 66.18 (d, $J=32.3$ Hz), 43.66 (d, $J=21.6$ Hz), 34.48, 32.65 (d, $J=23.6$ Hz), 25.77, 18.22, −5.50; FABMS (*m*/*z*) obsd 249. Anal. calcd for $C_{12}H_{25}FO_2Si$: C, 58.02; H, 10.14. Found: C, 58.28; H, 10.12.

*3.19. (−)-(1R,3S)-1-Benzoyloxy-3-*tert*-butyldimethylsilyloxymethyl-3-fluorocyclopentane **21***

To a stirred solution of β isomer **19** (37 mg, 0.149 mmol), triphenyl phosphine (195 mg, 0.743 mmol), and benzoic acid (91 mg, 0.745 mmol) in dry THF (10 ml), a solution of DEAD (0.117 ml, 0.743 mmol) in THF (5 ml) was slowly added. The resulting yellow solution was stirred at rt for 6 h. Solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel (40:1 hexanes/diethyl ether) to give 48 mg (0.136 mmol, 91% yield) of the benzoyloxycyclopentanol **21** as a colorless oil: $[\alpha]_D^{25}$ −15.7 (*c* 1.49, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 7.98–7.96 (m, 2H), 7.49–7.45 (m, 1H), 7.37–7.33 (m, 2H), 5.33 (m, 1H), 3.62 (dd, $J=14.4$, 1.60 Hz, 2H), 2.32–1.79 (m, 6H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.37, 132.87, 130.48, 129.64, 128.31, 104.41 (d, $J=179.0$ Hz), 75.74, 66.28 (d, $J=32.9$ Hz), 40.94 (d, $J=23.5$ Hz), 33.03 (d, $J=23.7$ Hz), 31.44, 25.82, 18.27, −5.45; FABMS (*m*/*z*) obsd 353, for $C_{19}H_{30}FO_3Si$. Anal. calcd for $C_{19}H_{29}FO_3Si$: C, 64.74; H, 8.29. Found: C, 64.85; H, 8.23.

*3.20. 9-[(1*S,*4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]-N^2-acetylamino-6-chloropurine **21** and (+)-9-[(1*S,*4*S*)-4-fluoro-4-hydroxymethylcyclopentan-1-yl]-N^2-acetylamino-6-chloropurine **22***

To a suspension of triphenylphosphine (108 mg, 0.41 mmol), N^2-acetylamino-6-chloropurine (106 mg, 0.50 mmol), and **20** (85 mg, 0.342 mmol) in anhydrous dioxane (6 ml) and DMF (3 ml), was added DEAD (0.08 ml, 0.51 mmol) over 30 minutes at 0°C. The yellow mixture was

stirred for 6 h at room temperature. Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (2:1 hexane/ethyl acetate) to give 97 mg of an inseparable mixture of the desired compound **21** and reduced DEAD. This mixture was used directly in the next step. The mixture obtained above was dissolved in anhydrous THF (10 ml) and treated with 1.0 M TBAF in THF (0.22 ml, 0.22 mmol). The solution was stirred for 30 minutes at room temperature and evaporated to give a colorless residue which was purified by column chromatography on silica gel (30:1 CH_2Cl_2/MeOH) to give 70 mg (0.214 mmol, 63% yield from 20) of **22** as a white solid: mp 208–210°C; $[\alpha]_D^{25}$ −127.8 (*c* 0.54, MeOH); UV (MeOH) λ_{max} 288.0 nm; ^{1}H NMR (CD_3OD) δ 8.71 (s, 1H), 5.50 (quintet, $J=8.3$ Hz, 1H), 4.03 (dd, $J=18.4$, 12.2 Hz, 1H), 4.00 (dd, $J=19.8$, 12.2 Hz, 1H), 2.81–2.19 (m, 6H), 2.53 (s, 3H); ^{13}C NMR (CD_3OD) δ 154.11, 153.63, 151.82, 146.79, 129.68, 106.54 (d, $J=176.1$ Hz), 67.01 (d, $J=27.4$ Hz), 57.23, 41.62 (d, $J=23.8$ Hz), 34.25 (d, $J=23.4$ Hz), 31.69, 25.09; HR-FABMS (*m*/*z*) obsd 328.0995, calcd for $C_{13}H_{16}ClFN_5O_2$ 328.0992 $(M+H)^+$. Anal. calcd for $C_{13}H_{15}ClFN_5O_2$: C, 47.64; H, 4.61; N, 21.37. Found: C, 47.76; H, 4.68; N, 21.19.

