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# Design, synthesis, and biological evaluation of novel iso-D-2',3'-dideoxy-3'-fluorothianucleoside derivatives

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**Abstract**—Novel iso-D-2',3'-dideoxythianucleoside derivatives **1–4** were designed and asymmetrically synthesized as a bioisostere of lamivudine to search for new anti-HIV agents. The information about using sulfur participation occurred on DAST fluorination and Mitsunobu reaction will be of great help in synthesizing sulfur-containing compounds. Final compounds **1–4** were evaluated against HIV-1 and 2, HSV-1 and 2, EMCV, Cox. B3, VSV, FluA (Taiwan), FluA (Johan.), FCV, and FIP. Only cytosine analogue **3** showed a potent anti-VSV activity ( $EC_{50} = 9.43 \mu\text{g/mL}$ ). This result implies that iso-2',3'-dideoxy sugar templates might play a role of a sugar surrogate of nucleosides for the development of anti-RNA virus agent.

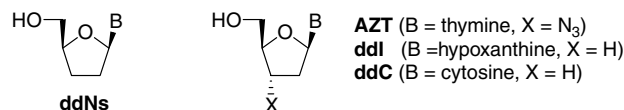
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## 1. Introduction

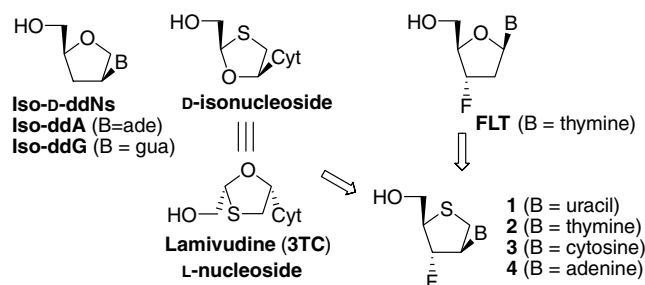
Since zidovudine (AZT)<sup>1</sup> has been known as a potent anti-human immunodeficiency virus (anti-HIV) agent, a number of nucleoside analogues have been designed, synthesized, and their antiviral activities were evaluated against a variety of viruses including HIV for the development of antiviral agents. Particularly, 2',3'-dideoxynucleosides (ddNs) have exhibited potent anti-HIV activity. Among them, didanosine (ddI),<sup>2</sup> zalcitabine (ddC),<sup>3</sup> and stavudine (d4T)<sup>4</sup> have been launched as drugs for the treatment of AIDS patients (Fig. 1). However, these 2',3'-ddNs have several drawbacks such as easy cleavage of their glycosidic bond under acidic conditions similar to a gastric environment and catabolism by adenosine deaminase (ADA), adenosine-5'-monophosphate (AMP) deaminase, and purine nucleoside phosphorylase (PNP).

Also, lamivudine (3TC)<sup>5</sup> has been clinically used for the treatment of AIDS and HBV (hepatitis B virus) infec-

tion (Fig. 2). Structural characteristics of lamivudine are that there is no hydroxyl substituent at both its 2'- and 3'-positions like 2',3'-ddN analogues and are two heteroatoms on the sugar moiety. In addition, lamivudine belongs to L-nucleoside unlike other anti-AIDS



**Figure 1.** The general structure of 2',3'-dideoxynucleosides and representative HIV drugs.



**Figure 2.** The rationale for the design of the desired nucleosides **1–4**.

**Keywords:** Iso-D-2',3'-dideoxythianucleosides; Lamivudine; Anti-VSV activity; Sulfur participation; Bioisostere; Mitsunobu reaction.

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drugs. Isonucleosides<sup>6</sup> in which their base is moved into C2'-position from anomeric position have been synthesized and evaluated for anti-HIV activity. Among them, iso-ddA and iso-ddG were found to be active against HIV-1 without cytotoxicity and this class of nucleosides were known to possess the intrinsic metabolic advantages such as resistance to ADA and enhanced stability of glycosidic bond under acidic and enzymatic conditions compared to natural nucleosides and 2',3'-ddNs including lamivudine.<sup>6a,7</sup>

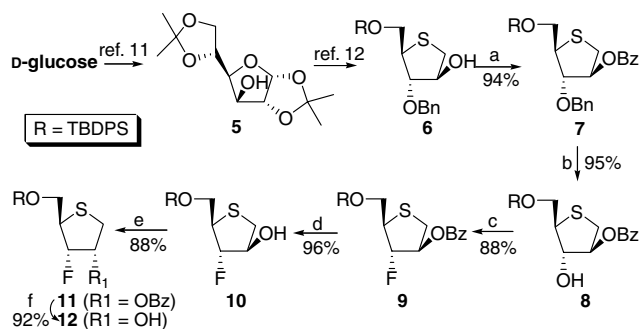
On the other hand, a fluorine atom has been used as a good bioisostere because many fluorinated nucleosides such as 2'-F-ddA,<sup>8</sup> 2'-F-ara-ddC,<sup>9</sup> and FLT<sup>10</sup> were found to exhibit significant antiviral activities. Furthermore, it is worthy to note that L-nucleoside analogues such as lamivudine can be considered as iso-D-nucleoside analogue as shown in Figure 2.

Therefore, as a part of our continuous efforts searching for novel antiviral agents, it was interesting to design and synthesize iso-D-2',3'-dideoxythianucleoside derivatives with a 3'-fluoro substituent and to evaluate them against various viruses because CH–F group might act as a bioisostere of sugar ring oxygen of lamivudine and/or as a hydrogen bonding acceptor at the active site of their target enzyme, and because the D-sugar skeleton of iso-D-2',3'-dideoxythianucleosides resembles L-1,3-oxathiolane ring of lamivudine. Here, we wish to report the asymmetric synthesis and biological activities of novel fluorinated iso-D-2',3'-dideoxythianucleosides **1–4**.

