

## Synthesis of 3'-Fluoro-2',3'-dideoxy-2',3'-didehydro-4'-ethynyl-D- and -L-furanosyl Nucleosides

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An efficient procedure has been developed for the synthesis of 3'-fluoro-2',3'-dideoxy-2',3'-didehydro-4'-ethynyl D- and L-furanosyl nucleosides (**1** and **2**) starting from 2,3-*O*-isopropylidene-D-glyceraldehyde. The key intermediate 1-*O*-benzoyl-3*E*-fluoro-3,4-unsaturated-5,6-di(*tert*-butyldimethylsilyloxy)-2-hexanone **8** was obtained in nine steps with the overall yield of 22%. The  $\alpha,\beta$ -unsaturated ketone **8** was then treated with ethynylmagnesium bromide in a typical Grignard reaction procedure to afford the two intermediates **9** and **10**, which after deprotection, oxidation, and acetylation gave the corresponding 4-ethynyl-substituted D- and L-sugar moieties **15** and **16**, respectively. A series of D- and L-pyrimidine and purine nucleosides were prepared by the coupling of the sugar moieties with various silylprotected bases. The anomeric mixtures were obtained after condensation. After separation, the  $\beta$ -isomers were further deprotected to yield the target nucleosides. All the newly synthesized 4'-substituted nucleosides were tested for their activities against HIV, among which the D-adenine derivative showed moderate anti-HIV activity ( $EC_{50} = 25.1 \mu\text{M}$ ) without significant cytotoxicity.

### Introduction

In the treatment of acquired immunodeficiency syndrome (AIDS), a number of anti-HIV chemotherapeutic agents have been developed, among which nucleoside analogues remain in the forefront of anti-HIV chemotherapeutic regimens. However, side effects and the emergence of drug-resistant mutants continue to be a problem with these antiviral agents.<sup>1-5</sup> It is now clear that judicious combination chemotherapy is the optimum way to improve the quality of life and survival of patients infected with HIV-1.<sup>6</sup> Therefore, the development of structurally new nucleoside derivatives, which have potent antiviral activities and low toxicity, as well as novel resistant profiles, are urgently needed to provide better choices for the combination chemotherapy.

Nucleosides with 2',3'-dideoxy-2',3'-didehydro sugars often exhibit potent antiviral activities.<sup>7</sup> Among the

series, 2',3'-didehydro-3'-deoxythymidine (D4T)<sup>8</sup> and the carbocyclic 2-amino-6-cyclopropylaminopurine analogue, abacavir,<sup>9</sup> have been approved by the FDA for the treatment of HIV infection. There has been considerable interest in the modification of nucleosides with a fluorine atom as potential antiviral agents.<sup>10</sup> It has been shown that the introduction of fluorine atoms enhances the drug activity,<sup>11</sup> and to discover novel drugs, varieties of nucleosides with a fluorinated sugar have been synthesized.<sup>10,12,13</sup> Besides the modification of the nucleosides focused on 2'- and 3'-positions, certain 4'-substituted nucleosides have been described in the literature as potential antiviral agents.<sup>14</sup> For example, 4'-azidothymi-

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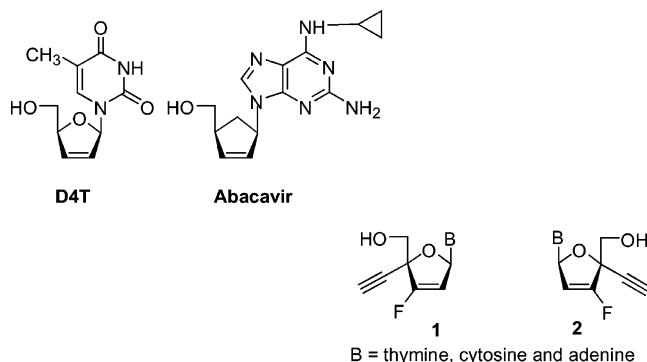
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dine (4'-AZT),<sup>15</sup> which has the hydrogen atom at the 4' position substituted with an azido group, exerted potent activity against HIV-1 in vitro. Other 4'-substitutions, such as fluoro,<sup>16</sup> cyano,<sup>17</sup> methyl,<sup>18</sup> ethynyl,<sup>19</sup> and even an unusual oxetane,<sup>17</sup> have also exhibited interesting antiviral activity. Therefore, it was of interest to synthesize additional 4'-substituted nucleosides as potential antiviral agents. In our previous studies, we found that the fluorinated 2',3'-dideoxy-2',3'-didehydro nucleosides showed antiviral activities without significant cytotoxicity.<sup>13</sup> Here, we report the synthesis of 3'-fluoro-2',3'-dideoxy-2',3'-didehydro-4'-ethynyl nucleosides.



## Results and Discussion

Several synthetic approaches have been reported for the synthesis of 4'-carbon-branched nucleosides, among which reactions of various 5'-oxo nucleoside derivatives such as 4'-formyl and 4'-acyl nucleosides have been utilized.<sup>17a,20</sup> The 4'-hydroxymethyl group is synthesized by the Cannizzaro reaction, which is then converted to the alkyl groups to afford various complex derivatives.<sup>21</sup> This lengthy sequence was not readily applicable to the purine nucleosides due to instability toward the necessary oxidation step. Another interesting route employs dimethyl L-tartrate and builds up the 4'-substituted

nucleoside in a multistep sequence.<sup>22</sup> Although it allows for the introduction of both purine and pyrimidine bases as well as modified bases, the synthetic steps become even longer and may not be applicable to the 2',3'-dideoxy-2',3'-didehydro nucleosides. To find a more efficient way to produce the fluorinated 2',3'-dideoxy-2',3'-didehydro-4'-C-substituted nucleosides, we recently developed a novel synthetic route for both D- and L-3'-fluoro-2',3'-dideoxy-2',3'-didehydro-4'-ethynyl nucleosides starting from 2,3-*O*-isopropylidene-D-glyceraldehyde.

The lactone **3**, prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde by a previously published method,<sup>13c,23,24</sup> was treated with methyltriphenylphosphonium bromide to give the diene **4** as an inseparable *E* and *Z* mixture in 91% yield (*E/Z* = 5:2 detected by NMR. The ratio of *E* and *Z* isomers was determined on the basis of the signals of 2-H in <sup>1</sup>H NMR. The *E* isomer had the 2-H signal ( $\delta$  6.57 ppm) at lower field than that of the *Z* isomer ( $\delta$  6.22 ppm) according to the NMR data of compounds **5** and **5a**). During the Wittig process, the allylic hydrogen atom, 4-H, was removed by the strong base to form a double bond between C-4 and C-3, and the original double bond between the position of C-2 and C-3 was migrated to the position between C-2 and C-1, which resulted in an *EZ* mixture. At the same time, the configuration at C-4 position in compound **3a**, which was equivalent to the C-5 position in compounds **4**, remained *R* by an unknown mechanism. Probably the interaction between the oxygen atom in the hydroxyl group and the silicon atom in the TBDMS protecting group of the hydroxyl group at C-5 position had some effect on the retention of the hydroxyl stereochemistry at the C-4 position. However, it should be stressed that the stereochemistry of C-4 in compound **3a** is not important because these two adjacent hydroxyl groups would be oxidized and cleaved by sodium periodate to form the aldehyde **13** or **14** (Scheme 2). The *EZ* mixture was further reacted with *tert*-butyldimethylsilyl chloride to afford the fully protected compounds, and the desired *E* isomer **5** could be readily separated from the *Z* isomer **5a** by silica gel column chromatography. The structures of compounds **5** and **5a** were determined by NMR on the basis of the coupling constants (*J*) of 4-H with the fluorine atom at C-3 position. The *J* value was bigger when 4-H and the fluorine atom were in *E* positions to each other (*J* = 35.87 Hz) than when they were in *Z* positions (*J* = 20.74 Hz). Extensive NOE studies of these two compounds also supported the structural assignment. NOE (1.40%) was observed between 2-H and 4-H in compound **5a** when 4-H was irradiated, while no NOE was observed between the same hydrogen atoms in compound **5**. Also, NOEs were observed between 5-H and 4-H in both compound **5** (4.12%) and compound **5a** (5.43%) when 5-H was irradiated, which confirmed that the configurations at the C-5 position in both compounds were *R*. Compound **5** was converted to an anomeric diol **6** through the typical oxidation procedure using OsO<sub>4</sub> and 4-methylmorpholine *N*-oxide. Selective benzylation of the primary hydroxyl

