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Original article

Synthesis and antiviral activity of *C*-fluoro-branched cyclopropyl nucleosides

Aihong Kim, Joon Hee Hong*

College of Pharmacy, Chosun University, Kwangju 501-759, Republic of Korea

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Abstract

A series of novel fluorocyclopropyl nucleosides were synthesized starting from acetol using the Simmons–Smith reaction as a key reaction. All the nucleosides synthesized were assayed against several viruses. Among the compounds synthesized, the uracil analogue **22** showed moderate anti-HCMV activity (10.61 μg/mL, in AD-169).

Keywords: Nucleoside; Antiviral agent; Simmons–Smith cyclopropanation

1. Introduction

A number of nucleosides comprising the cyclopropyl sugar moiety have been synthesized as conformationally constrained analogues of acyclonucleosides [1]. Regarding cyclopropyl derivatives [2], several structural modifications have been made with the purpose of improving or enhancing the antiviral activity of some of them. One of the most common modifications is the incorporation of a second hydroxymethyl group, either in the geminal position at *C*-3 or *C*-1 of the cyclopropane ring or in the vicinal position at *C*-2. For example, the guanine derivative (A-5021) **1** [3] showed more potent antiviral activity against HSV-1 than acyclovir (ACV) and penciclovir (PCV), and comparable activity against the VZV but no activity against HIV (Fig. 1).

Spaced cyclopropyl nucleosides avoiding high rigidity appear to be favorable either for the interaction with phosphorylating enzymes or for the interaction with viral DNA polymerase [4]. Among them, methylene-spacered cyclopropane analogues of purine nucleosides [5] such as synadenol **2** and synguanol **3** have shown potent antiviral activity, particularly against the human cytomegalovirus (HCMV) (Fig. 1).

The inclusion of other substituent such as halogens has been considered. The introduction of a fluorine atom to the carbohydrate moiety of nucleosides conferred interesting biological activity, as shown in the FLT [6], L-FMAU [7], and L-2′-F-d4N [8]. The electronegativity of fluorine (4 vs 3.5 for oxygen) can have pronounced effects on the electron distribution in the molecule, effecting the basicity or acidity of the neighboring groups, dipole moments within the molecule and the overall reactivity and stability of the neighboring functional groups [9].

Therefore, as a part of an ongoing study searching for novel antiviral agents, novel classes of nucleosides comprising cyclopropyl backbone and trisubstituted cyclopropyl nucleosides with an additional fluorine group at 1′-position were designed and synthesized to evaluate them against various viruses because fluorine group might act as a hydrogen bonding acceptor at the active site of their target enzyme. This paper reports the synthesis of these novel nucleoside analogues along with their biological activity against various viruses.

* Corresponding author. Tel.: +82 62 230 6378; fax: +82 62 222 5414.
E-mail address: hongjh@chosun.ac.kr (J.H. Hong).

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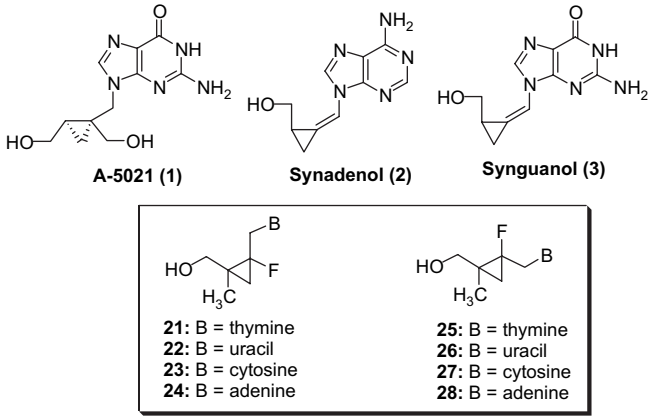
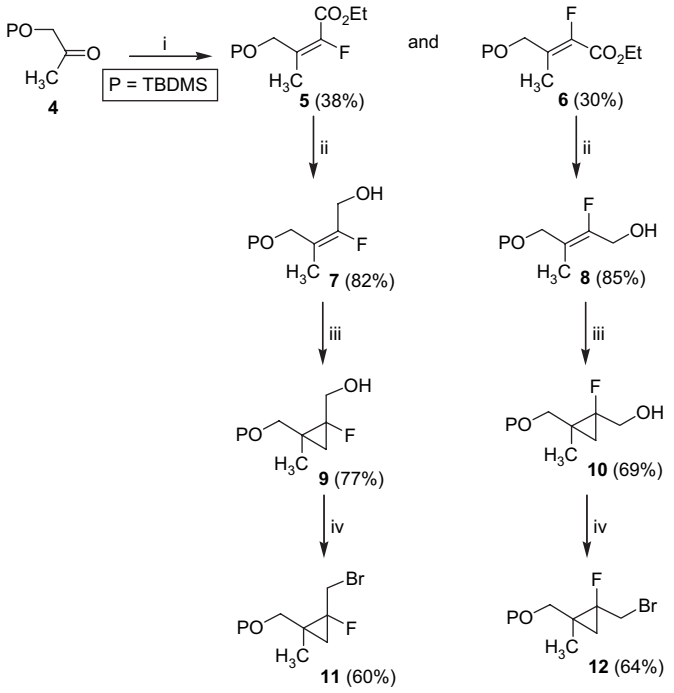