*3.21. (+)-9-[(1*S*,4*S*)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]guanine **23***

Compound **22** (64 mg, 0.196 mmol) was dissolved in 85% formic acid (15 ml) and the resulting colorless solution was stirred at 80°C for 6 h. After evaporation, the remaining oil was treated with methanolic ammonia (15 ml), and the solution was stirred overnight. Solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (6:1 CH_2Cl_2/MeOH) to give 40 mg (0.15 mmol, 76% yield) of **23** as a white solid: mp 220°C, dec.; $[\alpha]_D^{24}$ +6.4 (*c* 0.54, MeOH); UV (H_2O) λ_{max} 253.5 nm (ε 8 080, pH 2), 252.5 nm (ε 8 263, pH 7), 266.5 nm (ε 7 123, pH 11); ^{1}H NMR (CD_3OD) δ 8.09 (s, 1H, H-8), 5.26 (quintet, $J=8.4$ Hz, 1H, H-1′), 4.02–3.97 (m, 2H, H-5′), 2.71–2.20 (m, 6H, H-2′, H-3′, H-6′); ^{13}C NMR (CD_3OD) δ 198.77, 159.87, 155.36, 138.59, 118.43, 106.34 (d, $J=175.9$ Hz), 67.06 (d, $J=27.5$ Hz), 56.03, 41.95 (d, $J=23.7$ Hz), 34.13 (d, $J=23.8$ Hz), 31.77; HR-FABMS (*m*/*z*) obsd 268.1204, calcd for $C_{11}H_{15}FN_5O_2$ 268.1209 $(M+H)^+$. Anal. calcd for $C_{11}H_{14}FN_5O_2 \cdot 0.9CHCl_3$: C, 38.15; H, 4.01; N, 18.69. Found: C, 38.18; H, 4.56; N, 18.78.

*3.22. (+)-9-[(1*S*,4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]-6-chloropurine **24***

To a suspension of triphenylphosphine (602 mg, 2.30 mmol) and 6-chloropurine (372 mg, 2.41 mmol) in anhydrous THF (5 ml), a solution of DEAD (0.36 ml, 2.29 mmol) in THF was added over 30 min at rt. After 1 h, **20** (285 mg, 1.15 mmol) in THF (10 ml) was added to the yellow mixture, and then the resulting mixture was stirred for 6 h at room temperature. Solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel (10:1 hexanes/diethyl ether) to give 355 mg (0.922 mmol, 80% yield) of the desired compound **24** as a white solid: mp 80–82°C; $[\alpha]_D^{26}$ +13.4 (*c* 3.80 $CHCl_3$); UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1H), 8.17 (s, 1H), 5.22 (quintet, $J=7.9$ Hz, 1H), 3.82 (dd, $J=12.3$, 10.5 Hz, 1H), 3.78 (dd, $J=14.2$, 10.5 Hz, 1H), 2.65–1.97 (m, 6H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 151.65, 151.62, 151.14, 143.95, 132.26, 104.34 (d, $J=176.7$ Hz), 65.56 (d, $J=32.6$ Hz), 55.70, 40.42 (d, $J=23.7$ Hz), 32.89 (d, $J=23.3$ Hz), 30.86, 25.80, 18.28, −5.44; HR-FABMS (*m*/*z*) obsd 385.1642, calcd for $C_{17}H_{27}ClFN_4OSi$ 385.1626 $(M+H)^+$. Anal. calcd for $C_{17}H_{26}ClFN_4OSi$: C, 53.04; H, 6.81; N, 14.55. Found: C, 53.56; H, 6.90; N, 14.44.

3.23. (+)-9-[(1S,4S)-4-tert-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]adenine **25**

Compound **24** (140 mg, 0.36 mmol) was treated with methanolic ammonia and heated to 110°C in a steel bomb for 6 h. Solvent was removed under reduced pressure and the remaining residue was purified by column chromatography on silica gel (50:1 CH_2Cl_2/MeOH) to give 110 mg (0.30 mmol, 83% yield) of the aminated compound **25** as a white solid: mp 150–152°C; $[\alpha]_D^{26}$ +18.05 (*c* 0.62, $CHCl_3$); UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H), 7.77 (s, 1H), 5.65 (br s, 2H), 5.07 (quintet, J=7.9 Hz, 1H), 3.73 (dd, J=13.1, 10.6 Hz, 1H), 3.69 (dd, J=14.7, 10.6 Hz, 1H), 2.52–1.87 (m, 6H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.36, 151.62, 149.03, 138.06, 119.20, 103.42 (d, J=176.3 Hz), 64.79 (d, J=32.4 Hz), 53.85, 39.57 (d, J=23.7 Hz), 31.92 (d, J=23.4 Hz), 30.06, 24.80, 17.28, −6.46; HR-FABMS (*m*/*z*) obsd 366.2114, calcd for $C_{17}H_{29}FN_5OSi$ 366.2125 $(M+H)^+$. Anal. calcd for $C_{17}H_{28}FN_5OSi$: C, 55.86; H, 7.72; N, 19.16. Found: C, 55.79; H, 7.69; N, 19.16.