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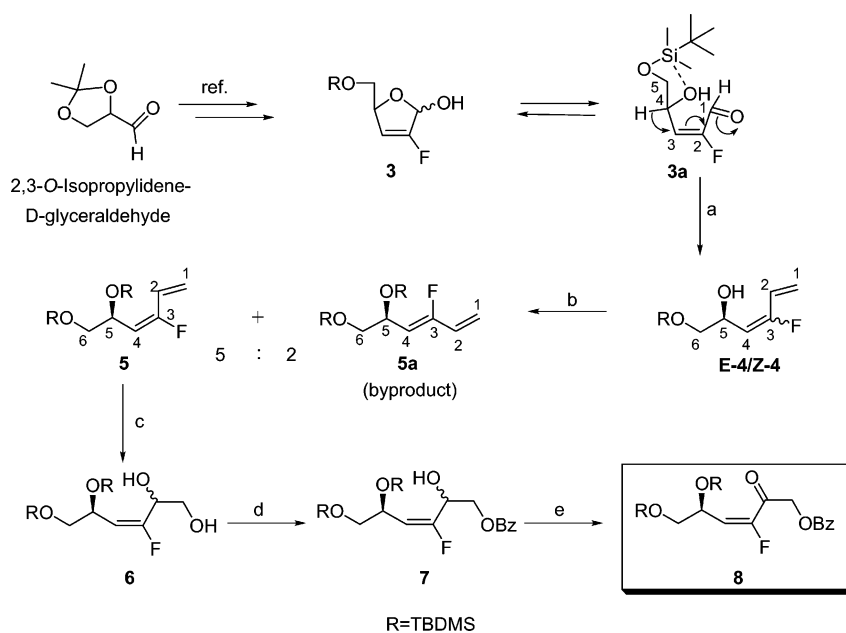
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SCHEME 1<sup>a</sup>

<sup>a</sup> Reagents: (a)  $\text{CH}_3\text{P}(\text{Ph})_3\text{Br}$ , NaH, DMSO, THF; (b) TBDMSCl, imidazole,  $\text{CH}_2\text{Cl}_2$ ; (c)  $\text{OsO}_4$ , NMO, acetone,  $\text{H}_2\text{O}$ ; (d)  $\text{BzCl}$ , Py,  $0\text{ }^\circ\text{C}$ ; (e) PCC, 4 Å molecular sieves,  $\text{CH}_2\text{Cl}_2$ .

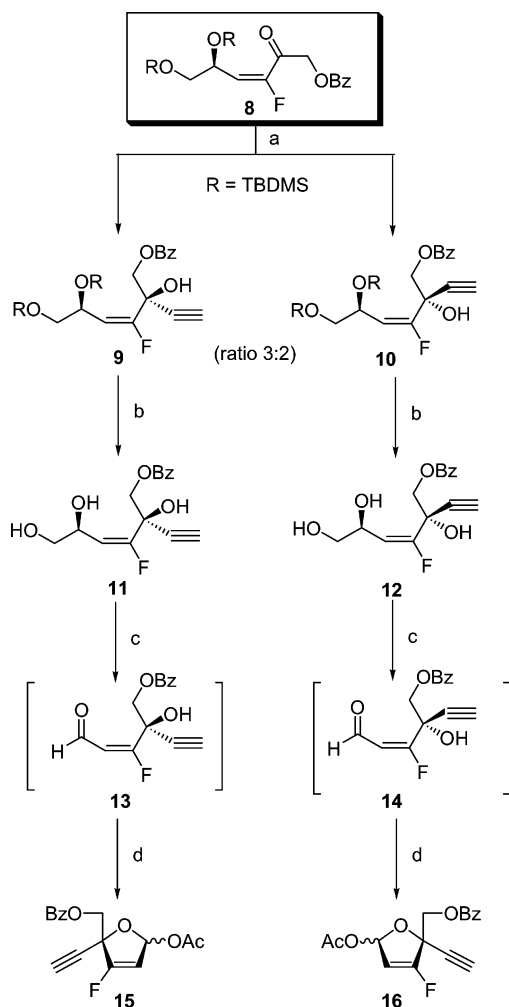
group of **6** by treatment with benzoyl chloride in the solution of dry pyridine at  $0\text{ }^\circ\text{C}$  gave the corresponding monobenzoate **7**. The monobenzoylated compound was then oxidized by pyridinium chlorochromate (PCC) in  $\text{CH}_2\text{Cl}_2$  to furnish the  $\alpha,\beta$ -unsaturated ketone **8**, the key intermediate in the whole synthetic route, which was subjected to a standard Grignard reaction procedure to give a separable mixture of **9** and **10** in a ratio of 3:2 with a total yield of 72%. The stereochemistry of these diastereomers **9** and **10** at C-2 was determined by  $^1\text{H}$  NMR as well as the NOE studies for **18** and **20** (vide infra). The signal of the proton of 2*R*-OH (or  $\beta$ -OH,  $\delta$  5.87 ppm) in compound **9** was significantly downfield ( $\Delta\delta = 0.78$  ppm) from that of the proton of 2*S*-OH ( $\alpha$ -OH,  $\delta$  5.09 ppm), overlapped with the signal of 5-H) in compound **10**, due to the interaction of the  $\beta$ -OH with the bulky 5-TBDMS group. The *tert*-butyldimethylsilyl groups in compound **9** were removed by tetrabutylammonium fluoride to afford the trihydroxy compound **11**. Oxidation of compound **11** with sodium periodate gave the aldehyde compound **13**, which was reacted with acetic anhydride in the solution of pyridine to produce the 3-fluoro-2,3-unsaturated-4-ethynyl-D-furanose **15**. The same series of reactions including the deprotection, oxidation, and acetylation was applied to compound **10** and furnished the modified L-sugar moiety **16**.

Compounds **15** and **16** proved to be suitable intermediates for coupling with various heterocyclic bases. Thus, treatment of acetonitrile solution of **15** or **16** with suitably protected forms of bases in the presence of trimethylsilyl trifluoromethane sulfonate (TMSOTf) provided D- or L-nucleosides in moderate to good yields as  $\alpha/\beta$  mixtures (Scheme 3). For trimethylsilylated pyrimidines, completion of the condensation reaction took less than 1 h, while a prolonged reaction time increased the formation of the  $\alpha$  isomers. However, for purines, specifically for adenine, it took about 12 h or more for the coupling reaction to be

completed. In all of the cases for thymine, cytosine, and adenine, the  $\alpha/\beta$  anomers were readily separated by silica gel column chromatography. The thymine nucleosides **17** and **26** were obtained together with their  $\alpha$  isomers **19** and **28** in 73% and 71% yield, respectively, with a ratio of  $\alpha/\beta = 1:3$  within 1 h. Likewise, condensation of compound **15** or **16** with silylated *N*<sup>6</sup>-benzoylcytosine in anhydrous acetonitrile gave the protected cytosine derivatives **18** or **27**, respectively, as well as the  $\alpha$  isomers ( $\alpha/\beta = 1:3$ ). After separation of the desired  $\beta$  anomers from their  $\alpha$  analogues on silica gel column chromatography, ammonolysis using saturated methanolic ammonia at room temperature was employed to deprotect the individual anomers to afford the free nucleosides **23**, **24**, **32**, and **33**.

Condensation of compound **15** or **16** with silylated *N*<sup>6</sup>-isobutyryladenine in dry acetonitrile at room temperature for 12 h gave a separable  $\alpha$  and  $\beta$  mixture of the protected adenine nucleosides **21/22** or **30/31** in a yield of 63% and 62%, respectively, with a ratio of  $\alpha/\beta = 1:1$  (Table 1). The  $\beta$  anomers (**21** and **30**) were separated and deprotected by saturated methanolic ammonia at room temperature for 12 h to give the target nucleosides **25** and **34**, respectively.

The stereochemical assignments of these  $\alpha$  and  $\beta$  anomers were determined on the basis of NOE experiments of the cytosine derivatives (**18/20**). NOE (3%) was observed between the 6-H and the proton in the 4'-ethynyl group in the  $\alpha$ -cytosine derivative **20** when the 6-H was irradiated, whereas no NOE was observed between the same positions in the  $\beta$ -isomer **18**. This assignment was also supported by lower-field chemical shifts on the proton of the 4'-ethynyl group in compound **20** ( $\alpha$ -form), compared to that of the 4'-ethynyl proton in compound **18** ( $\beta$ -form), due to the deshielding effects by the heterocyclic base. This assignment based on the NOE

SCHEME 2<sup>a</sup>

<sup>a</sup> Reagents: (a) HCCMgBr, THF, 50 °C; (b) TBAF, HOAc, THF; (c) NaIO<sub>4</sub>, EtOH, H<sub>2</sub>O; (d) Ac<sub>2</sub>O, Py.