Fig. 1. Synthesis rationale of target compounds.

2. Results and discussion

2.1. Chemistry

Scheme 1 shows the synthesis of the cyclopropyl compound, which is the key intermediate for the preparation of fluorinated cyclopropyl nucleosides. The fluoroesters **5** and **6** were prepared using similar procedure described elsewhere [10]. The structural determination of the synthesized isomers **5** and **6** was postponed to a latter stage. The reason for the higher reaction product of compound **5** compared with compound **6** is unclear at this stage. Compounds **5** and **6** were subjected to reduction conditions using diisobutylaluminum hydride (DIBAL-H) to afford the fluoroallylic alcohols, which then underwent a Simmons–Smith reaction [11] with Et_2Zn/CH_2I_2 to give compounds **9** and **10**, respectively. A systemic NOE study on the cyclopropane derivatives was performed. On irradiation of the methyl protons, a relatively strong NOE was observed at the hydroxymethylene protons of compound **10** (0.8%). However, a weak NOE was observed at the hydroxymethylene protons those of compound **9** (0.3%) (Fig. 2). The structural determinations of compounds **5** and **6** were readily determined from the results of cyclopropane structures (compounds **9** and **10**). The sugar moiety was alkylated via a nucleophilic substitution reaction (S_N2) by converting the allylic alcohols **9** and **10** to the allylic bromides **11** and **12** in high yield by the sequential addition of NBS to a solution of the alcohols and triphenylphosphine in CH_2Cl_2 (Scheme 1) [12]. The condensation of the allylic bromide **6** with the bases (thymine, uracil, cytosine, and adenine) in DMF with cesium carbonate as a basic catalyst ($CsCO_3$) afforded the nucleoside derivatives **13**–**20**. The deprotection of the *tert*-butyldimethylsilyl group (TBDMS) using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) gave the desired fluorocyclopropyl nucleosides **21**–**28** (Scheme 2).



Scheme 1. Synthesis of fluorocyclopropyl bromides. Reagents: (i) $(EtO)_2$-$POCHFCO_2Et$, *n*-BuLi, THF; (ii) DIBAL-H, CH_2Cl_2; (iii) CH_2I_2, $Zn(Et)_2$, CH_2Cl_2; (iv) PPh_3, NBS, CH_2Cl_2, rt.

2.2. Antiviral activity studies

Compounds **21**–**28** were tested against several viruses such as the HIV (MT-4 cells), HSV-1 (herpes simplex virus type 1; CCL-81), HSV-2 (herpes simplex virus type 2; CCL-81) cells, and HCMV (human cytomegalovirus; AD-169) (Table 1). None of the tested compounds showed excellent antiviral activity except against HCMV. Among the compounds tested, the uracil derivative **22** showed the most potent ($EC_{50} = 10.61$ μg/mL) anti-HCMV activity up to 100 μg/mL without showing any significant toxicity to the host cells when compared with positive control, ganciclovir ($EC_{50} = 1.01$ μg/mL, in AD-169).

In conclusion, novel fluorinated cyclopropyl nucleosides **21**–**28** were successfully synthesized starting from acetol using the Simmons–Smith reaction as a key step. It is interesting to note that the *cis*-like uracil analogue **22** showed higher anti-HCMV activity compared with the *trans*-like derivative **23**, indicating that this virus might allow the sugar moiety to serve as a template for phosphorylation as well as for DNA polymerase, which is unlike other viruses. These compounds were evaluated for their activity against various viruses because the fluorine group might act as a hydrogen bonding acceptor at the active site of their target enzyme. The information obtained in this study will be useful for the development of novel cyclopropyl nucleosides. Studies toward this end as well as to clarify the mechanism are underway.