3.24. General procedure for the desilylation reaction of tert-butyldimethylsilyl ether by using TBAF. This is representative of the preparation of adenine analogue **26** from **25**

3.24.1. (+)-9-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]adenine **26**

To a stirred solution of 100 mg (0.274 mmol) of **25** in anhydrous THF (5 ml), was added a 1.0 M solution of TBAF in THF (0.27 ml, 0.27 mmol). After 1 h, solvent was removed under reduced pressure and the remaining residue was purified by column chromatography on silica gel (10:1 CH_2Cl_2/MeOH) to give 65 mg (0.259 mmol, 95% yield) of **26** as a white solid: mp 170–172°C; $[\alpha]_D^{27}$ +10.5 (*c* 0.67, MeOH); UV (H_2O) λ_{max} 260.0 nm (ε 20 858, pH 2), 261.0 nm (ε 14 624, pH 7), 261.0 nm (ε 12 639, pH 11); ^{1}H NMR (CD_3OD) δ 8.39 (s, 1H, H-8), 8.35 (s, 1H, H-2), 5.34 (ddd, J=17.6, 10.0, 8.0 Hz, 1H, H-1′), 3.93 (dd, J=17.3, 12.4 Hz, 1H, H-5′), 3.90 (dd, J=19.6, 17.3 Hz, 1H, H-5′), 2.70–2.18 (m, 6H, H-2′, H-3′, H-6′); ^{13}C NMR ($CDCl_3$) δ 158.78, 154.96, 152.17, 142.76, 122.03, 107.36 (d, J=176.1 Hz), 68.16 (d, J=27.5 Hz), 57.61, 43.10 (d, J=23.7 Hz), 35.23 (d, J=23.9 Hz), 32.96; HR-FABMS (*m*/*z*) obsd 252.1244, calcd for $C_{11}H_{15}FN_5O$ 252.1260 $(M+H)^+$. Anal. calcd for $C_{11}H_{14}FN_5O{\cdot}0.2MeOH$: C, 52.21; H, 5.79; N, 27.18. Found: C, 52.06; H, 5.61; N, 27.03.

3.24.2. (+)-9-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]-6-chloropurine **27**

See the general procedure for deprotection of TBDMS group using TBAF. Mp 142–144°C; $[\alpha]_D^{24}$ +5.5 (*c* 0.80, MeOH); UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR (CD_3OD) δ 8.99 (s, 1H), 8.91 (s, 1H), 5.57 (ddd, J=17.6, 9.7, 7.9 Hz, 1H), 4.04 (dd, J=17.4, 12.1 Hz, 1H), 4.01 (dd, J=18.7, 12.1 Hz, 1H), 2.86–2.27 (m, 6H); ^{13}C NMR (CD_3OD) δ 194.17, 193.68, 192.26, 188.30, 173.87, 146.94 (d, J=176.5 Hz), 107.58 (d, J=27.4 Hz), 98.06, 82.39 (d, J=23.9 Hz), 74.78 (d, J=23.7 Hz), 72.22; HR-FABMS (*m*/*z*) obsd 271.0759, calcd for $C_{11}H_{13}ClFN_4O$ 271.0761 $(M+H)^+$. Anal. calcd for $C_{11}H_{12}ClFN_4O{\cdot}0.6CH_3COCH_3$: C, 50.32; H, 5.15; N, 18.34. Found: C, 50.23; H, 4.92; N, 18.31.

3.25. (+)-9-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]hypoxanthine **28**

Compound **27** (48 mg, 0.177 mmol) was dissolved in 85% formic acid (10 ml) and the resulting colorless solution was stirred for 2.5 h at 70°C. After evaporating the formic acid under reduced pressure, the remaining residue was treated with methanolic ammonia. The resulting solution

was stirred overnight at room temperature. After solvent evaporation, the remaining residue was purified by column chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to give 40 mg (0.159 mmol, 90% yield) of **28** as a white solid: mp 220°C, dec.; $[\alpha]_D^{23}$ +22.0 (*c* 0.60, MeOH); UV (H_2O) λ_{max} 250.0 nm (ε 16 612, pH 2), 251.0 nm (ε 16 913, pH 7), 252.0 nm (ε 17 930, pH 11); ^{1}H NMR (CD_3OD) δ 8.33 (s, 1H, H-8), 8.19 (s, 1H, H-2), 5.35 (ddd, J=17.7, 9.9, 7.9 Hz, 1H, H-1′), 3.92 (dd, J=17.3, 12.2 Hz, 1H, H-5′), 3.89 (dd, J=18.5, 12.2 Hz, 1H, H-5′), 2.74–2.16 (m, 6H, H-2′, H-3′, H-6′); ^{13}C NMR (CD_3OD) δ 159.43, 150.55, 146.64, 141.14, 126.16, 106.30 (d, J=176.1 Hz), 67.00 (d, J=27.5 Hz), 56.81, 42.22 (d, J=23.8 Hz), 34.12 (d, J=23.6 Hz), 32.03; HR-FABMS (*m*/*z*) obsd 253.1102, calcd for $C_{11}H_{14}FN_4O_2$ 253.1100 $(M+H)^+$. Anal. calcd for $C_{11}H_{13}FN_4O_2 \cdot 0.2MeOH$: C, 52.01; H, 5.38; N, 21.66. Found: C, 51.80; H, 5.18; N, 21.40.