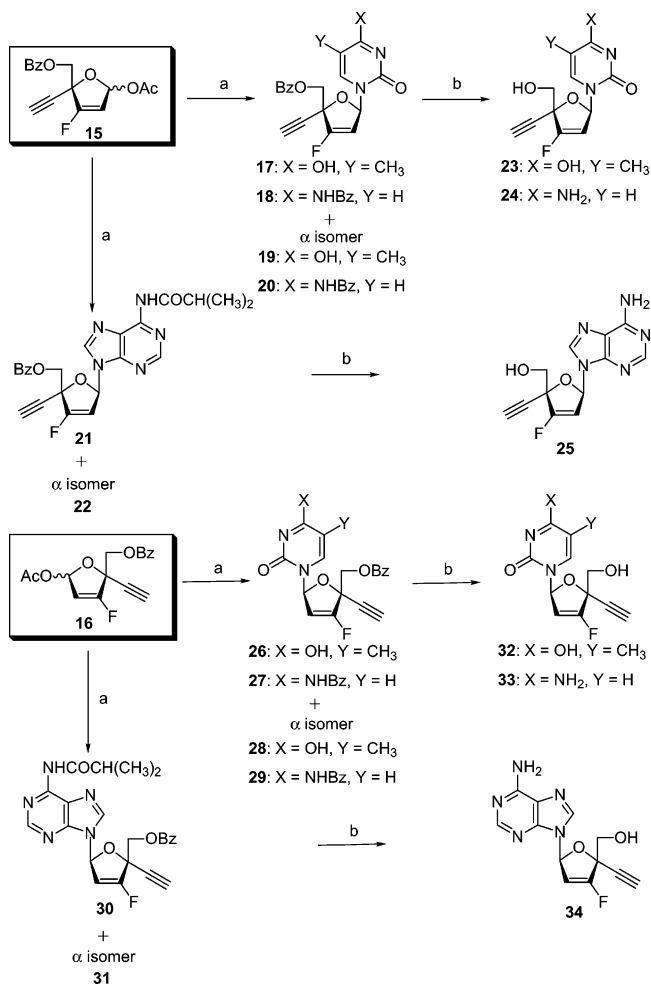
experiments was one of the major determinants for the assignment of the intermediates **9** and **10**.

All the synthesized 3'-fluoro-2',3'-dideoxy-2',3'-didehydro-4'-ethynyl-D- and -L-furanosyl nucleosides (**23–25**, **32–34**) were evaluated against HIV-1 in human peripheral blood mononuclear (PBM) cells in vitro.<sup>25</sup> Among the tested nucleosides, only the D-adenine analogue shows moderate anti-HIV activity with an EC<sub>50</sub> value of 25.1 μM (EC<sub>50</sub> = 0.004 μM for AZT) without cytotoxicity up to 100 μM.

In conclusion, we described a new and efficient route for the synthesis of 3'-fluoro-2',3'-dideoxy-2',3'-didehydro-4'-ethynyl-D- and -L-furanosyl nucleosides. Our scheme features a convergent approach in which D- and L-nucleosides can be synthesized from the same starting material to produce a series of 4'-ethynyl nucleosides. This general method can be applied to the synthesis of both 3'- and 4'-substituted 2',3'-dideoxy-2',3'-didehydro nucleosides of biological interest.

## Experimental Section

**(5R)-5-Hydroxy-6-[(tert-butyldimethylsilyloxy)methyl]-3-fluoro-1,3-dihexene (4).** A suspension of NaH (11.8 g, 0.492 mol) in THF (960 mL) was cooled to 5 °C and then treated

SCHEME 3<sup>a</sup>

<sup>a</sup> Reagents: (a) silylated base, TMSOTf, CH<sub>3</sub>CN; (b) NH<sub>3</sub>/CH<sub>3</sub>OH.

**TABLE 1.** α/β Ratio Obtained from the Condensation Reaction

	<b>15</b>	<b>16</b>
thymine	<b>19</b> (α)/ <b>17</b> (β) = 1:3	<b>28</b> (α)/ <b>26</b> (β) = 1:3
N <sup>4</sup> -benzoylcytosine	<b>20</b> (α)/ <b>18</b> (β) = 1:3	<b>29</b> (α)/ <b>27</b> (β) = 1:3
N <sup>6</sup> -isobutyryladenine	<b>22</b> (α)/ <b>21</b> (β) = 1:1	<b>31</b> (α)/ <b>30</b> (β) = 1:1

with DMSO. After being stirred at room temperature for 30 min, the mixture was cooled to 0 °C again and then methyl-triphenylphosphonium bromide (112 g, 0.314 mol) was added. After being stirred at room temperature for 1 h, the resulting slightly green mixture was cooled to 5 °C and treated with a solution of compound **3** (33.01 g, 0.133 mol) in 200 mL of THF. The reaction mixture was stirred at room temperature for another 2 h, and then 200 mL of Et<sub>2</sub>O was added, the yellowish solid was filtered off, and the filtrate was concentrated to dryness. Purification on silica gel (hexanes/EtOAc, 25:1) gave compound **4** (E/Z mixture, E-4/Z-4, 5:2) as a pale yellow oil (29.8 g, 91.0%); MS (ESI) *m/z* 269 (M + Na)<sup>+</sup>. Anal. Calcd for C<sub>12</sub>H<sub>23</sub>O<sub>2</sub>FSi: C, 58.50; H, 9.41. Found: C, 58.48; H, 9.49.

**(5R)-5,6-Di[(tert-butyldimethylsilyloxy)methyl]-3E-fluoro-1,3-dihexene (5).** Compound **4** (29.8 g, 0.121 mol) was dissolved in 200 mL of CH<sub>2</sub>Cl<sub>2</sub>, and then *tert*-butyldimethylsilyl chloride (27.44 g, 0.182 mol) was added together with imidazole

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(12.36 g, 0.182 mmol). The resulting mixture was stirred at room temperature for 2 h until it was treated with ice and diluted with  $\text{CH}_2\text{Cl}_2$ . The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to dryness. The residue obtained was purified on column chromatography (100% hexanes) to afford compound **5** as a yellowish oil (27.42 g, 62.9%). The *Z*-form isomer **5a** was also obtained as a yellowish oil (10.5 g, 24.1%).

Compound **5**:  $[\alpha]_D^{27} -4.85$  (*c* 0.75, acetone);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.43 (m, 1H), 5.60 (d, *J* = 17.08 Hz), 5.28 (dd, 1H, *J* = 1.46, 11.23 Hz), 5.12 (dd, 1H, *J* = 8.79, 20.74 Hz), 4.37 (m, 1H), 3.61 (ddd, 1H, *J* = 0.98, 6.10, 10.01 Hz), 3.47 (dd, 1H, *J* = 6.35, 10.01 Hz), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (d, 6H, *J* = 8.05 Hz), 0.04 (d, 6H, *J* = 4.64 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  156.7 (d, *J* = 247.40 Hz), 125.1 (d, *J* = 25.89 Hz), 116.5 (d, *J* = 5.75 Hz), 110.9 (d, *J* = 21.10 Hz), 63.7 (d, *J* = 12.47 Hz), 67.8, 31.3, 25.9, 18.3, 18.1, -4.5 (d, *J* = 21.10 Hz), -5.4; MS (ESI) *m/z* 383 (M + Na) $^+$ . Anal. Calcd for  $\text{C}_{18}\text{H}_{37}\text{O}_2\text{FSi}_2$ : C, 59.95; H, 10.34. Found: C, 60.18; H, 10.39.

Compound **5a**:  $[\alpha]_D^{24} +4.57$  (*c* 1.25, acetone);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.05 (m, 1H), 5.59 (d, *J* = 17.08 Hz), 5.15 (dd, 1H, *J* = 1.49, 10.98 Hz), 4.75 (dd, 1H, *J* = 8.79, 35.87 Hz), 4.63 (dd, *J* = 6.35, 15.13 Hz, 1H), 3.55 (dd, 1H, *J* = 6.35, 10.01 Hz), 3.44 (dd, 1H, *J* = 5.37, 10.01 Hz), 0.84 (s, 9H), 0.83 (s, 9H), 0.03 (d, 6H, *J* = 5.98 Hz), 0.02 (d, 6H, *J* = 4.64 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  156.1 (d, *J* = 212.20 Hz), 128.6 (d, *J* = 25.89 Hz), 115.4 (d, *J* = 4.79 Hz), 111.9 (d, *J* = 13.43 Hz), 67.6, 67.5, 25.9, 25.8, 18.3, 18.2, -4.8 (d, *J* = 2.88 Hz), -5.3 (*J* = 10.55 Hz); MS (ESI) *m/z* 383 (M + Na) $^+$ . Anal. Calcd for  $\text{C}_{18}\text{H}_{37}\text{O}_2\text{FSi}_2$ : C, 59.95; H, 10.34. Found: C, 60.21; H, 10.43.

**(5*R*)-1,2-Dihydroxy-5,6-di[(*tert*-butyldimethylsilyloxy)methyl]-3*E*-fluoro-3-hexene (**6**)**. To a solution of compound **5** (36.4 g, 0.101 mol) in 500 mL of acetone at room temperature was added 500 mL of a stock osmylation solution (prepared by dissolving 85.58 g of 4-methylmorpholine *N*-oxide and 2 g of osmium tetroxide in 597 mL of water). The reaction mixture was stirred at room temperature for 4 h. After the reaction mixture was concentrated to half of the original volume, the resulting solution was dissolved in EtOAc and washed with saturated sodium bisulfite solution and brine. The organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to give the crude diol **6** (anomeric mixture), which was purified on column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 50:1) to give the pure compound **6** (33.03 g, 82.9% yield) as a yellowish oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.19 (dd, 1H, *J* = 8.54, 23.43 Hz), 4.73 (m, 1H), 4.41 (m, 1H), 3.95 (s, 1H), 3.79 (m, 1H), 3.72 (m, 1H), 3.65 (m, 1H), 3.33 (t, 1H, *J* = 9.03 Hz), 2.22 (bs, 1H), 0.91 (s, 9H), 0.88 (s, 9H), 0.10 (d, 6H, *J* = 0.98 Hz), 0.08 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  158.2 (d, *J* = 254.11 Hz), 111.6 (d, *J* = 18.18 Hz), 70.1 (d, *J* = 33.56 Hz), 67.2, 66.9 (d, *J* = 12.47 Hz), 64.0, 25.9, 25.7, 18.5, 18.1, -4.6, -4.9; MS (ESI) *m/z* 395 (MH) $^+$ , 417 (M + Na) $^+$ . Anal. Calcd for  $\text{C}_{18}\text{H}_{39}\text{O}_4\text{FSi}_2$ : C, 54.78; H, 9.96. Found: C, 54.97; H, 10.12.