## 2. Results and discussion

### 2.1. Chemistry

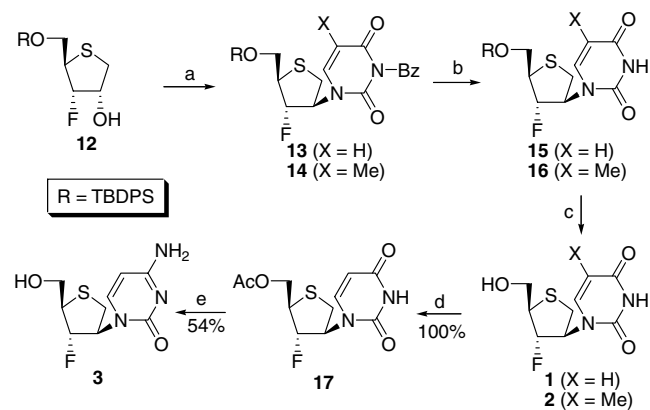
A strategy for the synthesis of glycone of iso-D-2',3'-dideoxy-3'-fluorothianucleosides is outlined in Scheme 1. It was envisioned that 1,4-anhydro-4-thioarabitol **6** derived from D-glucose via 1,2;5,6-di-O-isopropylidene-D-glucofuranose (**5**) could be an appropriate intermediate to synthesize D-4-fluoro-3-thiophenol **12**, which could be condensed with nucleobases to afford lamivudine analogues **1–4**.



**Scheme 1.** Reagents and conditions: (a) BzCl, DMAP, pyridine, 88 °C, 3 h; (b) BCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 40 min; (c) DAST, CH<sub>2</sub>Cl<sub>2</sub>, –10 °C, 30 min; (d) 1 M NaOMe, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, rt, 4 h; (e) BzOH, PPh<sub>3</sub>, DEAD, THF, 60 °C, 5 h; (f) 1 M NaOMe, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, rt, 7 h.

Diacetone glucose **5** was derived from D-glucose by the known one-pot synthesis method reported by Moravcova and his co-workers.<sup>11</sup> Compound **5** was converted into 1,4-anhydro-4-thioarabitol **6** according to the known procedure developed by Yoshimura and his co-workers over 10 steps.<sup>12</sup> Surprisingly, benzylation of compound **6** with benzoyl chloride, DMAP, and pyridine at room temperature was very slowly converted to the corresponding benzoate **7**. Elevated temperature (88 °C) completed the benzylation reaction in 3 h in 94% yield. Debenzylation of **7** with BCl<sub>3</sub> at –78 °C gave  $\alpha$  secondary alcohol **8** whose stereochemistry has the appropriate configuration to introduce  $\alpha$ -fluoro substituent when treated with (diethylamino)sulfur trifluoride (DAST). Fluorination of **8** with DAST gave the fluorinated compound **9** in 88% yield with the desired ' $\alpha$ ' stereochemistry through double inversion mechanism by the nucleophilic participation of the ring sulfur atom.<sup>13</sup> Removal of benzoyl group of **9** using cat. NaOMe in MeOH gave the corresponding alcohol **10** in nearly quantitative yield, which was used for coupling with benzoic acid under Mitsunobu conditions.<sup>14</sup> During Mitsunobu reaction the nucleophilic participation of sulfur atom occurred only to the extent of 3–5%. The major product **11** which underwent a single inversion was formed in 88% yield with its epimer (3–5%) at 3-position. The structures of major and minor product, **11** and its epimer, were confirmed by comparing <sup>1</sup>H NMR data of the corresponding alcohols generated from each epimer after debenylation with those of compound **10**. Debenzylation of **11** afforded the glycosyl donor **12**, which was ready for the condensation with nucleobases.

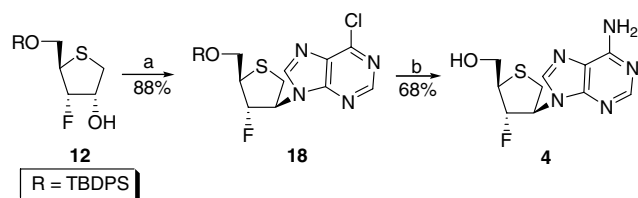
Synthesis of pyrimidine nucleoside analogues under Mitsunobu conditions is illustrated in Scheme 2. Coupling of **12** with N<sup>3</sup>-benzoyluracil and N<sup>3</sup>-benzoylthymine, PPh<sub>3</sub>, and DEAD gave the desired  $\beta$ -nucleosides **13** (62%) and **14** (66%), respectively. It is worthy to note that the participation of sulfur atom did not occur at all during coupling of glycosyl donor **12** with nucleobases. Deprotection of



**Scheme 2.** Reagents and conditions: (a) N<sup>3</sup>-benzoyl uracil or N<sup>3</sup>-benzoyl thymine, PPh<sub>3</sub>, DEAD, THF, rt, overnight, 62% for **13**, 66% for **14**; (b) 1 M NaOMe, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, rt, 6 h, 82% for **15**, overnight, 94% for **16**; (c) 1 M TBAF, THF, rt, 2 h, 97% for **1**, 98% for **2**; (d) Ac<sub>2</sub>O, pyridine, rt, overnight; (e) (i) 1,2,4-triazole, POCl<sub>3</sub>, pyridine, rt, overnight; (ii) 1,4-dioxane, 28% NH<sub>4</sub>OH, rt, overnight; (iii) NH<sub>3</sub>, MeOH, rt, overnight.

*N*-benzoyl group with 1 M NaOMe produced TBDPS-protected compounds **15** and **16** in 82% and 94% yield, respectively. Finally, treatment of **15** and **16** with TBAF gave the desired final compounds **1** and **2**, respectively. Confirmation of *N*-alkylated nucleosides **1** and **2** was determined by  $^{13}\text{C}$  value of anomeric carbon of each nucleoside.<sup>15</sup> Compound **1** was converted into lamivudine analogue, cytosine nucleoside **3**, via acetylation of the hydroxyl group followed by successive three conventional steps (1,2,4-triazole, POCl<sub>3</sub>, pyridine; 1,4-dioxane, NH<sub>4</sub>OH; NH<sub>3</sub>, MeOH)<sup>16</sup> in overall 54% yield.