*3.26. (+)-9-[(1*S*,4*S*)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]-6-mercaptopurine* ***29***

A solution containing **27** (50 mg, 0.185 mmol) and thiourea (21 mg, 0.276 mmol) in ethanol (4 ml) was refluxed for 1.5 h. After evaporation under reduced pressure, the remaining off-white solid was purified by fractional recrystallization in ethyl alcohol to give **29** (40 mg, 0.149 mmol, 81% yield) as a white solid: mp 268–270°C; $[\alpha]_D^{24}$ +16.5 (*c* 0.17, MeOH); UV (H_2O) λ_{max} 322.5 nm (ε 24 531, pH 2), 320.5 nm (ε 24 374, pH 7), 310.5 nm (ε 22 724, pH 11); ^{1}H NMR (DMSO) δ 14.00 (br s, 1H, N-*H*), 8.65 (s, 1H, H-8), 8.44 (s, 1H, H-2), 5.43 (t, J=5.8 Hz, 1H, 5′-O*H*), 5.31 (dt, J=17.7, 8.0 Hz, 1H, H-1′), 3.87–3.80 (m, 2H, H-5′), 2.66–2.07 (m, 6H, H-2′, H-3′, H-6′); ^{13}C NMR (DMSO) δ 176.20, 145.04, 144.33, 142.00, 135.79, 105.58 (d, J=175.7 Hz), 64.93 (d, J=27.2 Hz), 54.44, 40.84 (d, J=23.1 Hz), 32.70 (d, J=23.5 Hz), 30.42; HR-FABMS (*m*/*z*) obsd 269.0885, calcd for $C_{11}H_{14}FN_4OS$ 269.0892 $(M+H)^+$. Anal. calcd for $C_{11}H_{13}FN_4O_2 \cdot 0.3MeOH$: C, 48.83; H, 5.15; N, 20.16. Found: C, 48.74; H, 5.02; N, 20.38.

*3.27. (+)-1-[(1*S*,4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]-*N_3*-benzoyluracil* ***30***

To a solution of triphenylphosphine (647 mg, 2.47 mmol), N_3-benzoyluracil (533 mg, 2.47 mmol), and **20** (245 mg, 0.986 mmol) in anhydrous dioxane (6 ml) and DMF (3 ml), was added DEAD (0.4 ml, 2.54 mmol) over 30 min at 0°C. The resulting homogeneous yellow solution was stirred for 3 h at room temperature. Solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel (1:1 hexanes/ethyl acetate) to give 240 mg (0.537 mmol, 54% yield) of the desired N_1-alkylated product **30** as a colorless oil, and 64 mg (0.143 mmol, 15% yield) of an inseparable mixture of the O^2-alkylated product **33** and reduced DEAD as a pale yellow oil, respectively: For **30**, $[\alpha]_D^{25}$ +1.65 (*c* 1.30, $CHCl_3$); UV (MeOH) λ_{max} 253.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J=7.4 Hz, 2H), 7.57 (t, J=7.4 Hz, 1H), 7.42 (d, J=7.8 Hz, 2H), 7.26 (d, J=8.1 Hz, 1H), 5.74 (d, J=8.1 Hz, 1H), 4.98 (quintet, J=8.2 Hz, 1H), 3.67 (dd, J=11.8, 10.5 Hz, 1H), 3.63 (dd, J=13.8, 10.5 Hz, 1H), 2.35–2.24 (m, 2H), 2.16–2.00 (m, 2H), 1.92–1.76 (m, 2H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.81, 161.97, 149.69, 141.33, 131.40, 130.46, 129.16, 104.13 (d, J=176.7 Hz), 102.48, 65.67 (d, J=33.0 Hz), 57.25, 39.16 (d, J=23.7 Hz), 32.94 (d, J=23.2 Hz), 29.81, 25.80, 18.26; HR-FABMS (*m*/*z*) obsd 447.2104, calcd for $C_{23}H_{32}FN_2O_4Si$ 447.2115 $(M+H)^+$. Anal. calcd for $C_{23}H_{31}FN_2O_4Si$: C, 61.86; H, 7.00; N, 6.27. Found: C, 61.78; H, 7.00; N, 6.05.

3.28. (−)-1-[(1S,4S)-4-tert-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]-N_3-benzoylthymine **31**

To a solution of triphenylphosphine (186 mg, 0.709 mmol), N_3-benzoylthymine (171 mg, 0.743 mmol), and **20** (88 mg, 0.354 mmol) in anhydrous dioxane (2 ml) and DMF (1 ml), was added DEAD (0.11 ml, 0.699 mmol) over 30 min at 0°C. The resulting homogeneous yellow solution was stirred for 3 h at room temperature. Solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel (1:1 hexanes/ethyl acetate) to give 73 mg (0.16 mmol, 45% yield) of the desired N_1-alkylated product **31** as a colorless oil, and 37 mg (0.081 mmol, 23% yield) of an inseparable mixture of the O^2-alkylated product **34** and reduced DEAD as a pale yellow oil, respectively: $[\alpha]_D^{24}$ −8.1 (*c* 2.20, $CHCl_3$); UV (MeOH) λ_{max} 254.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J=8.1 Hz, 2H), 7.56 (t, J=7.5 Hz, 1H), 7.41 (t, J=7.9 Hz, 2H), 7.01 (br d, J=1.2 Hz, 1H), 4.98 (quintet, J=8.6 Hz, 1H), 3.66 (dd, J=12.5, 10.6 Hz, 1H), 3.62 (dd, J=14.6, 10.6 Hz, 1H), 2.30–1.97 (m, 4H), 1.92–1.75 (m, 2H), 1.87 (br d, J=1.2 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.53, 163.10, 150.15, 137.58, 135.41, 132.01, 130.86, 129.55, 111.58, 104.56 (d, J=176.9 Hz), 66.21 (d, J=32.3 Hz), 57.21, 39.47 (d, J=23.4 Hz), 33.43 (d, J=23.0 Hz), 29.90, 26.23, 18.66, 13.06, −5.02;. Anal. calcd for $C_{24}H_{33}FN_2O_4Si$: C, 62.58; H, 7.22; N, 6.08. Found: C, 62.75; H, 7.22; N, 5.89.