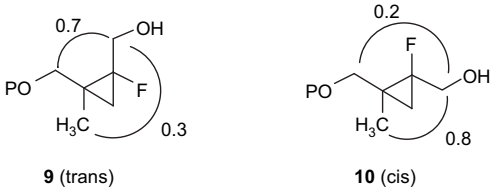
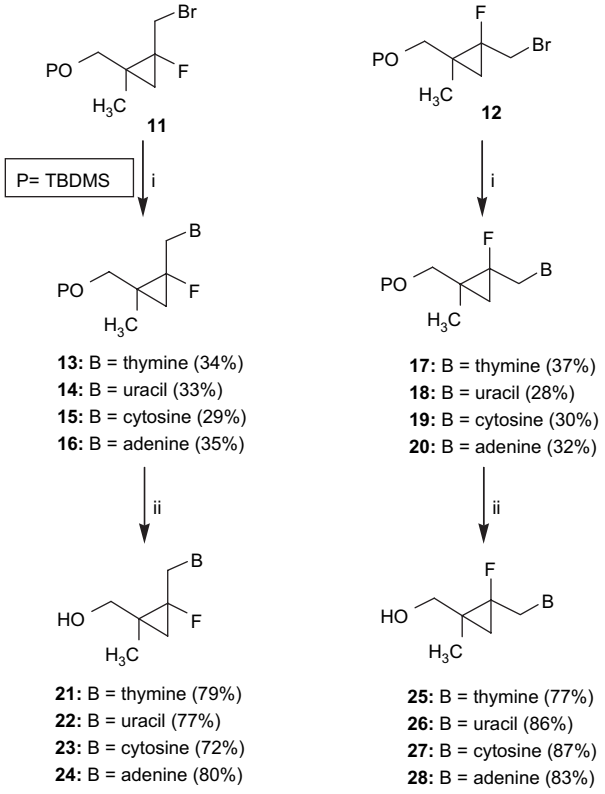


Fig. 2. NOE comparisons of *cis*- and *trans*-fluorocyclopropanes.



Scheme 2. Synthesis of fluorocyclopropyl nucleosides. Reagents: (i) nucleosidic bases, $CsCO_3$, DMF, rt; (ii) TBAF, THF, rt.

2.3. Evaluation of anti-HCMV activity and cytotoxicity

The anti-HCMV activity and cytotoxicity were determined as described elsewhere [13].

3. Materials and method

All the chemicals were of reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in an inert atmosphere containing either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer. The chemical shifts are reported in parts per million (δ), and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. The elemental analysis was performed using an Elemental Analyzer System (Profile HV-3). The mass spectra were obtained on a Finnigan MAT SSQ 7000 spectrometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. The dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

Table 1
The antiviral activities of the synthesized compounds

Compound	EC_{50} (μM)				Cytotoxicity CC_{50} (μM)
	HIV-1	HSV-1	HSV-2	HCMV	
21	89	>100	>100	51.43	>90
22	19.43	>100	>100	*10.61*	>98
23	>100	>100	>100	>100	>100
24	>100	67	>100	71	>90
25	35	>100	>100	>100	>100
26	>100	>100	>100	43	>100
27	65	>100	>100	>100	>100
28	>100	87	>100	>100	>100
AZT	0.0008	ND	ND	ND	1.2
GCV	ND	1.5	1.5	1.01	>10

ND: Not determined; EC_{50} (μM): concentration required for inhibiting 50% of virus-induced cytopathicity; CC_{50} (μM): concentration required to reduce cell viability by 50%.