Synthesis of adenine nucleoside analogue **4** is shown in Scheme 3. Whereas reaction of *D*-4-fluoro-3-thiophenol **12** with *N*<sup>6</sup>-benzoyladenine at room temperature for 2 d under Mitsunobu conditions (PPh<sub>3</sub> and DEAD) did not give a clear spot expected as the desired product on TLC, reaction with 6-chloropurine as a nucleobase instead of *N*<sup>6</sup>-benzoyladenine afforded the protected 6-chloropurine nucleoside **18** in 88% yield. Participation degree of sulfur atom on the sugar ring seems like depending on electron density on the sugar ring, ring strain of the generated episulfonium cation, and properties of nucleophile and leaving group. Mitsunobu reaction of fluorinated compounds (**10** and **12**) with benzoic acid or nucleobases might have difficulty in forming episulfonium cation because the sugar ring is already electron-poor by electron-withdrawing fluoro



**Scheme 3.** Reagents and conditions: (a) 6-chloropurine, PPh<sub>3</sub>, DEAD, rt, overnight; (b) NH<sub>3</sub>, MeOH, 80 °C, overnight.

group. Therefore, the major product was single inverted one (**11**, **13**, **14**, and **18**). On the other hand, in case of DAST reaction of compound **8** there is no strong electron-withdrawing group such as a fluorine atom on the sugar ring, implying that participation of the sulfur atom is expected and the major product is double inverted one (**9**). The remaining things are conversion of 6-chloropurine into adenine base and desilylation of TBDPS group in sequence. Surprisingly, treatment of compound **18** with methanolic ammonia at 80 °C overnight accomplished not only amination at 6-position of 6-chloropurine base but also desilylation of TBDPS group, giving the final product **4** in 68% yield.

## 2.2. Biological activity

Antiviral activities of all iso-*D*-2',3'-dideoxy-3'-fluoro-thianucleoside derivatives **1–4** synthesized as a bioisostere of lamivudine were measured against a variety of viruses such as HIV (human immunodeficiency virus) type 1 and 2, EMCV (encephalomyocarditis virus), Cox. B3 (Coxsackie B virus type 3), VSV (vesicular stomatitis virus), and HSV (herpes simplex virus) type 1 and 2 (Table 1). EC<sub>50</sub> of compounds **1**, **2**, and **4** exceeded 100 μg/mL and also did not show any cytotoxicity up to 100 μg/mL at all tested cells such as MT4, HeLa, and Vero cells. On the other hand, cytosine nucleoside derivative **3** exhibited potent anti-VSV activity (EC<sub>50</sub> = 9.43 μg/mL), whereas inactive (EC<sub>50</sub> > 100 μg/mL) and non-cytotoxic (CS<sub>50</sub> and CC<sub>50</sub> > 100 μg/mL) against the other viruses. However, selectivity index (SI) of **3** showed low value of 1.56 due to its high cytotoxicity (CC<sub>50</sub> = 14.54 μg/mL) in HeLa cell. It is very interesting that cytosine nucleoside analogue **3** designed as a bioisostere of lamivudine showed anti-VSV activity instead of the expected anti-HIV activity. Considering that VSV belongs to RNA virus, it is worthy to note that **3** classified into ddNs exhibited potent anti-VSV activity.

**Table 1.** Antiviral activities of the final compounds **1–4** against HIV type 1 and 2, EMCV, Cox. B3, VSV, and HSV type 1 and 2<sup>a</sup>

Compound	MT4 <sup>b</sup> CS <sub>50</sub> <sup>c</sup>	HIV (EC <sub>50</sub> )		HeLa <sup>f</sup> CC <sub>50</sub> <sup>g</sup>	Anti-RNA (EC <sub>50</sub> )			Vero <sup>k</sup> CC <sub>50</sub>	Anti-HSV (EC <sub>50</sub> )	
		IIIB <sup>d</sup>	ROD <sup>e</sup>		EMCV <sup>h</sup>	Cox.B3 <sup>i</sup>	VSV <sup>j</sup>		HSV-1 <sup>l</sup>	HSV-2 <sup>m</sup>
<b>1</b>	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
<b>2</b>	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
<b>3</b>	>100	>100	>100	14.54	>14.54	>14.54	9.43	>100	>100	>100
<b>4</b>	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Ribavirin				>300	23.45	64.09	10.32			
ddI	>100	6.62	16.00					>10	0.17	0.47

<sup>a</sup> The potency is given as an EC<sub>50</sub> (50% effective concentration, μg/mL) and evaluated by the degree of inhibition of virus-induced cytopathogenic effects (CPE).

<sup>b</sup> HTLV-1-infected human T-lymphocyte.

<sup>c</sup> 50% cytostatic concentration.

<sup>d</sup> Human immunodeficiency virus type 1 strain IIIB.

<sup>e</sup> Human immunodeficiency virus type 1 strain ROD.

<sup>f</sup> Human cervical carcinoma cell.

<sup>g</sup> 50% cytotoxic concentration.

<sup>h</sup> Encephalomyocarditis virus.

<sup>i</sup> Coxsackie B virus type 3.

<sup>j</sup> Vesicular stomatitis virus.

<sup>k</sup> African Green monkey kidney cell.

<sup>l</sup> Herpes simplex virus type 1.

<sup>m</sup> Herpes simplex virus type 2.

Antiviral evaluation of compounds **1–4** was also performed against FluA (influenza virus type A) (H1N1) strain Taiwan, FluA (H3N2) strain Johannesburg, FCV (Feline coronavirus) strain WSU, and FIP (Feline infectious peritonitis virus) strain WSU, but all compounds did not show antiviral activity and cytotoxicity up to 100  $\mu\text{g/mL}$  (not shown in Table 1).