3.29. (−)-1-[(1S,4S)-4-tert-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]-N_3-benzoyl-5-fluorouracil **32**

To a solution of triphenylphosphine (154 mg, 0.587 mmol), N_3-benzoyl-5-fluorouracil (167 mg, 0.713 mmol), and **20** (71 mg, 0.286 mmol) in anhydrous dioxane (2 ml) and DMF (1 ml), was added DEAD (0.113 ml, 0.718 mmol) over 30 min at 0°C. The resulting homogeneous yellow solution was stirred for 3 h at room temperature. Solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel (4:1 hexanes/ethyl acetate) to give 75 mg (0.161 mmol, 56% yield) of the desired N_1-alkylated product **32** as a colorless oil: $[\alpha]_D^{24}$ −0.64 (*c* 4.80, $CHCl_3$); UV (MeOH) λ_{max} 265.0 nm; ^{1}H NMR (CD_3OD) δ 7.92 (d, J=7.4 Hz, 2H), 7.68 (t, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 2H), 7.46 (d, J=6.0 Hz, 1H), 5.10 (quintet, J=8.2 Hz, 1H), 3.76 (dd, J=11.3, 10.5 Hz, 1H), 3.72 (dd, J=13.3, 10.5 Hz, 1H), 2.41–1.85 (m, 6H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (CD_3OD) δ 167.75, 156.26 (d, J=27.2 Hz), 148.69, 140.53 (d, J=240.0 Hz), 135.87, 131.41, 130.97, 129.69, 104.25 (d, J=177.1 Hz), 66.15 (d, J=33.6 Hz), 57.50, 39.55 (d, J=23.9 Hz), 33.36 (d, J=23.3 Hz), 30.26, 26.23, 18.72, −5.05; HR-FABMS (*m*/*z*) obsd 465.2029, calcd for $C_{23}H_{31}F_2N_2O_4Si$ 465.2021 $(M+H)^+$. Anal. calcd for $C_{23}H_{30}F_2N_2O_4Si{\cdot}0.2C_6H_{14}$: C, 60.33; H, 6.86; N, 5.81. Found: C, 60.66; H, 6.89; N, 5.77.

3.30. General procedure for N_3-debenzoylation. This is representative of the synthesis of uridine analogue **36** from compound **30**

3.30.1. (+)-1-[(1S,4S)-4-tert-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]uracil **36**

The N_3-benzoylated uridine analogue **30** (240 mg, 0.537 mmol) was treated with methanolic ammonia (10 ml) for 3 h at 0°C. After evaporation, the residue was purified by column chromatography on silica gel (1:1 hexanes/ethyl acetate) to give 181 mg (0.528 mmol, 98% yield) of **36** as a white solid: $[\alpha]_D^{28}$ +2.5 (*c* 1.10, $CHCl_3$); UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$)

δ 9.55 (br s, 1H), 7.16 (d, $J=8.0$ Hz, 1H), 5.65 (d, $J=8.0$ Hz, 1H), 5.02 (quintet, $J=8.3$ Hz, 1H), 3.67 (dd, $J=10.5$, 8.8 Hz, 1H), 3.63 (dd, $J=13.8$, 10.5 Hz, 1H), 2.31–1.69 (m, 6H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.88, 151.31, 141.84, 104.49 (d, $J=176.5$ Hz), 103.02, 66.15 (d, $J=33.31$ Hz), 56.87, 39.59 (d, $J=23.5$ Hz), 33.36 (d, $J=23.3$ Hz), 30.24, 26.22, 18.68, −5.04; HR-FABMS (m/z) obsd 343.1840, calcd for $C_{16}H_{28}FN_2O_3Si$ 343.1853 $(M+H)^+$. Anal. calcd for $C_{16}H_{27}FN_2O_3Si\cdot 0.11C_6H_{14}$: C, 56.85; H, 8.17; N, 7.96. Found: C, 56.98; H, 8.03; N, 7.76.