**(5*R*)-1-*O*-Benzoyl-2-hydroxy-5,6-di[(*tert*-butyldimethylsilyloxy)methyl]-3*E*-fluoro-3-hexene (**7**)**. To a solution of compound **6** (21.2 g, 53.8 mmol) in dry pyridine (300 mL) was added benzoyl chloride (6.81 g, 48.43 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h with the exclusion of water. Then 20 mL of  $\text{CH}_3\text{OH}$  was added to quench the reaction. After removal of the solvents, the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and washed successively with saturated  $\text{NaHCO}_3$  and  $\text{CuSO}_4$  solutions, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The pure compound **7** (20.27 g, 84.0% yield) was obtained by purification on a flash column (hexanes/EtOAc, 50:1) as a yellowish oil. Some starting material remained and was recovered:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.05 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.22 (dd, 1H, *J* = 20.99, 8.55 Hz), 4.75 (m, 1H), 4.49 (d, 2H, *J* = 5.13 Hz), 4.42 (m, 1H), 3.63 (m, 1H), 3.38 (m, 1H), 3.30 (s, 1H), 0.87 (d, 9H, *J* = 0.82 Hz), 0.82 (d, 9H, *J* = 0.82 Hz), 0.04 (d, 6H, *J* = 1.1 Hz), -0.02 (d, 6H, *J* = 1.1 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  166.3, 159.1 (d, *J* = 261.79 Hz), 133.1, 129.7, 128.3, 112.7 (d, *J* = 18.22 Hz), 68.6 (d, *J* = 11.51 Hz),

67.5 (d, *J* = 2.88 Hz), 65.8 (d, *J* = 27.81 Hz), 64.3 (d, *J* = 3.84 Hz), 26.0, 25.7, 18.7, 18.1, -4.8 (d, *J* = 25.89 Hz), -5.4; MS (ESI) *m/z* 499 (MH) $^+$ , 512 (M + Na) $^+$ . Anal. Calcd for  $\text{C}_{25}\text{H}_{43}\text{O}_5\text{FSi}_2$ : C, 60.20; H, 8.69. Found: C, 60.48; H, 8.83.

**(5*R*)-1-*O*-Benzoyl-5,6-di[(*tert*-butyldimethylsilyloxy)methyl]-3,4-dihydro-3-fluoro-2-hexanone (**8**)**. To a solution of compound **7** (14 g, 28.11 mmol) in  $\text{CH}_2\text{Cl}_2$  (300 mL) were added pyridium chlorochromate (14 g, 64.95 mmol) and 4 Å molecular sieves (14 g). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was then filtered through a pad of silica gel, and the filtrate was condensed. The residue was purified on the column chromatography (hexanes/EtOAc, 50:1) to give compound **8** (10.04 g, 72.0% yield) as a yellowish oil:  $[\alpha]_D^{25} -2.12$  (*c* 0.35, acetone);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.12 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 5.82 (dd, 1H, *J* = 22.29, 8.81 Hz), 5.19 (m, 3H), 3.62 (m, 1H), 3.54 (m, 1H), 0.92 (d, 9H, *J* = 3.03 Hz), 0.88 (d, 9H, *J* = 1.41 Hz), 0.06 (d, 6H, *J* = 2.69 Hz), 0.04 (d, 6H, *J* = 6.39 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  188.3 (d, *J* = 38.6 Hz), 165.6, 151.1 (d, *J* = 256.9 Hz), 133.4, 130.1, 128.6, 128.5, 124.6 (d, *J* = 13.4 Hz), 67.7 (d, *J* = 8 Hz), 67.3 (d, *J* = 3.13 Hz), 67.0, 25.9, 18.3, 18.1, -4.8, -5.4; MS (ESI) *m/z* 497 (MH) $^+$ , 519 (M + Na) $^+$ . Anal. Calcd for  $\text{C}_{25}\text{H}_{41}\text{O}_5\text{FSi}_2 \cdot 0.1\text{hexane}$ : C, 60.84; H, 8.46. Found: C, 60.95; H, 8.49.

**(2*R*,5*R*)-1-*O*-Benzoyl-5,6-di[(*tert*-butyldimethylsilyloxy)methyl]-3*E*-fluoro-2-hydroxyl-2-ethynyl-3-hexene (**9**) and (2*S*,5*R*)-1-*O*-Benzoyl-5,6-di[(*tert*-butyldimethylsilyloxy)methyl]-3*E*-fluoro-2-hydroxyl-2-ethynyl-3-hexene (**10**)**. To a stirred solution of compound **8** (5.56 g, 11.21 mmol) in dry THF (200 mL) was added ethynylmagnesium bromide (0.5 M in THF, 34 mL, 17 mmol) under  $\text{N}_2$  atmosphere. The resulting mixture was then stirred at 50 °C for 2 h until 50 mL of EtOAc was added to terminate the reaction. After removal of the solvent, saturated  $\text{NH}_4\text{Cl}$  solution was added, and the mixture was extracted several times with EtOAc. The organic layers were combined, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was separated on column chromatography over silica gel (hexanes/EtOAc, 50:1) to give the compound **9** (2.53 g, 43.2% yield) and compound **10** (1.69 g, 28.9% yield) as yellowish oils.

Compound **9**:  $[\alpha]_D^{24} +5.06$  (*c* 5.40, acetone);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.09 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 5.87 (s, 1H), 5.37 (dd, 1H, *J* = 7.43, 25.04 Hz), 4.92 (dd, 1H, *J* = 7.43, 12.91 Hz), 4.63 (d, 1H, *J* = 11.35 Hz), 4.54 (d, 1H, *J* = 11.35 Hz), 3.69 (m, 1H), 3.39 (t, 1H, *J* = 8.3 Hz), 2.53 (s, 1H), 0.92 (s, 9H), 0.87 (s, 9H), 0.12 (d, 3H, *J* = 3.13 Hz), 0.04 (d, 3H, *J* = 3.91 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  166.0, 156.1 (d, *J* = 258.9 Hz), 133.1, 129.9, 129.8, 128.3, 112.3, 81.6, 73.9, 69.5 (d, *J* = 32.3 Hz), 67.9, 66.9 (d, *J* = 10.1 Hz), 26.2, 25.7, 18.6, 18.0, -4.8 (d, *J* = 17.14 Hz), -5.4 (d, *J* = 17.14 Hz); MS (ESI) *m/z* 523 (MH) $^+$ , 545 (M + Na) $^+$ . Anal. Calcd for  $\text{C}_{27}\text{H}_{43}\text{O}_5\text{FSi}_2 \cdot 0.1\text{hexane}$ : C, 62.38; H, 8.42. Found: C, 62.51; H, 8.26.

Compound **10**:  $[\alpha]_D^{24} +11.71$  (*c* 1.15, acetone);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.03 (m, 2H), 7.53 (m, 1H), 7.39 (m, 2H), 5.28 (ddd, *J* = 2.44, 8.54, 24.16 Hz, 1H), 5.09 (m, 2H), 4.58 (dd, 1H, *J* = 11.10 Hz), 4.51 (d, 1H, *J* = 11.10 Hz), 3.67 (m, 1H), 3.39 (td, 1H, *J* = 2.20, 9.03 Hz), 2.55 (s, 1H), 0.86 (d, 9H, *J* = 2.67 Hz), 0.83 (d, 9H, *J* = 2.44 Hz), 0.08 (d, 3H, *J* = 1.46 Hz), 0.01 (dd, 3H, *J* = 2.44, 8.30 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  166.1, 157.2 (d, *J* = 262.74 Hz), 133.2, 129.9, 129.7, 128.3, 112.9, 80.9, 73.8, 68.9 (d, *J* = 3.84 Hz), 67.4, 66.7 (d, *J* = 10.55 Hz), 26.0, 25.8, 18.6, 18.1, -5.4, -5.5 (d, *J* = 17.14 Hz); MS (ESI) *m/z* 523 (MH) $^+$ , 545 (M + Na) $^+$ . Anal. Calcd for  $\text{C}_{27}\text{H}_{43}\text{O}_5\text{FSi}_2$ : C, 62.03; H, 8.29. Found: C, 62.07; H, 8.28.