### 3. Conclusion

We have designed and synthesized novel iso-D-2',3'-dideoxythianucleoside derivatives **1–4** as a bioisostere of lamivudine to search for new anti-HIV agents. Among compounds tested, only cytosine analogue **3** showed potent anti-VSV activity even if it pertains to ddNs classification and VSV is RNA virus. This observation implies that iso-D-2',3'-dideoxy sugar templates might act as a sugar surrogate of nucleosides for the development of anti-RNA virus agent. The information about participation of sulfur atom during fluorination reaction using DAST and Mitsunobu reaction will be of great help in synthesizing sulfur-containing compounds.

## 4. Experimental

### 4.1. General procedure

Melting points are uncorrected. Ultraviolet (UV) spectra were recorded on a JASCO V-530 UV/vis spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. NMR data were recorded on a Bruker AC200 and Varian Unity AS 500 spectrometer, using  $\text{CDCl}_3$ , or  $\text{CD}_3\text{OD}$  and chemical shifts were reported in parts per million (ppm) with reference to the respective residual solvent or deuteriated peaks ( $\delta_{\text{H}}$  3.30 and  $\delta_{\text{C}}$  49.0 for  $\text{CD}_3\text{OD}$ ,  $\delta_{\text{H}}$  7.26 and  $\delta_{\text{C}}$  77.0 for  $\text{CDCl}_3$ ). Coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), q (quartet), m (multiplet), dd (doublet of doublets), br s (broad singlet), ddd (doublet of doublets of doublets), or td (triplet of doublets). FAB mass spectra were recorded on Jeol HX 110 spectrometer. Elemental analyses were performed by the General Instrument Laboratory of Ewha Womans University, Korea. All the reactions described below were performed under nitrogen or argon atmosphere and monitored by thin-layer chromatography (TLC). TLC was performed on Merck precoated 60  $\text{F}_{254}$  plates. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). All anhydrous solvents were distilled over  $\text{CaH}_2$  or Na/benzophenone prior to use.

### 4.2. (+)-Benzoic acid (3*S*,4*S*,5*R*)-4-benzyloxy-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-thiophen-3-yl ester (**7**)

To a stirred solution of alcohol **6** (6.070 g, 12.68 mmol) and 4-dimethylaminopyridine (15 mg, 0.12 mmol) in anhydrous pyridine (30 mL) was dropwise added benzoyl chloride (1.62 mL, 13.96 mmol) at 0 °C and the reaction mixture was heated to 88 °C for 3 h. After the

volatiles were removed under reduced pressure, the resulting residue was partitioned between ethyl acetate and 0.5 M HCl aqueous solution, and the organic layer was washed with saturated  $\text{NaHCO}_3$  aqueous solution and brine successively, dried over  $\text{MgSO}_4$ , filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (15:1) as the eluent to give the corresponding benzoate **7** (6.927 g, 94%) as a colorless oil:  $[\alpha]_{\text{D}}^{25} +2.1$  ( $c$  1.58,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97–7.27 (m, 20H, 4 $\times$  Ar), 5.71 (td, 1 H,  $J = 3.0, 5.0$  Hz, 3-H), 4.73 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 4.47 (t, 1H,  $J = 3.0$  Hz, 4-H), 3.89 (dd, 1H,  $J = 8.5, 10.0$  Hz,  $\text{TBDPSOCHH}$ ), 3.77 (dd, 1H,  $J = 6.0, 10.5$  Hz,  $\text{TBDPSOCHH}$ ), 3.69 (ddd, 1H,  $J = 3.0, 6.5, 9.0$  Hz, 5-H), 3.46 (dd, 1H,  $J = 4.5, 12.0$  Hz,  $\text{SCHH}$ ), 3.04 (dd, 1H,  $J = 3.0, 12.0$  Hz,  $\text{SCHH}$ ), 1.60 (s, 9H, *t*-Bu);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.9, 138.0, 135.8, 135.7, 133.5, 133.5, 133.5, 130.0, 130.0, 129.9, 129.9, 128.7, 128.7, 128.1, 128.0, 127.9, 127.9, 85.2, 80.0, 72.2, 66.0, 53.3, 34.6, 27.0, 19.5; LRMS(FAB)  $m/z$  605 ( $\text{M}^+ + \text{Na}$ ); Anal. Calcd for  $\text{C}_{35}\text{H}_{38}\text{O}_4\text{Si}$ : C, 72.13; H, 6.57; S, 5.50. Found: C, 72.46; H, 6.71; S, 5.84.

### 4.3. (–)-Benzoic acid (3*S*,4*S*,5*R*)-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-hydroxy-tetrahydro-thiophen-3-yl ester (**8**)

To a stirred solution of benzoate **7** (6.927 g, 11.89 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (50 mL) was slowly added boron trichloride (28.5 mL, 28.50 mmol, 1 M solution in  $\text{CH}_2\text{Cl}_2$ ) at  $-78$  °C and the reaction mixture was stirred at the same temperature for 40 min. Pyridine (28.5 mL) and methanol (28.5 mL) were successively added and the reaction mixture was kept at room temperature for 1 h. The mixture was partitioned between methylene chloride and 0.5 M HCl aqueous solution, and the organic layer was washed with saturated  $\text{NaHCO}_3$  aqueous solution and brine successively, dried over  $\text{MgSO}_4$ , filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (5:1) as the eluent to give the corresponding alcohol **8** (5.570 g, 95%) as a colorless oil:  $[\alpha]_{\text{D}}^{25} -17.5$  ( $c$  0.87,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03–7.31 (m, 15H, 3 $\times$  Ar), 5.46 (q, 1H,  $J = 6.5$  Hz, 3-H), 4.47 (t, 1H,  $J = 6.0$  Hz, 4-H), 3.92 (irregular t, 1H,  $J = 8.5, 10.0$  Hz,  $\text{TBDPSOCHaHb}$ ), 3.84 (dd, 1H,  $J = 6.0, 10.0$  Hz,  $\text{TBDPSOCHaHb}$ ), 3.49 (br s, 1H,  $\text{SCHaHb}$ ), 3.35 (br s, 1H,  $\text{SCHaHb}$ ), 2.96 (br s, 1H, 5-H), 2.41 (br s, 1H, OH), 1.07 (s, 9H, *t*-Bu);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.2, 135.6, 135.5, 133.3, 132.9, 132.9, 129.9, 129.9, 129.8, 129.5, 128.4, 127.8, 127.8, 80.4, 79.4, 66.8, 50.6, 31.1, 26.8, 19.2; LRMS(ESI)  $m/z$  515 ( $\text{M} + \text{Na}$ ) $^+$ ; Anal. Calcd for  $\text{C}_{28}\text{H}_{32}\text{O}_4\text{Si}$ : C, 68.26; H, 6.55; S, 6.51. Found: C, 68.02; H, 6.42; S, 6.76.