*3.30.2. (−)-1-[(1*S*,4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]thymine* ***37***

See the general procedure for deprotection of benzoyl group using methanolic ammonia. $[\alpha]_D^{24}$ −4.75 (*c* 0.50, $CHCl_3$); UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H), 6.90 (s, 1H), 5.00 (tt, $J=8.3$, 8.2 Hz, 1H), 3.66 (dd, $J=11.9$, 10.6 Hz, 1H), 3.62 (dd, $J=14.0$, 10.6 Hz, 1H), 2.28–1.68 (m, 6H), 1.83 (s, 3H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.78, 150.99, 137.52, 111.53, 104.41 (d, $J=176.5$ Hz), 66.17 (d, $J=32.9$ Hz), 56.41, 39.50 (d, $J=23.4$ Hz), 33.43 (d, $J=23.3$ Hz), 30.04 (d, $J=13.8$ Hz), 26.22, 18.65, 12.99, −5.03; HR-FABMS (m/z) obsd 357.2008, calcd for $C_{17}H_{30}FN_2O_3Si$ 357.2009 $(M+H)^+$. Anal. calcd for $C_{17}H_{29}FN_2O_3Si\cdot 0.2C_6H_{14}$: C,58.49; H, 8.58; N, 7.50. Found: C, 58.23; H, 8.41; N, 7.15.

*3.30.3. (+)-1-[(1*S*,4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]-5-fluorouracil* ***38***

See the general procedure for deprotection of benzoyl group using methanolic ammonia. $[\alpha]_D^{24}$ +1.9 (*c* 4.00, $CHCl_3$); UV (MeOH) λ_{max} 273.5 nm; ^{1}H NMR ($CDCl_3$) δ 9.76 (br s, 1H), 7.24 (d, $J=5.9$ Hz, 1H), 5.06 (quintet, $J=8.3$ Hz, 1H), 3.66 (dd, $J=10.5$, 10.5 Hz, 1H), 3.62 (dd, $J=12.6$, 10.5 Hz, 1H), 2.32–2.22 (m, 2H), 2.15–1.79 (m, 3H), 1.73–1.64 (m, 1H), 0.81 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (CD_3OD) δ 156.80 (d, $J=26.4$ Hz), 149.57, 140.63 (d, $J=238.4$ Hz), 125.38 (d, $J=32.6$ Hz), 103.72 (d, $J=177.0$ Hz), 65.71 (d, $J=33.9$ Hz), 56.31, 39.13 (d, $J=23.7$ Hz), 32.95 (d, $J=23.4$ Hz), 29.90, 25.78, 18.27, −5.51. Anal. calcd for $C_{16}H_{26}F_2N_2O_3Si\cdot 0.1C_6H_{14}$: C, 54.02; H, 7.48; N, 7.59. Found: C, 54.09; H, 7.22; N, 7.63.

*3.30.4. (+)-O^2-[(1*S*,4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]uracil* ***39***

See the general procedure for deprotection of benzoyl group using methanolic ammonia. $[\alpha]_D^{23}$ +27.4 (*c* 4.46, $CHCl_3$); UV (MeOH) λ_{max} 267.5 nm; ^{1}H NMR ($CDCl_3$) δ 7.69 (d, $J=6.6$ Hz, 1H), 6.03 (d, $J=6.6$ Hz, 1H), 5.51–5.48 (m, 1H), 3.67 (d, $J=17.9$ Hz, 2H), 2.40–1.83 (m, 6H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.12, 157.38, 155.69, 109.15, 105.38 (d, $J=177.0$ Hz), 80.14, 66.97 (d, $J=29.3$ Hz), 41.80 (d, $J=24.0$ Hz), 32.77 (d, $J=23.5$ Hz), 31.12, 26.22, 18.70, −5.03; FABMS (m/z) obsd 343. Anal. calcd for $C_{16}H_{27}FN_2O_3Si$: C, 56.11; H, 7.95; N, 8.18. Found: C, 56.26; H, 7.99; N, 7.95.

*3.30.5. (+)-O^2-[(1*S*,4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]thymine* ***40***

See the general procedure for deprotection of benzoyl group using methanolic ammonia. $[\alpha]_D^{23}$ +23.4 (*c* 1.07, $CHCl_3$); UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.53 (br s, 1H), 5.46 (br s, 1H), 3.67 (d, $J=17.1$ Hz, 2H), 2.43–1.81 (m, 6H), 1.93 (s, 3H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 175.15, 155.32, 151.68, 118.52, 105.41 (d, $J=176.8$ Hz), 79.84, 66.92 (d, $J=29.7$ Hz), 41.90 (d, $J=23.8$ Hz), 32.88 (d, $J=23.7$ Hz), 31.30, 26.21, 18.68, 12.82, −5.00; FABMS (m/z) obsd 357. Anal. calcd for $C_{17}H_{29}FN_2O_3Si\cdot 0.2C_6H_{14}$: C, 58.49; H, 8.58; N, 7.50. Found: C, 58.75; H, 8.45; N, 7.16.