**(2*R*,5*R*)-1-*O*-Benzoyl-5,6-dihydroxy-3*E*-fluoro-2-hydroxy-2-ethynyl-3-hexene (**11**)**. To a solution of compound **9** (1.57 g, 3.0 mmol) in 100 mL of THF were added tetrabutylammonium fluoride (1.0 M in THF, 9 mL, 9.0 mmol) and HOAc (0.18 g, 3.0 mmol). The resulting mixture was then stirred at room temperature for 2 h. After removal of the solvent, the residue was subjected to column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 20:1) to give the compound **11** as a yellowish oil (0.86 g, 97.5%

yield):  $[\alpha]^{24}_D +5.96$  (*c* 0.30, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.03 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 5.88 (bs, 1H), 5.39 (dd, 1H, *J* = 8.05, 24.40 Hz), 4.97 (m, 1H), 4.61 (dd, 1H, *J* = 1.46, 11.23 Hz), 4.57 (dd, 1H, *J* = 1.71, 11.23 Hz), 3.62 (dd, 1H, *J* = 2.63, 11.20 Hz), 3.52 (dd, 1H, *J* = 7.57, 11.20 Hz), 2.66 (s, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  166.7, 158.7 (d, *J* = 260.83 Hz), 133.8, 130.1, 129.5, 128.8, 109.9 (d, *J* = 21.10 Hz), 80.6, 75.3, 69.8 (d, *J* = 34.52 Hz), 68.4, 66.4 (d, *J* = 10.55 Hz), 66.0; MS (ESI) *m/z* 317 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{O}_5\text{F}$ : C, 61.22; H, 5.14. Found: C, 60.96; H, 5.36.

**(2S,5R)-1-O-Benzoyl-5,6-dihydroxyl-3E-fluoro-2-hydroxyl-2-ethynyl-3-hexene (12)**. Using the same procedure described for compound **11**, compound **10** (1.44 g, 2.76 mmol) was deprotected by TBAF (1.0 M in THF, 8.28 mL, 8.28 mmol) and HOAc (0.17 g, 2.8 mmol) to give compound **12** (0.79 g, 97.3% yield) as a yellowish oil:  $[\alpha]^{23}_D +8.43$  (*c* 0.27, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.05 (m, 2H), 7.58 (m, 1H), 7.44 (m, 2H), 5.66 (s, 1H), 5.45 (dd, 1H, *J* = 8.05, 24.41 Hz), 4.92 (s, 1H), 4.61 (m, 2H), 3.88 (d, 1H, *J* = 11.35 Hz), 3.60 (m, 1H), 3.52 (m, 1H), 2.66 (d, 1H, *J* = 1.71 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  166.5, 157.4 (d, *J* = 259.87 Hz), 133.6, 129.9, 129.3, 128.6, 109.6 (d, *J* = 21.10 Hz), 80.3, 75.1, 70.0 (d, *J* = 34.52 Hz), 68.3, 66.1 (d, *J* = 10.55 Hz), 66.0; MS (ESI) *m/z* 295 ( $\text{MH}$ )<sup>+</sup>, 317 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{O}_5\text{F}$ : C, 61.22; H, 5.14. Found: C, 61.11; H, 5.36.

**2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl-5-O-benzoyl-1-O-acetyl-D-furanose (15)**. To a solution of compound **11** (1.44 g, 4.90 mmol) in 24 mL of EtOH was added dropwise a suspension of sodium periodate (2.52 g, 11.77 mmol) in 20 mL of water. The suspension mixture was stirred at room temperature for 30 min, and then EtOAc and water were added. The organic layer was separated and dried over  $\text{Na}_2\text{SO}_4$ . After removal of the solvent, the residue was purified by a short silica gel column (hexanes/EtOAc, 6:1) to give compound **13** (1.18 g, 91.9% yield) as a yellowish oil, which was not stable enough.

Compound **13** (1.18 g, 4.50 mmol) was stirred with acetic anhydride (11.8 mL) and dry pyridine (30 mL) at room temperature for 3 h. Then ice-water (20 mL) was added, and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  several times. The organic layers were combined, washed sequentially with saturated  $\text{NaHCO}_3$  solution, saturated  $\text{CuSO}_4$  solution, and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. Chromatography of the crude product in 10% hexanes/EtOAc gave the intermediate **15** (1.16 g, 84.8%) as a yellowish oil:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.14–7.27 (m, 5H), 6.86–6.79 (m, 1H), 5.50, 5.47 (2 × s, 1H), 4.82–4.44 (m, 2H), 2.80, 2.72 (2 × s, 1H), 2.13, 1.73 (2 × s, 3H); MS (ESI) *m/z* 327 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{O}_5\text{F}$ : C, 63.16; H, 4.31. Found: C, 63.24; H, 4.35.

**2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl-5-O-benzoyl-1-O-acetyl-L-furanose (16)**. Using the same procedure described for compound **15**, a solution of compound **12** (1.17 g, 3.98 mmol) in 21 mL of EtOH was oxidized by sodium periodate (2.07 g, 9.67 mmol) in water (16 mL) to give compound **14** (0.95 g, 3.63 mmol, 91.1% yield) as a yellowish oil, which was then stirred with acetic anhydride (9.5 mL) and dry pyridine (20 mL) at room temperature for 3 h to give compound **16** (0.94 g, 85.2% yield) as yellowish syrup:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.12–7.26 (m, 5H), 6.85–6.78 (m, 1H), 5.49, 5.46 (2 × s, 1H), 4.81–4.43 (m, 2H), 2.80, 2.72 (2 × s, 1H), 2.11, 1.72 (2 × s, 3H); MS (ESI) *m/z* 327 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{O}_5\text{F}$ : C, 63.16; H, 4.31. Found: C, 63.09; H, 4.41.

**General Procedure for Condensation of Acetate 15 or 16 with Heterocyclic Bases.** *N,O*-Bis(trimethylsilyl)acetamide was added at room temperature to a solution of the heterocyclic base in anhydrous acetonitrile under argon atmosphere. The resulting mixture was then stirred at 50–60 °C for 2 h under argon atmosphere to form a clear solution. After being cooled to room temperature, a solution of the acetate **15** or **16** in dry acetonitrile was added followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf), and the mixture was stirred at room temperature under argon atmo-

sphere until the acetate was consumed (detected by TLC). The reaction was subsequently quenched with saturated aqueous  $\text{NaHCO}_3$  solution and stirred until the evolution of  $\text{CO}_2$  ceased. The resulting mixture was diluted with ethyl acetate, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was subjected to silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) to give the D- or L-  $\alpha$  and  $\beta$  anomers of the protected nucleosides.

**1-(5-O-Benzoyl-2,3-dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -D-furanosyl)thymine (17) and Its  $\alpha$ -Isomer (19)**. A mixture of silylated thymine [prepared from 0.13 g (1.03 mmol) of thymine and 0.7 mL of *N,O*-bis(trimethylsilyl)acetamide (2.84 mmol)], **15** (0.24 g, 0.79 mmol), and TMSOTf (0.16 mL, 0.86 mmol) in 10 mL of acetonitrile was stirred under an argon atmosphere at room temperature for 1 h. After extractive workup, purification by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) gave  $\beta$  anomer **17** (0.16 g, 54.7% yield) as white needles and  $\alpha$ -anomer **19** (0.053 g, 18.1%) as a white solid.

Compound **17**: mp 189.5–191.0 °C;  $[\alpha]^{23}_D +37.36$  (*c* 0.4, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.05 (bs, 1H), 8.02 (m, 2H), 7.63 (m, 1H), 7.49 (m, 2H), 7.09 (m, 2H), 5.47 (s, 1H), 4.84 (d, 1H, *J* = 12.69 Hz), 4.54 (d, 1H, *J* = 12.69 Hz), 2.76 (s, 1H), 1.57 (s, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  165.3, 162.8, 159.5 (d, *J* = 293.20 Hz), 150.1, 134.4, 133.9, 129.7, 129.1, 128.9, 112.0, 101.3 (d, *J* = 9.67 Hz), 84.7 (d, *J* = 13.69 Hz), 65.0, 11.5; MS (ESI) *m/z* 371 ( $\text{MH}$ )<sup>+</sup>, 393 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_5\text{F}$ : C, 61.62; H, 4.08; N, 7.56. Found: C, 61.32; H, 4.20; N, 7.27.

Compound **19**: mp 72.0–72.9 °C;  $[\alpha]^{23}_D +138.23$  (*c* 0.31, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  9.53 (m, 1H), 8.03 (d, 2H, *J* = 7.81 Hz), 7.60 (m, 2H), 7.46 (m, 2H), 7.05 (d, 1H, *J* = 2.91 Hz), 5.48 (s, 1H), 4.62 (m, 2H), 2.94 (s, 1H), 1.95 (s, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  165.4, 163.9, 158.9 (d, *J* = 292.47 Hz), 150.6, 134.9, 133.7, 129.8, 129.0, 128.7, 112.2, 101.5 (d, *J* = 9.59 Hz), 85.8 (d, *J* = 13.43 Hz), 78.8, 78.3 (d, *J* = 24.93 Hz), 77.0, 65.0, 12.7; MS (ESI) *m/z* 371 ( $\text{MH}$ )<sup>+</sup>, 393 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_5\text{F}$ : C, 61.62; H, 4.08; N, 7.56. Found: C, 61.65; H, 4.13; N, 7.32.