### 4.4. (–)-Benzoic acid (3*S*,4*S*,5*R*)-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-fluoro-tetrahydro-thiophen-3-yl ester (**9**)

To a stirred solution of alcohol **8** (3.050 g, 6.19 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (20 mL) was dropwise added (dieth-

ylamino)sulfur trifluoride (DAST, 1.23 mL, 9.31 mmol) at  $-10^{\circ}\text{C}$  and the reaction mixture was stirred at the same temperature for 30 min. After saturated  $\text{NaHCO}_3$  aqueous solution was added, the reaction mixture was stirred for 5 min and partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The organic layer was dried over  $\text{MgSO}_4$ , filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (45:1) as the eluent to give the corresponding fluoro compound **9** (2.688 g, 88%) as a colorless oil:  $[\alpha]_{\text{D}}^{25} -22.9$  ( $c$  0.83,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98–7.30 (m, 15H, 3 $\times$  Ar), 5.76–5.70 (m, 1H, 3-H), 5.39 (td, 1H,  $J = 3.0$ , 49.0 Hz, 4-H), 3.93–3.89 (m, 1H,  $\text{CHaHbOTBDPS}$ ), 3.81–3.71 (m, 2H, 5-H and  $\text{CHaHbOTBDPS}$ ), 3.42 (ddd, 1H,  $J = 2.0$ , 5.5, 12.0 Hz,  $\text{SCHaCHb}$ ), 3.04 (dd, 1H,  $J = 4.0$ , 12.0 Hz,  $\text{SCHaCHb}$ ), 1.06 (s, 9H,  $t\text{-Bu}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.3, 135.5, 135.4, 133.4, 133.1, 133.0, 129.9, 129.8, 129.2, 128.5, 127.8, 127.7, 96.8 (d,  $J = 181.8$  Hz), 78.4 (d,  $J = 30.0$  Hz), 64.8 (d,  $J = 6.8$  Hz), 51.7 (d,  $J = 21.4$  Hz), 32.9 (d,  $J = 2.3$  Hz), 26.7, 19.2;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$   $-185.63$ ; LRMS(ESI)  $m/z$  517 ( $\text{M}+\text{Na}$ ) $^+$ ; Anal. Calcd for  $\text{C}_{28}\text{H}_{31}\text{FO}_3\text{SSi}$ : C, 67.98; H, 6.32; S, 6.48. Found: C, 67.88; H, 6.54; S, 6.41.

#### 4.5. (+)-(3*S*,4*S*,5*R*)-5-(*tert*-Butyl-diphenyl-silanyloxy methyl)-4-fluoro-tetrahydro-thiophen-3-ol (**10**)

To a stirred solution of fluoro compound **9** (2.655 g, 5.37 mmol) in methanol (7 mL) and  $\text{CH}_2\text{Cl}_2$  (3 mL) was added 1 M  $\text{NaOMe}$  (0.54 mL, 0.54 mmol) at  $0^{\circ}\text{C}$  and the reaction mixture was stirred for 4 h at room temperature. The mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  and water, dried over  $\text{MgSO}_4$ , filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (8:1) as the eluent to give the corresponding alcohol **8** (2.005 g, 96%) as a colorless oil:  $[\alpha]_{\text{D}}^{25} +34.9$  ( $c$  0.65,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74–7.40 (m, 10H, 2 $\times$  Ar), 5.02 (td, 1H,  $J = 2.0$ , 49.5 Hz, 4-H), 4.51–4.48 (m, 1H, 3-H), 3.87–3.84 (m, 1H,  $\text{CHaHbOTBDPS}$ ), 3.72–3.63 (m, 2H, 5-H and  $\text{CHaHbOTBDPS}$ ), 3.23 (br td, 1H,  $J = 3.5$ , 12.0 Hz,  $\text{SCHaCHb}$ ), 2.99 (br d, 1H,  $\text{SCHaCHb}$ ), 1.09 (s, 9H,  $t\text{-Bu}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  135.8, 135.6, 132.4, 132.1, 130.0, 130.0, 127.9, 127.9, 100.1 (d,  $J = 182.3$  Hz), 76.3 (d,  $J = 27.4$  Hz), 64.6 (d,  $J = 9.1$  Hz), 53.1 (d,  $J = 22.9$  Hz), 37.8, 26.7, 19.2;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$   $-178.32$ ; LRMS(ESI)  $m/z$  413 ( $\text{M}+\text{Na}$ ) $^+$ ; Anal. Calcd for  $\text{C}_{21}\text{H}_{27}\text{FO}_2\text{SSi}$ : C, 64.58; H, 6.97; S, 8.21. Found: C, 64.34; H, 7.16; S, 8.47.