3.31. (−)-1-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]uracil **41**

See the general procedure for deprotection of TBDMS group using TBAF. Mp 75°C; $[\alpha]_D^{25}$ −2.9 (*c* 1.31, MeOH); UV (H_2O) λ_{max} 271.5 nm (ε 1 602, pH 2), 271.0 nm (ε 1 308, pH 7), 270.0 nm (ε 1 238, pH 11); ^{1}H NMR ($CDCl_3$) δ 7.74 (d, *J*=8.0 Hz, 1H, H-6), 5.75 (d, *J*=8.0 Hz, 1H, H-5), 5.10 (ddd, *J*=16.0, 10.6, 8.2 Hz, 1H, H-1′), 3.78 (dd, *J*=15.1, 12.1 Hz, 1H, H-5′), 3.73 (dd, *J*=19.4, 12.1 Hz, 1H, H-5′), 2.39–1.96 (m, 6H, H-2′, H-3′, H-6′); ^{13}C NMR ($CDCl_3$) δ 166.71, 153.15, 144.82, 106.14 (d, *J*=175.9 Hz), 103.00, 67.03 (d, *J*=27.2 Hz), 58.21, 40.38 (d, *J*=23.4 Hz), 33.90 (d, *J*=23.7 Hz), 30.04; HR-FABMS (*m*/*z*) obsd 229.0989, calcd for $C_{10}H_{14}FN_2O_3$ 229.0988 $(M+H)^+$. Anal. calcd for $C_{10}H_{14}FN_2O_3 \cdot 0.2H_2O$: C, 51.81; H, 5.83; N, 12.08. Found: C, 51.74; H, 5.93; N, 11.70.

3.32. (+)-1-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]thymine **42**

See the general procedure for deprotection of TBDMS group using TBAF. Mp 156–158°C; $[\alpha]_D^{22}$ +4.6 (*c* 1.32, MeOH); UV (H_2O) λ_{max} 267.0 nm (ε 21 659, pH 2), 267.0 nm (ε 21 233, pH 7), 265.0 nm (ε 16 569, pH 11); ^{1}H NMR (CD_3OD) δ 7.68 (d, *J*=1.1 Hz, 1H, H-6), 5.22 (ddd, *J*=18.9, 10.8, 8.1 Hz, 1H, H-1′), 3.88 (dd, *J*=18.4, 12.1 Hz, 1H, H-5′), 3.86 (dd, *J*=19.4, 12.1 Hz, 1H, H-5′), 2.46–2.05 (m, 6H, H-2′, H-3′, H-6′), 2.05 (d, *J*=1.1 Hz, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 166.83, 153.31, 140.45, 112.00, 106.16 (d, *J*=175.9 Hz), 67.07 (d, *J*=27.4 Hz), 57.76, 40.32 (d, *J*=23.4 Hz), 33.89 (d, *J*=23.4 Hz), 29.98, 12.74; HR-FABMS (*m*/*z*) obsd 243.1154, calcd for $C_{11}H_{16}FN_2O_3$ 243.1144 $(M+H)^+$. Anal. calcd for $C_{11}H_{15}FN_2O_3$: C, 54.54; H, 6.24; N, 11.56. Found: C, 54.24; H, 6.20; N, 11.34.

3.33. (−)-1-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]-5-fluorouracil **43**

See the general procedure for deprotection of TBDMS group using TBAF. Mp 142–144°C; $[\alpha]_D^{25}$ −4.2 (*c* 1.21, MeOH); UV (H_2O) λ_{max} 273.0 nm (ε 8 758, pH 2), λ_{max} 273.5 nm (ε 8 217, pH 7), λ_{max} 271.5 nm (ε 6 839, pH 11); ^{1}H NMR (CD_3OD) δ 7.97, (d, *J*=6.9 Hz, 1H, H-6), 5.09 (dt, *J*=18.4, 8.0 Hz, 1H, H-1′), 3.75 (dd, *J*=21.0, 12.1 Hz, 1H, H-5′), 3.72 (dd, *J*=19.6, 12.1 Hz, 1H, H-5′), 2.36–1.87 (m, 6H, H-2′, H-3′, H-6′); ^{13}C NMR (CD_3OD) δ 159.83 (d, *J*=25.7 Hz), 151.84, 142.26 (d, *J*=232.4 Hz), 128.68 (d, *J*=33.7 Hz), 106.04 (d, *J*=176.0 Hz), 67.05 (d, *J*=27.3 Hz), 58.19, 40.20 (d, *J*=23.5 Hz), 33.79 (d, *J*=23.5 Hz), 29.91; HR-FABMS (*m*/*z*) obsd 247.0888, calcd for $C_{10}H_{13}F_2N_2O_3$ 247.0889 $(M+H)^+$. Anal. calcd for $C_{10}H_{12}F_2N_2O_3 \cdot 0.1CH_3CH_2OCH_2OCH_3$: C, 49.25; H, 5.17; N, 11.05. Found: C, 49.39; H, 5.23; N, 10.81.

3.34. (+)-O^2-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]uracil **46**

See the general procedure for deprotection of TBDMS group using TBAF. $[\alpha]_D^{22}$ +20.9 (*c* 0.91, MeOH); UV (MeOH) λ_{max} 267.5 nm; ^{1}H NMR (CD_3OD) δ 7.72 (d, *J*=6.7 Hz, 1H, H-6), 6.01 (d, *J*=6.7 Hz, 1H, H-5), 5.56 (m, 1H, H-1′), 3.66 (d, *J*=19.7 Hz, 2H, H-5′), 2.46–1.91 (m, 6H, H-2′, H-3′, H-6′); HR-FABMS (*m*/*z*) obsd 229.0988, calcd for $C_{10}H_{14}FN_2O_3$ 229.0983 $(M+H)^+$. Anal. calcd for $C_{10}H_{13}FN_2O_3$: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.91; H, 5.96; N, 12.00.