3.1. (E)-4-(tert-Butyldimethylsilanyloxy)-2-fluoro-3-methyl-but-2-enoic acid ethyl ester (**5**); and (Z)- 4-(tert-butyldimethylsilanyloxy)-2-fluoro-3-methyl-but-2-enoic acid ethyl ester (**6**)

n-Butyllithium (10.8 mmol, 6.75 mL of 1.6 M solution in hexane) was added slowly to a stirred solution of triethyl-2-fluoro-2-phosphonoacetate (10 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was then stirred at the same temperature for further 30 min. A solution of compound **4** (1.79 g, 9.5 mmol) in tetrahydrofuran (5 mL) was added to the above reaction mixture, stirred at −78 °C for 1 h and allowed to warm slowly to room temperature. The mixture was quenched with water (3 mL), and the reaction mixture was extracted with ethyl acetate. The combined extract was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column eluting with hexane/EtOAc (50:1) to give compounds **5** (945 mg, 36%) and **6** (788 mg, 30%) as colorless oils. Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35 (d, $J = 3.3$ Hz, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 2.11 (d, $J = 3.3$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 0.88 (m, 9H), 0.02 (m, 6H); MS (EI) for $C_{13}H_{25}FO_3Si$: *m/z* 276 (M^+). Compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 (d, $J = 2.1$ Hz, 2H), 4.31 (q, $J = 7.2$ Hz, 2H), 1.89 (d, $J = 4.5$ Hz, 3H), 1.33 (t, $J = 7.$ 2 Hz, 3H), 0.86 (s, 9H), 0.02 (m, 12H); MS (EI) for $C_{13}H_{25}FO_3Si$: *m/z* 276 (M^+).

3.2. (E)-4-(tert-Butyldimethylsilanyloxy)-2-fluoro-3-methyl-but-2-en-1-ol (**7**)

DIBAL-H (12.1 mL, 1.0 M solution in hexane) was added slowly to a solution of compound **5** (1.52 g, 5.5 mmol) in CH_2Cl_2 (80 mL) at 0 °C, and stirred for 2 h at the same temperature. Methanol (12 mL) was then added. The resulting mixture was stirred at room temperature for 3 h, and the precipitated solid was filtered through a Celite pad. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:25) to give compound **7** (1.05 g, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.19 (d, $J = 3.0$ Hz, 2H), 4.17 (d, $J =$ 21.9 Hz, 2H), 1.65 (d, $J = 3.0$ Hz, 3H), 0.87 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 153.99, 150.73, 116.00,

115.83, 59.44, 58.24, 57.83, 25.60, 18.29, 12.64, 12.59, −5.41; MS (EI) for $C_{11}H_{23}FO_2Si$: *m/z* 234 (M^+).

3.3. (Z)-4-(tert-Butyldimethylsilanyloxy)-2-fluoro-3-methyl-but-2-en-1-ol (**8**)

Compound **8** was synthesized from compound **6** using a similar procedure to that described for synthesizing compound **7**: yield 85%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.20 (d, $J = 3.3$ Hz, 2H), 4.15 (d, $J = 19.8$ Hz, 2H), 1.70 (d, $J = 2.4$ Hz, 3H), 0.88 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 154.12, 150.98, 116.21, 115.99, 59.51, 59.41, 58.31, 57.94, 25.74, 18.65, 12.87, 12.95, −5.54; MS (EI) for $C_{11}H_{23}FO_2Si$: *m/z* 234 (M^+).

3.4. (±)-(1R,2R)-[2-(tert-Butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropyl]-methanol (**9**)

Diethylzinc solution (1 M in hexanes, 12.33 mL, 12.33 mmol) was added to a solution of compound **7** (811 mg, 3.46 mmol) in CH_2Cl_2 (30 mL) at −30 °C under argon followed by the addition of diiodomethane (2.23 mL, 27.66 mmol). The resulting mixture was stirred for 1 h at 0 °. The reaction was quenched by adding a saturated NH_4Cl solution. The reaction mixture was extracted with chloroform, and the combined extracts were washed with a saturated NaCl solution, dried ($NaSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel column eluting with hexane–EtOAc (30:1) to give compound **9** (662 mg, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (d, $J = 2.8$ Hz, 2H), 4.13 (dd, $J = 12.2$, 0.9 Hz, 2H), 1.35 (d, $J = 3.2$ Hz, 3H), 1.00 (dd, $J = 18.8$, 7.0 Hz, 1H), 0.89 (m, 9H), 0.74 (t, $J = 8.0$ Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 85.67, 83.21, 63.76, 63.51, 60.59, 60.43, 32.76, 32.65, 25.87, 19.42, 18.71, 11.61, −5.70; MS (EI) for $C_{12}H_{25}FO_2Si$: *m/z* 248 (M^+).