#### 4.6. (+)-Benzoic acid (3*R*,4*S*,5*R*)-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-fluoro-tetrahydro-thiophen-3-yl ester (**11**)

To a stirred solution of alcohol **10** (1.360 g, 3.48 mmol), triphenyl phosphine (3.099 g, 11.82 mmol), and benzoic acid (1.440 g, 11.79 mmol) in anhydrous THF (20 mL) was dropwise added diethyl azodicarboxylate (1.9 mL, 12.07 mmol, DEAD) at  $0^{\circ}\text{C}$  over 5 min, and the reac-

tion mixture was heated to  $60^{\circ}\text{C}$  for 5 h. After cooling, the reaction mixture was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (8:1  $\rightarrow$  6:1) as the eluent to give benzoate **11** (1.516 g, 88%) as a colorless oil:  $[\alpha]_{\text{D}}^{25} +44.1$  ( $c$  1.03,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15–7.42 (m, 15H, 3 $\times$  Ar), 5.50–5.42 (m, 1H, 3-H), 5.32 (td, 1H,  $J = 2.5$ , 52.5 Hz, 4-H), 3.81–3.70 (m, 3H,  $\text{CH}_2\text{OTBDPS}$  and 5-H), 3.25 (dd, 1H,  $J = 6.0$ , 10.0 Hz,  $\text{SCHaCHb}$ ), 3.14 (td, 1H,  $J = 1.0$ , 10.0 Hz,  $\text{SCHaCHb}$ ), 1.13 (s, 9H,  $t\text{-Bu}$ );  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  165.8, 135.8, 135.7, 133.5, 133.1, 133.0, 130.0, 129.6, 128.6, 128.0, 93.8 (d,  $J = 187.0$  Hz), 75.0 (d,  $J = 16.5$  Hz), 65.1 (d,  $J = 7.8$  Hz), 49.9 (d,  $J = 20.6$  Hz), 29.6 (d,  $J = 3.7$  Hz), 26.7, 19.4;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$   $-198.04$ ; LRMS(ESI)  $m/z$  389 ( $\text{M}-\text{Bz}$ ) $^+$ ; Anal. Calcd for  $\text{C}_{28}\text{H}_{31}\text{FO}_3\text{SSi}$ : C, 67.98; H, 6.32; S, 6.48. Found: C, 68.20; H, 6.32; S, 6.59.

#### 4.7. (+)-(3*R*,4*S*,5*R*)-5-(*tert*-Butyl-diphenyl-silanyloxy methyl)-4-fluoro-tetrahydro-thiophen-3-ol (**12**)

Compound **11** (1.453 g, 2.94 mmol) was converted to **12** (1.052 g, 92%) as a colorless oil according to the similar procedure used in the preparation of compound **10**:  $[\alpha]_{\text{D}}^{25} +45.4$  ( $c$  1.06,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69–7.40 (m, 10H, 2 $\times$  Ar), 5.04 (td, 1H,  $J = 2.5$ , 51.5 Hz, 4-H), 4.37–4.29 (m, 1H, 3-H), 3.75–3.59 (m, 3H,  $\text{CH}_2\text{OTBDPS}$  and 5-H), 3.02 (dd, 1H,  $J = 6.0$ , 10.5 Hz,  $\text{SCHaCHb}$ ), 2.86 (irregular t, 1H,  $J = 9.0$ , 10.0 Hz,  $\text{SCHaCHb}$ ), 1.08 (s, 9H,  $t\text{-Bu}$ );  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  135.7, 135.7, 133.1, 133.0, 130.0, 127.9, 127.9, 96.3 (d,  $J = 180.6$  Hz), 74.7 (d,  $J = 18.9$  Hz), 65.0 (d,  $J = 7.4$  Hz), 49.4 (d,  $J = 19.9$  Hz), 32.5 (d,  $J = 4.4$  Hz), 26.9, 19.4;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$   $-136.53$ ; LRMS(FAB)  $m/z$  413 ( $\text{M}+\text{Na}$ ) $^+$ ; Anal. Calcd for  $\text{C}_{21}\text{H}_{27}\text{FO}_2\text{SSi}$ : C, 64.58; H, 6.97; S, 8.21. Found: C, 64.71; H, 7.26; S, 8.51.

#### 4.8. (+)-3-Benzoyl-1-(3*S*,4*S*,5*R*)-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-fluoro-tetrahydro-thiophen-3-yl]-1*H*-pyrimidine-2,4-dione (**13**)

To a stirred solution of alcohol **12** (218 mg, 0.56 mmol), triphenyl phosphine (439 mg, 1.67 mmol), and  $N^3$ -benzoyluracil (361 mg, 1.67 mmol) in anhydrous THF (6 mL) was dropwise added DEAD (0.26 mL, 1.65 mmol) at  $0^{\circ}\text{C}$  over 5 min, and the reaction mixture was stirred at room temperature overnight. After the volatiles were removed in vacuo, the resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (3:1) as the eluent to give  $N^3$ -benzoyluracil nucleoside **13** (203 mg, 62%) as a colorless sticky oil: UV ( $\text{CHCl}_3$ )  $\lambda_{\text{max}}$  254 nm;  $[\alpha]_{\text{D}}^{25} +3.6$  ( $c$  1.06,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95–7.38 (m, 15H, 3 $\times$  Ar), 7.32 (d, 1H,  $J = 8.0$  Hz, H-6), 5.84 (d, 1H,  $J = 8.5$  Hz, H-5), 5.34 (td, 1H,  $J = 7.0$ , 53.0 Hz, 4-H), 5.03–4.95 (m, 1H, 3-H), 3.91 (dd, 1H,  $J = 6.0$ , 11.0 Hz,  $\text{CHaHbOTBDPS}$ ), 3.85 (dd, 1H,  $J = 6.0$ , 10.5 Hz,  $\text{CHaHbOTBDPS}$ ), 3.68–3.60 (m, 1H, 5-H), 3.19 (irregular t, 1H,  $J = 9.5$ , 11.0 Hz,  $\text{SCHaCHb}$ ), 3.11 (dd, 1H,  $J = 8.0$ , 11.5 Hz,  $\text{SCHaCHb}$ ), 1.09 (s, 9H,  $t\text{-Bu}$ );  $^{13}\text{C}$

NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 161.9, 149.9, 141.7, 136.0, 135.9, 135.6, 133.3, 133.2, 131.7, 130.8, 130.3, 129.6, 128.2, 103.5, 94.9 (d,  $J = 189.7$  Hz), 65.8 (d,  $J = 25.6$  Hz), 65.0 (d,  $J = 1.7$  Hz), 48.9 (d,  $J = 19.5$  Hz), 28.2 (d,  $J = 7.1$  Hz), 27.2, 19.7; LRMS(FAB)  $m/z$  589 ( $\text{M}+\text{H}$ )<sup>+</sup>; Anal. Calcd for  $\text{C}_{32}\text{H}_{33}\text{FN}_2\text{O}_4\text{SSi}$ : C, 65.28; H, 5.65; N, 4.76; S, 5.45. Found: C, 64.97; H, 5.70; N, 4.97; S, 5.66.

**4.9. (–)-3-Benzoyl-1-[(3*S*,4*S*,5*R*)-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-fluoro-tetrahydro-thiophen-3-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (14)**

Compound **12** (100 mg, 0.26 mmol) was converted to **14** (102 mg, 66%) as a colorless sticky oil according to the similar procedure used in the preparation of compound **13**: UV ( $\text{CHCl}_3$ )  $\lambda_{\text{max}}$  253 nm;  $[\alpha]_{\text{D}}^{25} -0.7$  ( $c$  1.45,  $\text{CHCl}_3$ ); <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95–7.36 (m, 15H, 3× Ar), 7.15 (d, 1H,  $J = 1.0$  Hz, H-6), 5.35 (ddd, 1H,  $J = 6.5, 8.0, 53.0$  Hz, 4-H), 5.04–4.96 (m, 1H, 3-H), 3.91 (dd, 1H,  $J = 6.0, 11.0$  Hz, TBDPSOCHaHb), 3.84 (dd, 1H,  $J = 6.0, 10.5$  Hz, TBDPSOCHaHb), 3.64 (qd, 1H,  $J = 6.0, 19.0$  Hz, 5-H), 3.22 (irregular t, 1H,  $J = 10.0, 11.0$  Hz, SCHaHb), 3.08 (dd, 1H,  $J = 7.5, 11.0$  Hz, SCHaHb), 1.98 (d, 3H,  $J = 1.0$  Hz,  $\text{CH}_3$ ), 1.08 (s, 9H, *t*-Bu); <sup>13</sup>C NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 162.4, 149.6, 137.1, 135.6, 135.6, 135.1, 132.9, 132.8, 131.5, 130.4, 129.9, 129.2, 127.8, 127.8, 111.9, 94.4 (d,  $J = 190.0$  Hz), 64.6, 62.2, 48.2 (d,  $J = 19.1$  Hz), 27.4 (d,  $J = 7.8$  Hz), 26.8, 19.3, 12.6; <sup>19</sup>F NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  –187.58; LRMS(FAB)  $m/z$  625 ( $\text{M}+\text{Na}$ )<sup>+</sup>; Anal. Calcd for  $\text{C}_{33}\text{H}_{35}\text{FN}_2\text{O}_4\text{SSi}$ : C, 65.75; H, 5.85; N, 4.65; S, 5.32. Found: C, 65.40; H, 5.83; N, 4.75; S, 5.17.

**4.10. (–)-1-[(3*S*,4*S*,5*R*)-5-(*tert*-Butyl-diphenyl-silanyl-oxymethyl)-4-fluoro-tetrahydro-thiophen-3-yl]-1*H*-pyrimidine-2,4-dione (15)**

To a stirred solution of **13** (110 mg, 0.19 mmol) in methanol (4.5 mL) and  $\text{CH}_2\text{Cl}_2$  (1.5 mL) was added 1 M NaOMe (0.40 mL, 0.40 mmol, in MeOH) at 0 °C and the reaction mixture was stirred for 6 h at room temperature. The mixture was partitioned between EtOAc and water, dried over  $\text{MgSO}_4$ , filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (1.5:1) as the eluent to give the uracil nucleoside **15** (74 mg, 82%) as a colorless sticky oil:  $[\alpha]_{\text{D}}^{25} -2.9$  ( $c$  0.90,  $\text{CHCl}_3$ ); <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 (br s, 1H, NH), 7.69–7.40 (m, 10H, 2× Ar), 7.22 (d, 1H,  $J = 8.0$  Hz, H-6), 5.73 (d, 1H,  $J = 7.5$  Hz, H-5), 5.29 (td, 1H,  $J = 7.0, 53.0$  Hz, 4-H), 5.06–4.98 (m, 1H, 3-H), 3.87 (d, 1H,  $J = 1.0$  Hz, CHaHbOTBDPS), 3.86 (s, 1H, CHaHbOTBDPS), 3.68–3.61 (m, 1H, 5-H), 3.15–3.10 (m, 2H,  $\text{SCH}_2$ ), 1.10 (s, 9H, *t*-Bu); <sup>13</sup>C NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.7, 150.5, 141.3, 135.6, 135.6, 132.9, 132.8, 129.9, 129.9, 127.8, 103.1, 94.5 (d,  $J = 190.0$  Hz), 64.3 (d,  $J = 26.0$  Hz), 62.2, 48.6 (d,  $J = 19.5$  Hz), 27.8 (d,  $J = 7.3$  Hz), 26.8, 19.3; Anal. Calcd for  $\text{C}_{25}\text{H}_{29}\text{FN}_2\text{O}_3\text{SSi}$ : C, 61.95; H, 6.03; N, 5.78; S, 6.62. Found: C, 62.08; H, 5.74; N, 5.99; S, 6.45.