**1-(5-O-Benzoyl-2,3-dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -D-furanosyl)-*N*<sup>4</sup>-benzoylcytosine (18) and Its  $\alpha$ -Isomer (20)**. Silylated *N*<sup>4</sup>-benzoylcytosine [prepared from 0.24 g (1.04 mmol) of *N*<sup>4</sup>-benzoylcytosine and 0.72 mL of *N,O*-bis(trimethylsilyl)acetamide (2.92 mmol)], **15** (0.24 g, 0.79 mmol), and TMSOTf (0.16 mL, 0.86 mmol) in 10 mL of acetonitrile were reacted at room temperature under an argon atmosphere for 1 h. After extractive workup, isolation by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) afforded  $\beta$  anomer **18** (0.19 g, 52.4% yield) and  $\alpha$ -anomer **20** (0.065 g, 17.9%) as white solids.

Compound **18**: mp 90.5–91.7 °C;  $[\alpha]^{24}_D +25.85$  (*c* 0.3, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.59 (bs, 1H), 7.97 (d, 2H), 7.91 (bs, 1H), 7.86 (m, 2H), 7.63 (m, 2H), 7.51 (m, 4H), 7.10 (d, 1H, *J* = 4.88 Hz), 5.70 (s, 1H), 4.74 (m, 2H), 2.79 (d, 1H, *J* = 1.95 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  167.6, 165.3, 159.1 (d, *J* = 291.37 Hz), 144.2, 134.2, 133.6, 129.8, 129.2, 129.0, 127.8, 102.3 (d, *J* = 10.49 Hz), 87.6 (d, *J* = 15.29 Hz), 79.3, 79.0 (d, *J* = 24.93 Hz), 69.9, 65.1; MS (ESI) *m/z* 460 ( $\text{MH}$ )<sup>+</sup>, 482 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{25}\text{H}_{18}\text{N}_3\text{O}_5\text{F}$ : C, 65.36; H, 3.95; N, 9.15. Found: C, 65.45; H, 3.89; N, 9.02.

Compound **20**: mp 170.1–170.9 °C;  $[\alpha]^{23}_D +149.80$  (*c* 0.37, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.74 (bs, 1H), 8.10 (bs, 1H), 8.07 (m, 2H), 7.91 (m, 2H), 7.63 (m, 2H), 7.52 (m, 4H), 7.02 (t, 1H, *J* = 1.95 Hz), 5.75 (s, 1H), 4.77 (dd, 1H, *J* = 1.46, 12.20 Hz), 4.65 (dd, 1H, *J* = 1.46, 12.20 Hz), 2.99 (d, 1H, *J* = 1.95 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  168.2, 165.4, 158.4 (d, *J* = 290.55 Hz), 144.3, 134.8, 133.4, 129.8, 129.2, 128.9, 127.6, 102.6 (d, *J* = 10.49 Hz), 88.6 (d, *J* = 15.29 Hz), 79.3, 79.0 (d, *J* = 24.93 Hz), 67.9, 64.7; MS (ESI) *m/z* 460 ( $\text{MH}$ )<sup>+</sup>, 482 ( $\text{M} + \text{Na}$ )<sup>+</sup>. Anal. Calcd for  $\text{C}_{25}\text{H}_{18}\text{N}_3\text{O}_5\text{F}$ : C, 65.36; H, 3.95; N, 9.15. Found: C, 65.38; H, 3.96; N, 8.99.

**9-(5-O-Benzoyl-2,3-dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -D-furanosyl)-*N*<sup>6</sup>-isobutylryladenine (21) and**



**Its  $\alpha$ -Isomer (22).** Silylated  $N^6$ -isobutylryladenine [prepared from 0.36 g (1.18 mmol) of  $N^6$ -isobutylryladenine and 1.08 mL of  $N,O$ -bis(trimethylsilyl)acetamide (4.38 mmol)], **15** (0.36 g, 1.18 mmol), and TMSOTf (0.24 mL, 1.29 mmol) in 12 mL of acetonitrile were reacted at room temperature under an argon atmosphere for 12 h. After extractive workup, purification by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) afforded  $\beta$  anomer **21** (0.17 g, 32.1% yield) and  $\alpha$ -anomer **22** (0.18 g, 34.0%) as white solids.

Compound **21**: mp 98.5–99.3 °C;  $[\alpha]^{25}_{\text{D}} +13.30$  (*c* 0.23, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.70 (s, 1H), 8.60 (s, 1H), 8.03 (s, 1H), 7.86 (m, 2H), 7.56 (m, 1H), 7.42 (m, 2H), 7.16 (d, 1H, *J* = 3.42 Hz), 5.87 (s, 1H), 4.74 (d, 1H, *J* = 12.45 Hz), 4.67 (d, 1H, *J* = 12.45 Hz), 3.21 (m, 1H), 2.81 (s, 1H), 1.30 (d, 6H, *J* = 6.83 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  176.4, 165.6, 159.7 (d, *J* = 293.43 Hz), 153.2, 151.2, 149.6, 140.5, 133.9, 129.8, 128.8, 122.1, 101.0 (d, *J* = 10.55 Hz), 84.5 (d, *J* = 13.43 Hz), 79.1 (d, *J* = 23.97 Hz), 77.7, 68.4, 65.2, 36.3, 19.4; MS (ESI) *m/z* 450 (MH)<sup>+</sup>, 472 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_5\text{O}_4\text{F}\cdot 1.1\text{H}_2\text{O}$ : C, 58.87; H, 4.77; N, 14.92. Found: C, 58.84; H, 4.30; N, 14.80.

Compound **22**: mp 81.1–82.6 °C;  $[\alpha]^{24}_{\text{D}} +162.15$  (*c* 0.25, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.73 (s, 1H), 8.58 (s, 1H), 8.29 (s, 1H), 8.06 (m, 2H), 7.63 (m, 1H), 7.50 (m, 2H), 7.15 (dd, 1H, *J* = 3.91, 1.46 Hz), 5.74 (s, 1H), 4.73 (d, 1H, *J* = 12.20 Hz), 4.66 (d, 1H, *J* = 12.20 Hz), 3.17 (m, 1H), 2.89 (s, 1H), 1.32 (d, 6H, *J* = 6.83 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  176.0, 165.4, 159.8 (d, *J* = 292.47 Hz), 153.1, 151.1, 149.5, 140.6, 133.7, 129.8, 128.7, 122.2, 101.0 (d, *J* = 10.55 Hz), 83.9 (d, *J* = 13.43 Hz), 78.9, 78.4 (d, *J* = 24.93 Hz), 68.2, 64.6, 36.3, 19.2; MS (ESI) *m/z* 450 (MH)<sup>+</sup>, 472 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_5\text{O}_4\text{F}\cdot 0.6\text{H}_2\text{O}$ : C, 60.02; H, 4.64; N, 15.22. Found: C, 60.18; H, 4.59; N, 14.96.

**1-(5-*O*-Benzoyl-2,3-dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -L-furanosyl)thymine (26) and Its  $\alpha$ -Isomer (28).** A mixture of silylated thymine [prepared from 0.13 g (1.03 mmol) of thymine and 0.7 mL of  $N,O$ -bis(trimethylsilyl)acetamide (2.84 mmol)], **16** (0.24 g, 0.79 mmol), and TMSOTf (0.16 mL, 0.86 mmol) in 10 mL of acetonitrile was stirred under an argon atmosphere at room temperature for 1 h. After extractive workup, purification by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) gave  $\beta$  anomer **26** (0.16 g, 54.7% yield) as white needles and  $\alpha$ -anomer **28** (0.057 g, 19.5%) as a white solid.

Compound **26**: mp 191.1–191.6 °C;  $[\alpha]^{23}_{\text{D}} -36.57$  (*c* 0.4, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.05 (bs, 1H), 8.02 (m, 2H), 7.63 (m, 1H), 7.49 (m, 2H), 7.09 (m, 2H), 5.47 (s, 1H), 4.84 (d, 1H, *J* = 12.69 Hz), 4.54 (d, 1H, *J* = 12.69 Hz), 2.76 (s, 1H), 1.57 (s, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  165.3, 162.8, 159.5 (d, *J* = 293.20 Hz), 150.1, 134.4, 133.9, 129.7, 129.1, 128.9, 112.0, 101.3 (d, *J* = 9.67 Hz), 84.7 (d, *J* = 13.69 Hz), 65.0, 11.5; MS (ESI) *m/z* 371 (MH)<sup>+</sup>, 393 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_5\text{F}$ : C, 61.62; H, 4.08; N, 7.56. Found: C, 61.60; H, 4.25; N, 7.34.