3.5. (±)-(1S,2R)-[2-(tert-Butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropyl]-methanol (**10**)

Fluorocyclopropane derivative **10** was obtained from compound **8** using a similar procedure to that described for synthesizing compound **9**: yield 69%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.26–4.19 (m, 4H), 1.30 (d, $J = 3.0$ Hz, 3H), 1.05 (dd, $J = 18.2$, 4.2 Hz, 1H), 0.88 (m, 9H), 0.77 (m, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 84.98, 83.03, 62.45, 59.71, 59.62, 33.81, 33.73, 25.65, 19.76, 18.62, 11.43, 11.36, −5.51; MS (EI) for $C_{12}H_{25}FO_2Si$: *m/z* 248 (M^+).

3.6. (±)-(1R,2R)-1-Bromomethyl-2-(tert-butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropane (**11**)

N-Bromosuccinimide (0.9 g, 2.6 mmol) was added slowly to a solution of compound **9** (320 mg, 1.29 mmol) and triphenylphosphine (675 mg, 2.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The resulting mixture was stirred for 4 h at room temperature, and diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by quick flash silica gel column chromatography (EtOAc/*n*-hexane, 1:30) to give the bromide derivative **11** (241 mg, 60%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.24 (d, $J = 3.2$ Hz, 2H), 4.17 (d, $J = 16.4$ Hz, 2H), 1.32 (d, $J = 2.8$ Hz, 3H), 0.99 (m, 1H), 0.87 (m, 9H), 0.72 (t, $J = 7.6$ Hz, 1H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 83.98, 81.02, 61.43, 61.35, 38.57, 33.54, 33.43, 25.72, 19.12, 18.58, 11.87, −5.45; MS (EI) for $C_{12}H_{24}BrFOSi$: *m/z* 311 (M^+).

3.7. (±)-(1S,2R)-1-Bromomethyl-2-(tert-butyldimethylsilanyloxymethyl)-2-methyl-1-fluoro-cyclopropane (**12**)

Compound **12** was synthesized from compound **10** using a similar procedure to that described for synthesizing **11**: yield 64%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.21 (m, 2H), 4.11 (d, $J = 10.2$ Hz, 2H), 1.37 (d, $J = 2.8$ Hz, 3H), 1.04 (m, 1H), 0.89 (m, 9H), 0.73 (t, $J = 7.2$ Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 84.54, 82.1, 61.43, 61.31, 37.92, 32.65, 32.73, 25.39, 19.43, 18.54, 11.76, 11.68, −5.50; MS (EI) for $C_{12}H_{24}BrFOSi$: *m/z* 311 (M^+).

3.8. (±)-(1′R,2′R)-1-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]thymine (**13**)

A solution of the fluorocyclopropyl derivative **11** (165 mg, 0.53 mmol), thymine (103 mg, 0.81 mmol) and cesium carbonate (262 mg, 0.81 mmol) in anhydrous DMF (7 mL) was stirred overnight at room temperature. Water was added to quench the mixture, which was then diluted with ethyl acetate. The organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 4:1) to give compound **13** (64 mg, 34%) as a solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 7.24 (s, 1H), 4.19 (d, $J = 3.2$ Hz, 2H), 3.24 (dd, $J = 8.2$, 2.8 Hz, 2H), 1.43 (d, $J = 2.8$ Hz, 3H), 1.21 (s, 3H), 1.02 (dd, $J = 8.0$, 2.8 Hz, 1H), 0.87 (s, 9H), 0.73 (dd, $J = 10.8$, 2.8 Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 164.74, 150.98, 143.54, 109.00, 84.32, 82.19, 62.76, 62.65, 48.54, 48.47, 32.34, 32.27, 25.65, 19.45, 18.54, 12.81, 11.43, −5.61; MS (EI) for $C_{17}H_{29}FN_2O_3Si$: *m/z* 358 ($M + 1^+$).

The fluorocyclopropyl nucleoside derivatives **14–20** were synthesized using a similar procedure to that described for synthesizing compound **13**.

3.9. (±)-(1′R,2′R)-1-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]uracil (**14**)

Yield 33%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 7.22 (d, $J = 7.4$ Hz, 1H), 5.43 (d, $J = 7.2$ Hz, 1H), 4.20

(d, $J = 2.8$ Hz, 2H), 3.19 (dd, $J = 10.6$, 2.8 Hz, 2H), 1.37 (d, $J = 2.8$ Hz, 3H), 0.98 (m, 1H), 0.88 (s, 9H), 0.72 (m, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 164.54, 152.76, 145.65, 101.87, 83.41, 81.76, 62.87, 62.77, 47.54, 32.43, 32.31, 25.54, 19.32, 18.65, 11.45, −5.50; MS (EI) for $C_{16}H_{27}FN_2O_3Si$: *m/z* 343 ($M + 1^+$).