3.35. (+)-O^2-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]thymine **47**

See the general procedure for deprotection of TBDMS group using TBAF. $[\alpha]_D^{23}$ +31.7 (*c* 0.19, MeOH); UV (MeOH) λ_{max} 270.0 nm; ^{1}H NMR (CD_3OD) δ 7.57 (d, $J=1.0$ Hz, 1H, H-6), 5.51 (m, 1H, H-1′), 3.66 (d, $J=19.8$ Hz, 2H, H-5′), 2.44–1.92 (m, 6H, H-2′, H-3′, H-6′), 1.92 (d, $J=1.0$ Hz, 3H, CH_3); HR-FABMS (*m*/*z*) obsd 243.1145, calcd for $C_{11}H_{16}FN_2O_3$ 243.1158 $(M+H)^+$.

3.36. (+)-1-[(1S,4S)-4-tert-Butyldimethylsilyloxymethyl-4-fluorocyclopentan-1-yl]cytosine **44**

To a solution of **36** (73 mg, 0.213 mmol) and 1,2,4-triazole (97 mg, 1.40 mmol) in anhydrous pyridine (10 ml), 4-chlorophenyldichlorophosphate (0.111 ml, 0.682 mmol) was slowly added at 0°C. The resulting solution was stirred for 24 h at rt, and then evaporated to dryness in vacuo. The residue was dissolved in $CHCl_3$, and the solution was washed with water (2×5 ml) and saturated aq. $NaHCO_3$ solution. After drying over $MgSO_4$, the remaining residue was carefully dried and used for the next step without further purification. The crude product obtained above was treated with methanolic ammonia and heated to 100°C for 6 h in a steel bomb. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (2:1 hexanes/acetone) to give 45 mg (0.132 mmol, 62% yield) of the aminated product **44** as a pale yellow syrup: $[\alpha]_D^{25}$ +6.2 (*c* 1.59, $CHCl_3$); UV (MeOH) λ_{max} 276.0 nm; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, $J=7.3$ Hz, 1H), 5.74 (d, $J=7.3$ Hz, 1H), 5.04 (quintet, $J=8.3$ Hz, 1H), 3.68 (dd, $J=13.0$, 10.5 Hz, 1H), 3.64 (dd, $J=14.7$, 10.5 Hz, 1H), 2.30–1.70 (m, 6H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.11, 156.42, 143.23, 104.76 (d, $J=176.7$ Hz), 94.90, 66.44 (d, $J=32.5$ Hz), 57.88, 39.79 (d, $J=23.3$ Hz), 33.42 (d, $J=23.2$ Hz), 30.35, 26.25, 18.70, −5.02; HR-FABMS (*m*/*z*) obsd 342.2018, calcd for $C_{16}H_{29}FN_3O_2Si$ 342.2013 $(M+H)^+$. Anal. calcd for $C_{16}H_{28}FN_3O_2Si\cdot 0.4CH_3COCH_3$: C, 56.64; H, 8.40; N, 11.52. Found: C, 56.62; H, 8.33; N, 11.23.

3.37. (−)-1-[(1S,4S)-4-Fluoro-4-hydroxymethylcyclopentan-1-yl]cytosine **45**

See the general procedure for deprotection of TBDMS group using TBAF. $[\alpha]_D^{25}$ −2.1 (*c* 1.37, MeOH); UV (H_2O) λ_{max} 283.0 nm (ε 7 718, pH 2), λ_{max} 274.0 nm (ε 5 321, pH 7), λ_{max} 274.0 nm (ε 5 223, pH 11); ^{1}H NMR (CD_3OD) δ 7.77 (d, $J=7.4$ Hz, 1H, H-6), 5.99 (d, $J=7.4$ Hz, 1H, H-5), 5.17 (ddd, $J=18.5$, 10.5, 8.0 Hz, 1H, H-1′), 3.80 (dd, $J=18.5$, 12.1 Hz, 1H, H-5′), 3.77 (dd, $J=19.5$, 12.1 Hz, 1H, H-5′), 2.41–1.92 (m, 6H, H-2′, H-3′, H-6′); ^{13}C NMR (CD_3OD) δ 167.60, 159.24, 144.94, 106.26 (d, $J=175.9$ Hz), 96.55, 67.14 (d, $J=27.4$ Hz), 59.01, 40.72 (d, $J=23.4$ Hz), 34.04 (d, $J=23.8$ Hz), 30.46; HR-FABMS (*m*/*z*) obsd 228.1155, calcd for $C_{10}H_{15}FN_3O_2$ 228.1148 $(M+H)^+$. Anal. calcd for $C_{10}H_{14}FN_3O_2\cdot 0.39CH_2Cl_2$: C, 47.93; H, 5.72; N, 16.14. Found: C, 48.09; H, 6.04; N, 15.96.

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