Compound **28**: mp 71.6–73.0 °C;  $[\alpha]^{27}_{\text{D}} -139.11$  (*c* 1.41, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  9.53 (m, 1H), 8.03 (d, 2H, *J* = 7.81 Hz), 7.60 (m, 2H), 7.46 (m, 2H), 7.05 (d, 1H, *J* = 2.91 Hz), 5.48 (s, 1H), 4.62 (m, 2H), 2.94 (s, 1H), 1.95 (s, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  165.4, 163.9, 158.9 (d, *J* = 292.47 Hz), 150.6, 134.9, 133.7, 129.8, 129.0, 128.7, 112.2, 101.5 (d, *J* = 9.59 Hz), 85.8 (d, *J* = 13.43 Hz), 78.8, 78.3 (d, *J* = 24.93 Hz), 77.0, 65.0, 12.7; MS (ESI) *m/z* 371 (MH)<sup>+</sup>, 393 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_5\text{F}$ : C, 61.62; H, 4.08; N, 7.56. Found: C, 61.65; H, 4.25; N, 7.36.

**1-(5-*O*-Benzoyl-2,3-dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -L-furanosyl)- $N^4$ -benzoylcytosine (27) and Its  $\alpha$ -Isomer (29).** Silylated  $N^4$ -benzoylcytosine [prepared from 0.24 g (1.04 mmol) of  $N^4$ -benzoylcytosine and 0.72 mL of  $N,O$ -bis(trimethylsilyl)acetamide (2.92 mmol)], **16** (0.24 g, 0.79 mmol), and TMSOTf (0.16 mL, 0.86 mmol) in 10 mL of acetonitrile were reacted at room temperature under an argon atmosphere for 1 h. After extractive workup, isolation by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) afforded

$\beta$  anomer **27** (0.19 g, 52.4% yield) and  $\alpha$ -anomer **29** (0.063 g, 17.4%) as white solids.

Compound **27**: mp 90.9–91.6 °C;  $[\alpha]^{23}_{\text{D}} -26.47$  (*c* 0.2, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.59 (bs, 1H), 7.97 (d, 2H), 7.91 (bs, 1H), 7.86 (m, 2H), 7.63 (m, 2H), 7.51 (m, 4H), 7.10 (d, 1H, *J* = 4.88 Hz), 5.70 (s, 1H), 4.74 (m, 2H), 2.79 (d, 1H, *J* = 1.95 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  167.7, 165.3, 159.1 (d, *J* = 291.30 Hz), 144.2, 134.2, 133.7, 129.9, 129.2, 129.0, 128.7, 127.8, 102.6 (d, *J* = 10.49 Hz), 87.6 (d, *J* = 15.29 Hz), 79.3, 79.0 (d, *J* = 24.93 Hz), 69.8, 66.1; MS (ESI) *m/z* 460 (MH)<sup>+</sup>, 482 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{25}\text{H}_{18}\text{N}_3\text{O}_5\text{F}$ : C, 65.36; H, 3.95; N, 9.15. Found: C, 65.19; H, 3.93; N, 9.05.

Compound **29**: mp 170.5–172.6 °C;  $[\alpha]^{25}_{\text{D}} -148.65$  (*c* 1.31, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.74 (bs, 1H), 8.10 (bs, 1H), 8.07 (m, 2H), 7.91 (m, 2H), 7.63 (m, 2H), 7.52 (m, 4H), 7.02 (t, 1H, *J* = 1.95 Hz), 5.75 (s, 1H), 4.77 (dd, 1H, *J* = 1.46, 12.20 Hz), 4.65 (dd, 1H, *J* = 1.46, 12.20 Hz), 2.99 (d, 1H, *J* = 1.95 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  168.1, 165.4, 158.4 (d, *J* = 290.55 Hz), 144.3, 134.8, 133.4, 129.8, 129.2, 128.9, 128.8, 127.6, 102.7 (d, *J* = 10.49 Hz), 88.6 (d, *J* = 15.29 Hz), 79.3, 79.0 (d, *J* = 24.93 Hz), 67.9, 64.7; MS (ESI) *m/z* 460 (MH)<sup>+</sup>, 482 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{25}\text{H}_{18}\text{N}_3\text{O}_5\text{F}$ : C, 65.36; H, 3.95; N, 9.15. Found: C, 65.14; H, 3.83; N, 9.17.

**9-(5-*O*-Benzoyl-2,3-dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -L-furanosyl)- $N^6$ -isobutylryladenine (30) and Its  $\alpha$ -Isomer (31).** Silylated  $N^6$ -isobutylryladenine [prepared from 0.36 g (1.18 mmol) of  $N^6$ -isobutylryladenine and 1.08 mL of  $N,O$ -bis(trimethylsilyl)acetamide (4.38 mmol)], **16** (0.36 g, 1.18 mmol), and TMSOTf (0.24 mL, 1.29 mmol) in 12 mL of acetonitrile were reacted at room temperature under an argon atmosphere for 12 h. After extractive workup, purification by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 100:1) afforded  $\beta$  anomer **30** (0.17 g, 32.1% yield) and  $\alpha$ -anomer **31** (0.16 g, 30.2% yield) as white solids.

Compound **30**: mp 98.3–99.6 °C;  $[\alpha]^{23}_{\text{D}} -13.37$  (*c* 0.53, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.70 (s, 1H), 8.60 (s, 1H), 8.03 (s, 1H), 7.86 (m, 2H), 7.56 (m, 1H), 7.42 (m, 2H), 7.16 (d, 1H, *J* = 3.42 Hz), 5.87 (s, 1H), 4.74 (d, 1H, *J* = 12.45 Hz), 4.67 (d, 1H, *J* = 12.45 Hz), 3.21 (m, 1H), 2.81 (s, 1H), 1.30 (d, 6H, *J* = 6.83 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  176.4, 165.6, 159.7 (d, *J* = 293.43 Hz), 153.2, 151.2, 149.6, 140.5, 133.9, 129.8, 128.8, 122.1, 101.0 (d, *J* = 10.55 Hz), 84.5 (d, *J* = 13.43 Hz), 79.1 (d, *J* = 23.97 Hz), 77.7, 68.4, 65.2, 36.3, 19.4; MS (ESI) *m/z* 450 (MH)<sup>+</sup>, 472 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_5\text{O}_4\text{F}\cdot 1.2\text{H}_2\text{O}$ : C, 58.64; H, 4.79; N, 14.87. Found: C, 58.69; H, 4.72; N, 14.61.

Compound **31**: mp 81.5–83.2 °C;  $[\alpha]^{28}_{\text{D}} -161.52$  (*c* 1.21, acetone);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.73 (s, 1H), 8.58 (s, 1H), 8.29 (s, 1H), 8.06 (m, 2H), 7.63 (m, 1H), 7.50 (m, 2H), 7.15 (dd, 1H, *J* = 3.91, 1.46 Hz), 5.74 (s, 1H), 4.73 (d, 1H, *J* = 12.20 Hz), 4.66 (d, 1H, *J* = 12.20 Hz), 3.17 (m, 1H), 2.89 (s, 1H), 1.32 (d, 6H, *J* = 6.83 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  176.0, 165.4, 159.8 (d, *J* = 292.47 Hz), 153.1, 151.1, 149.5, 140.6, 133.7, 129.8, 128.7, 122.2, 101.0 (d, *J* = 10.55 Hz), 83.9 (d, *J* = 13.43 Hz), 78.9, 78.4 (d, *J* = 24.93 Hz), 68.2, 64.6, 36.3, 19.2; MS (ESI) *m/z* 450 (MH)<sup>+</sup>, 472 (M + Na)<sup>+</sup>. Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_5\text{O}_4\text{F}\cdot 0.9\text{H}_2\text{O}$ : C, 59.33; H, 4.72; N, 15.04. Found: C, 59.50; H, 4.56; N, 14.67.

**1-(2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -D-furanosyl)thymine (23).** Compound **17** (120 mg, 0.32 mmol) was stirred in saturated methanolic ammonia solution (30 mL) at room temperature overnight. Upon completion, the solvent was removed under reduced pressure by rotary evaporation. The resulting syrup was purified on a silica gel column ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 20:1) to afford pure free nucleoside **23** (78 mg, 90.5%) as a white solid: mp 195.0–196.2 °C;  $[\alpha]^{24}_{\text{D}} -90.83$  (*c* 0.7,  $\text{CH}_3\text{OH}$ );  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  7.84 (s, 1H), 7.00 (dd, 1H, *J* = 4.34, 1.07 Hz), 5.57 (s, 1H), 3.83 (d, 1H, *J* = 12.52 Hz), 3.72 (d, 1H, *J* = 12.52 Hz), 3.22 (s, 1H), 1.84 (s, 3H);  $^{13}\text{C NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  165.3, 160.1 (d, *J* = 287.55 Hz), 151.5, 137.4, 110.3, 101.0 (d, *J* = 10.74 Hz), 84.9 (d, *J* = 15.34 Hz), 80.7 (d, *J* = 23.77 Hz), 78.0, 76.6, 64.0, 11.3; UV ( $\text{CH}_3\text{OH}$ )  $\lambda_{\text{max}}$  262.0 nm ( $\epsilon$  21280); MS (ESI) *m/z* 267 (MH)<sup>+</sup>, 289 (M + Na)<sup>+</sup>. Anal. Calcd

for  $C_{12}H_{11}N_2O_4F$ : C, 54.14; H, 4.16; N, 10.52. Found: C, 53.91; H, 4.28; N, 10.33.