*3.10. (±)-(1′R,2′R)-1-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]cytosine (**15**)*

Yield 29%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $J = 7.8$ Hz, 1H), 5.80 (d, $J = 7.6$ Hz, 1H), 4.22 (d, $J = 3.0$ Hz, 2H), 3.25 (dd, $J = 10.2$ Hz, 2.8 Hz, 2H), 1.47 (d, $J = 2.8$ Hz, 3H), 1.09 (m, 1H), 0.89 (s, 9H), 0.75 (dd, $J = 10.8$, 2.8 Hz, 1H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 166.00, 156.32, 145.61, 94.91, 84.82, 82.56, 62.45, 62.36, 48.51, 33.51, 33.42, 25.52, 19.73, 18.56, 11.27, −5.40; MS (EI) for $C_{16}H_{28}FN_3O_2Si$: *m/z* 343 ($M + 1^+$).

*3.11. (±)-(1′R,2′R)-9-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]adenine (**16**)*

Yield 35%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.90 (s, 1H), 6.10 (br d, 2H), 4.24 (d, $J = 2.8$ Hz, 2H), 3.19 (dd, $J = 12.4$, 3.0 Hz, 2H), 1.40 (s, 3H), 1.02 (d, $J = 2.8$ Hz, 1H), 0.88 (s, 9H), 0.78 (t, $J = 7.8$ Hz, 1H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 156.32, 151.56, 149.97, 143.32, 118.43, 85.54, 83.61, 62.65, 47.71, 33.54, 33.43, 25.78, 19.32, 18.49, 11.98, −5.54; MS (EI) for $C_{17}H_{28}FN_5OSi$: *m/z* 367 ($M + 1^+$).

*3.12. (±)-(1′S,2′R)-1-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]thymine (**17**)*

Yield 37%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (br s, 1H), 7.21 (s, 1H), 4.21 (d, $J = 3.0$ Hz, 2H), 3.18 (m, 2H), 1.38 (d, $J = 2.8$ Hz, 3H), 1.18 (s, 3H), 1.00 (m, 1H), 0.88 (s, 9H), 0.74 (t, $J = 7.6$ Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.11, 151.65, 142.32, 108.89, 85.71, 83.69, 63.61, 63.65, 49.12, 33.54, 33.46, 25.32, 19.10, 18.59, 12.48, 11.54, 11.47, −5.39; MS (EI) for $C_{17}H_{29}FN_2O_3Si$: *m/z* 358 ($M + 1^+$).

*3.13. (±)-(1′S,2′R)-1-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]uracil (**18**)*

Yield 28%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.20 (d, $J = 7.2$ Hz, 1H), 5.39 (d, $J = 7.2$ Hz, 1H), 4.21 (d, $J = 2.8$ Hz, 2H), 3.20 (m, 2H), 1.39 (d, $J = 2.6$ Hz, 3H), 1.03 (d, $J = 2.8$ Hz, 1H), 0.87 (s, 9H), 0.75 (t, $J = 8.8$ Hz, 1H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.21, 153.72, 144.33, 102.59, 84.82, 82.78, 61.79, 61.68, 48.41, 48.32, 32.76, 32.68, 25.49, 19.82, 19.74, 18.45, 11.92, 11.85, −5.63; MS (EI) for $C_{16}H_{27}FN_2O_3Si$: *m/z* 343 ($M + 1^+$).

*3.14. (±)-(1′S,2′R)-1-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]cytosine (**19**)*

Yield 30%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, $J = 7.6$ Hz, 1H), 5.79 (d, $J = 7.4$ Hz, 1H), 4.18 (d, $J = 3.0$ Hz, 2H), 3.89 (m, 2H), 1.40 (d, $J = 3.0$ Hz, 3H), 1.01 (m, 1H), 0.87 (s, 9H), 0.72 (m, 1H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 165.85, 155.21, 144.76, 94.39, 83.67, 81.70, 62.76, 47.97, 32.31, 32.24, 25.49, 19.65, 18.42, 11.90, −5.71; MS (EI) for $C_{16}H_{28}FN_3O_2Si$: *m/z* 343 ($M + 1^+$).

*3.15. (±)-(1′S,2′R)-9-[2′-[(tert-Butyldimethylsilanyloxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]adenine (**20**)*

Yield 32%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.94 (s, 1H), 6.12 (br d, 2H), 4.20 (d, $J = 2.8$ Hz, 2H), 3.33 (m, 2H), 1.38 (d, $J = 2.6$ Hz, 3H), 1.02 (m, 1H), 0.87 (s, 9H), 0.73 (dd, $J = 10.2$, 2.6 Hz, 1H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 155.71, 152.54, 148.91, 143.32, 119.43, 83.43, 81.70, 62.65, 62.55, 48.54, 32.40, 32.32, 25.52, 19.39, 18.49, 11.69, −5.61; MS (EI) for $C_{17}H_{28}FN_5OSi$: *m/z* 367 ($M + 1^+$).

*3.16. (±)-(1′R,2′R)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]thymine (**21**)*

TBAF (0.86 mL, 1.0 M solution in THF) at 0 °C was added to a solution of compound **13** (203 mg, 0.57 mmol) in THF (5 mL). The mixture was stirred for 6 h at room temperature, and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:4) to give compound **21** (109 mg, 79%) as a white solid: mp 154–156 °C; UV (H_2O) λ_{max} 267.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.36 (br s, 1H), 7.31 (s, 1H), 4.89 (t, $J = 5.2$ Hz, 1H), 4.21 (d, $J = 3.0$ Hz, 2H), 3.19 (dd, $J = 10.8$, 2.8 Hz, 2H), 1.38 (d, $J = 2.8$ Hz, 3H), 1.17 (s, 3H), 0.91 (m, 1H), 0.74 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.45, 152.65, 142.54, 108.66, 84.32, 82.45, 62.76, 62.68, 48.89, 33.32, 33.24, 19.32, 12.65, 11.78. Anal calc for $C_{11}H_{15}FN_2O_3 \cdot 0.5H_2O$): C, 52.58; H, 6.42; N, 11.15. Found: C, 52.31; H, 6.67; N, 11.33.

The target nucleosides **22–28** were synthesized using a similar procedure to that described for synthesizing compound **21**.

*3.17. (±)-(1′R,2′R)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]uracil (**22**)*

Yield 77%; mp 161–163 °C; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.54 (br s, 1H), 7.40 (d, $J = 7.2$ Hz, 1H), 5.48 (d, $J = 7.0$ Hz, 1H), 4.98 (t, $J = 5.2$ Hz, 1H), 4.21 (m, 2H), 3.27 (dd, $J = 10.2$, 2.8 Hz, 2H), 1.34 (s, 3H), 1.02 (m, 1H), 0.74 (dd, $J = 10.4$, 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.71, 152.35, 144.19, 104.21, 83.32, 81.40, 62.54, 47.88, 33.61, 19.56, 19.48, 11.76. Anal calc for $C_{10}H_{13}FN_2O_3$: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.78; H, 5.65; N, 12.31.

*3.18. (±)-(1′R,2′R)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]cytosine (**23**)*

Yield 72%; mp 155–158 °C; UV (H_2O) λ_{max} 272.5 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.40 (d, $J = 7.6$ Hz, 1H), 5.60 (d, $J = 7.4$ Hz, 1H), 4.95 (t, $J = 5.2$ Hz, 1H), 4.20 (m, 2H), 3.21 (m, 2H), 1.42 (s, 3H), 0.99 (m, 1H), 0.78 (t, $J = 8.6$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 166.54, 155.43, 143.81, 93.38, 83.78, 81.44, 62.54, 62.46, 48.77, 32.71, 19.71, 11.45, 11.38. Anal calc for $C_{10}H_{14}FN_3O_2$: C, 52.86; H, 6.21; N, 18.49. Found: C, 52.99; H, 6.17; N, 18.54.