**1-(2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -D-furanosyl)cytosine (24).** Conversion of **18** (150 mg, 0.33 mmol) to **24** was accomplished by using the same procedure as described for **17**. The obtained residue was purified by a flash silica gel column chromatography with 10% MeOH in  $CH_2Cl_2$  to give **24** (74 mg, 89.3%) as a white solid: mp 219.3–219.6 °C dec;  $[\alpha]^{23}_D -88.37$  (*c* 0.3,  $CH_3OH$ );  $^1H$  NMR ( $CD_3OD$ )  $\delta$  8.01 (d, 1H, *J* = 7.44 Hz), 7.07 (d, 1H, *J* = 4.70 Hz), 5.86 (d, 1H, *J* = 7.44 Hz), 5.86 (s, 1H), 3.81 (d, 1H, *J* = 12.70 Hz), 3.71 (d, 1H, *J* = 12.70 Hz), 3.22 (s, 1H);  $^{13}C$  NMR ( $CD_3OD$ )  $\delta$  166.6, 159.9 (d, *J* = 288.63 Hz), 157.3, 142.3, 101.4 (d, *J* = 9.59 Hz), 95.2, 85.9 (d, *J* = 15.38 Hz), 80.7, 78.2, 76.5, 64.0; UV ( $CH_3OH$ )  $\lambda_{max}$  238.0 nm ( $\epsilon$  11 370), 268.0 nm ( $\epsilon$  10 893); MS (ESI) *m/z* 252 (MH)<sup>+</sup>, 274 (M + Na)<sup>+</sup>. Anal. Calcd for  $C_{11}H_{10}N_3O_3F \cdot 0.25H_2O$ : C, 51.66; H, 4.14; N, 16.43. Found: C, 52.05; H, 4.14; N, 16.05.

**9-(2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -D-furanosyl)adenine (25).** Compound **25** was prepared on a 0.35 mmol scale following the same procedure used for compound **17**. Purification on silica gel using 5% MeOH in  $CH_2Cl_2$  as eluent gave **25** (88.3%) as a white solid.

Compound **25**: mp 168.3–169.4 °C;  $[\alpha]^{27}_D -136.61$  (*c* 0.33,  $CH_3OH$ );  $^1H$  NMR ( $CD_3OD$ )  $\delta$  8.35 (s, 1H), 8.20 (s, 1H), 7.10 (d, 1H, *J* = 4.39 Hz), 5.82 (s, 1H), 3.85 (d, 1H, *J* = 12.69 Hz), 3.74 (d, 1H, *J* = 12.69 Hz), 3.29 (s, 1H);  $^{13}C$  NMR ( $CD_3OD$ )  $\delta$  160.1 (d, *J* = 288.64 Hz), 156.3, 152.8, 149.3, 140.3, 119.0, 110.9 (d, *J* = 10.55 Hz), 84.2 (d, *J* = 14.38 Hz), 81.7, 81.5, 77.4, 64.4; UV ( $CH_3OH$ )  $\lambda_{max}$  258.0 nm ( $\epsilon$  14 252); MS (ESI) *m/z* 276 (MH)<sup>+</sup>, 298 (M + Na)<sup>+</sup>. Anal. Calcd for  $C_{12}H_{10}N_2O_2F \cdot 0.2H_2O$ : C, 51.69; H, 3.76; N, 25.12. Found: C, 52.02; H, 3.66; N, 24.82.

**1-(2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -L-furanosyl)thymine (32).** Using the same procedure described for compound **17**, compound **26** (100 mg, 0.27 mmol) was treated with the ammoniac saturated methanol (30 mL) at room-temperature overnight to give compound **32** (64 mg, 89.1%) as a white solid after flash column chromatography ( $CH_2Cl_2/MeOH$ , 20:1).

Compound **32**: mp 195.2–196.7 °C;  $[\alpha]^{23}_D +89.84$  (*c* 0.95,  $CH_3OH$ );  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.85 (d, 1H, *J* = 1.22 Hz), 7.00 (dd, 1H, *J* = 1.46, 4.64 Hz), 5.57 (d, 1H, *J* = 1.46 Hz), 3.83 (d, 1H, *J* = 12.69 Hz), 3.72 (dd, 1H, *J* = 12.69 Hz), 3.23 (s, 1H), 1.84 (d, 3H, *J* = 1.22 Hz);  $^{13}C$  NMR ( $CD_3OD$ )  $\delta$  165.3, 160.1 (d, *J* = 287.54 Hz), 151.5, 137.4, 110.3, 101.0 (d, *J* = 10.74

Hz), 84.9 (d, *J* = 15.34 Hz), 80.7 (d, *J* = 23.77 Hz), 78.1, 76.6, 64.1, 11.3; UV ( $CH_3OH$ )  $\lambda_{max}$  262.5 nm ( $\epsilon$  21 466); MS (ESI) *m/z* 267 (MH)<sup>+</sup>, 289 (M + Na)<sup>+</sup>. Anal. Calcd for  $C_{12}H_{11}N_2O_4F$ : C, 54.14; H, 4.16; N, 10.52. Found: C, 54.24; H, 4.16; N, 10.54.

**1-(2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -L-furanosyl)cytosine (33).** Conversion of **27** (120 mg, 0.26 mmol) to **33** was accomplished by using the same procedure as described for **17**. The obtained residue was purified by a flash silica gel column chromatography with 10% MeOH in  $CH_2Cl_2$  to give **33** (59 mg, 90.4%) as a white solid.

Compound **33**: mp 218.7–219.5 °C dec;  $[\alpha]^{23}_D 89.188$  (*c* 0.25,  $CH_3OH$ );  $^1H$  NMR ( $CD_3OD$ )  $\delta$  8.01 (d, 1H, *J* = 7.44 Hz), 7.07 (d, 1H, *J* = 4.70 Hz), 5.86 (d, 1H, *J* = 7.44 Hz), 5.86 (s, 1H), 3.81 (d, 1H, *J* = 12.70 Hz), 3.71 (d, 1H, *J* = 12.70 Hz), 3.22 (s, 1H);  $^{13}C$  NMR ( $CD_3OD$ )  $\delta$  166.6, 159.9 (d, *J* = 288.63 Hz), 157.3, 142.3, 101.4 (d, *J* = 9.59 Hz), 95.2, 85.9 (d, *J* = 15.38 Hz), 80.7, 78.2, 76.5, 64.0; UV ( $CH_3OH$ )  $\lambda_{max}$  238.0 nm ( $\epsilon$  11 395), 268.0 nm ( $\epsilon$  10 868); MS (ESI) *m/z* 252 (MH)<sup>+</sup>, 274 (M + Na)<sup>+</sup>. Anal. Calcd for  $C_{11}H_{10}N_3O_3F \cdot 0.2H_2O$ : C, 51.85; H, 4.11; N, 16.49. Found: C, 51.73; H, 4.08; N, 16.21.

**9-(2,3-Dideoxy-2,3-didehydro-3-fluoro-4-ethynyl- $\beta$ -L-furanosyl)adenine (34).** Compound **34** was prepared on a 0.30 mmol scale following the same procedure used for compound **17**. Purification on silica gel using 5% MeOH in  $CH_2Cl_2$  as eluent gave **34** (73 mg, 88.5%) as a white solid.

Compound **34**: mp 168.8–169.5 °C;  $[\alpha]^{24}_D +134.67$  (*c* 0.42,  $CH_3OH$ );  $^1H$  NMR ( $CD_3OD$ )  $\delta$  8.35 (s, 1H), 8.20 (s, 1H), 7.10 (d, 1H, *J* = 4.39 Hz), 5.82 (s, 1H), 3.85 (d, 1H, *J* = 12.69 Hz), 3.74 (d, 1H, *J* = 12.69 Hz), 3.29 (s, 1H);  $^{13}C$  NMR ( $CD_3OD$ )  $\delta$  160.1 (d, *J* = 288.64 Hz), 156.3, 152.8, 149.3, 140.3, 119.0, 110.9 (d, *J* = 10.55 Hz), 84.2 (d, *J* = 14.38 Hz), 81.7, 81.5, 77.4, 64.4; UV ( $CH_3OH$ )  $\lambda_{max}$  258.5 nm ( $\epsilon$  14 261); MS (ESI) *m/z* 276 (MH)<sup>+</sup>, 298 (M + Na)<sup>+</sup>. Anal. Calcd for  $C_{12}H_{10}N_2O_2F$ : C, 52.37; H, 3.66; N, 25.44. Found: C, 52.51; H, 3.66; N, 25.49.

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**Supporting Information Available:**  $^1H$  NMR and  $^{13}C$  NMR for compounds **2**, **5–11**, and **17–34** and  $^1H$  NMR for the mixture *E-4/Z-4*. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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