*3.19. (±)-(1′R,2′R)-9-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]adenine (**24**)*

Yield 80%; mp 183–185 °C; UV (H_2O) λ_{max} 264.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.21 (s, 1H), 8.01 (s, 1H), 7.27 (br s, 2H), 4.90 (t, $J = 5.4$ Hz, 1H), 4.22 (m, 2H), 3.13 (dd, $J = 10.6$, 2.8 Hz, 2H), 1.40 (s, 3H), 1.00 (m, 1H), 0.73 (dd, $J = 10.6$, 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 154.43, 151.76, 147.67, 142.60, 118.12, 84.76, 62.54, 62.47, 48.43, 34.02, 19.65, 11.21. Anal calc for $C_{11}H_{14}FN_5O \cdot 0.5MeOH$): C, 51.68; H, 6.03; N, 26.20. Found: C, 51.42; H, 5.88; N, 26.04.

*3.20. (±)-(1′S,2′R)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]thymine (**25**)*

Yield 77%; mp 158–160 °C; UV (H_2O) λ_{max} 267.5 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.47 (br s, 1H), 7.26 (s, 1H), 4.91 (t, $J = 5.4$ Hz, 1H), 4.18 (s, 2H), 3.19 (m, 2H), 1.40 (s, 3H), 1.15 (s, 3H), 0.98 (dd, $J = 6.8$, 2.8 Hz, 1H), 0.71 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.04, 153.71, 142.34, 109.18, 85.39, 83.45, 63.23, 49.65, 49.58, 33.43, 18.99, 12.21, 11.45, 11.35. Anal calc for $C_{11}H_{15}FN_2O_3$: C, 54.54; H, 6.24; N, 11.56. Found: C, 54.68; H, 6.12; N, 11.62.

*3.21. (±)-(1′S,2′R)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]uracil (**26**)*

Yield 86%; mp 160–162 °C; UV (H_2O) λ_{max} 263.5 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.42 (br s, 1H), 7.35 (d, $J =$ 7.4 Hz, 1H), 5.40 (d, $J = 7.2$ Hz, 1H), 4.91 (t, $J = 5.2$ Hz, 1H), 4.16 (d, $J = 3.0$ Hz, 2H), 3.19 (d, $J = 10.4$, 2H), 1.36 (d, $J = 2.6$ Hz, 3H), 1.02 (m, 1H), 0.78 (d, $J = 10.4$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.54, 153.77, 142.71, 103.69, 84.54, 82.49, 62.50, 62.41, 48.43, 34.12, 33.04, 19.02, 11.58, 11.49. Anal calc for $C_{10}H_{13}FN_2O_3$: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.78; H, 5.65; N, 12.31.

*3.22. (±)-(1′S,2′R)-1-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]cytosine (**27**)*

Yield 87%; mp 158–160 °C; UV (H_2O) λ_{max} 272.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.38 (d, $J = 7.8$ Hz, 1H), 5.46 (d, $J = 7.6$ Hz, 1H), 4.90 (t, $J = 5.2$ Hz, 1H), 4.14 (dd, $J = 6.2$, 2.8 Hz, 2H), 3.21 (m, 2H), 1.42 (d, $J = 3.0$ Hz, 3H), 0.96 (m, 1H), 0.70 (dd, $J = 8.8$, 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.21, 154.53, 141.27, 94.67, 85.48, 83.21, 62.21, 47.33, 33.32, 33.24, 19.32, 19.22, 11.67. Anal calc for $C_{10}H_{14}FN_3O_2 \cdot 0.7H_2O$): C, 50.07; H, 6.47; N, 17.52. Found: C, 49.96; H, 6.37; N, 17.54.

*3.23. (±)-(1′S,2′R)-9-[2′-[(Hydroxymethyl)-2′-methyl-1′-fluoro]cycloprop-1′-yl]adenine (**28**)*

Yield 83%; mp 187–189 °C; UV (H_2O) λ_{max} 263.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.20 (s, 1H), 7.99 (s, 1H), 7.21 (br s, 2H), 4.89 (t, $J = 5.2$ Hz, 1H), 4.17 (d, $J = 3.0$ Hz, 2H), 3.13 (dd, $J = 10.2$, 3.0 Hz, 2H), 1.38 (d, $J = 2.8$ Hz, 3H), 0.97 (m, 1H), 0.73 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 155.21, 152.43, 146.76, 141.54, 119.61, 83.97, 63.87, 63.79, 47.41, 33.82, 33.74, 19.21, 11.21, 11.14. Anal calc for $C_{11}H_{14}FN_5O$: C, 52.58; H, 5.62; N, 27.87. Found: C, 52.69; H, 5.48; N, 27.74.

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