**4.11. (–)-1-[(3*S*,4*S*,5*R*)-5-(*tert*-Butyl-diphenyl-silanyl-oxymethyl)-4-fluoro-tetrahydro-thiophen-3-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (16)**

Compound **14** (84 mg, 0.14 mmol) was converted to **16** (65 mg, 94%) as a colorless sticky oil according to the similar procedure used in the preparation of compound **15**: UV ( $\text{CHCl}_3$ )  $\lambda_{\text{max}}$  266 nm;  $[\alpha]_{\text{D}}^{25} -6.4$  ( $c$  2.44,  $\text{CHCl}_3$ ); <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (s, 1H, imide-H), 7.71–7.41 (m, 10 H, 2× Ar), 7.05 (s, 1H, H-6), 5.31 (ddd, 1H,  $J = 7.0, 8.0, 53.0$  Hz, 4-H), 5.08–5.00 (m, 1H, 3-H), 3.90 (dd, 1H,  $J = 6.0, 10.0$  Hz, TBDPSOCHaHb), 3.87 (dd, 1H,  $J = 5.5, 10.5$  Hz, TBDPSOCHaHb), 3.64 (qd, 1H,  $J = 6.0, 19.0$  Hz, 5-H), 3.16 (t, 1H,  $J = 10.5$  Hz, SCHaHb), 3.07 (dd, 1H,  $J = 7.5, 11.5$  Hz, SCHaHb), 1.94 (s, 3H,  $\text{CH}_3$ ), 1.10 (s, 9H, *t*-Bu); <sup>13</sup>C NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.1, 150.4, 137.0, 135.6, 135.6, 133.0, 132.8, 129.9, 129.9, 127.8, 127.8, 111.8, 94.3 (d,  $J = 190.0$  Hz), 64.5, 64.0 (d,  $J = 25.1$  Hz), 48.3 (d,  $J = 19.6$  Hz), 27.5 (d,  $J = 7.4$  Hz), 26.8, 19.3, 12.5; <sup>19</sup>F NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  –188.06; LRMS(FAB)  $m/z$  499 ( $\text{M}+\text{H}$ )<sup>+</sup>; Anal. Calcd for  $\text{C}_{26}\text{H}_{31}\text{FN}_2\text{O}_3\text{SSi}$ : C, 62.62; H, 6.27; N, 5.62; S, 6.43. Found: C, 62.47; H, 6.60; N, 5.39; S, 6.68.

**4.12. (–)-1-[(3*S*,4*S*,5*R*)-4-Fluoro-5-hydroxymethyl-tetrahydrothiophen-3-yl]-1*H*-pyridine-2,4-dione (1)**

To a stirred solution of uracil nucleoside **15** (57 mg, 0.12 mmol) in THF (4 mL) was added 1 M tetrabutylammonium fluoride solution (0.34 mL, 0.34 mmol, TBAF, in THF) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by silica gel column chromatography using methylene chloride and methanol (15:1) as the eluent to give the final uracil nucleoside **1** (28 mg, 97%) as a colorless oil, which was crystallized in ether and a small amount of methanol to produce a white solid: mp 143.4–145.2 °C; UV (MeOH)  $\lambda_{\text{max}}$  262 nm;  $[\alpha]_{\text{D}}^{25} -23.6$  ( $c$  0.63, MeOH); <sup>1</sup>H NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.72 (d, 1H,  $J = 7.5$  Hz, H-6), 5.70 (d, 1H,  $J = 8.5$  Hz, H-5), 5.33 (ddd, 1H,  $J = 6.0, 8.0, 53.0$  Hz, 4-H), 5.10–5.01 (m, 1H, 3-H), 3.81 (dd, 1H,  $J = 6.0, 11.0$  Hz, HOCHaHb), 3.70 (dd, 1H,  $J = 6.5, 12.0$  Hz, HOCHaHb), 3.54 (qd, 1H,  $J = 6.0, 19.5$  Hz, 5-H), 3.23 (t, 1H,  $J = 11.0$  Hz, SCHaHb), 3.03 (dd, 1H,  $J = 8.0, 11.0$  Hz, SCHaHb); <sup>13</sup>C NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  166.2, 152.7, 144.7, 103.2, 96.0 (d,  $J = 187.3$  Hz), 66.0 (d,  $J = 24.6$  Hz), 64.4 (d,  $J = 1.4$  Hz), 49.7 (d,  $J = 19.1$  Hz), 27.8 (d,  $J = 7.8$  Hz); <sup>19</sup>F NMR (470 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  –186.21; LRMS(FAB)  $m/z$  247 ( $\text{M}+\text{H}$ )<sup>+</sup>; Anal. Calcd for  $\text{C}_9\text{H}_{11}\text{FN}_2\text{O}_3\text{S}$ : C, 43.90; H, 4.50; N, 11.38; S, 13.02. Found: C, 43.65; H, 4.61; N, 11.59; S, 13.30.

**4.13. (–)-1-[(3*S*,4*S*,5*R*)-4-Fluoro-5-hydroxymethyl-tetrahydro-thiophen-3-yl]-5-methyl-1*H*-pyrimidine-2,4-dione (2)**

Compound **16** (66 mg, 0.13 mmol) was converted to **2** (34 mg, 98%) as a white solid according to the similar

procedure used in the preparation of compound **1**: mp = 92.3–94.5 °C; UV (MeOH)  $\lambda_{\max}$  266 nm;  $[\alpha]_{\text{D}}^{25}$  –23.3 (*c* 0.77, MeOH);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.56 (d, 1H, *J* = 1.0 Hz, H-6), 5.32 (ddd, 1H, *J* = 7.0, 8.5, 54.0 Hz, 4-H), 5.10–5.01 (m, 1H, 3-H), 3.82 (dd, 1H, *J* = 5.5, 11.5 Hz, HOCHaHb), 3.70 (dd, 1H, *J* = 6.5, 11.0 Hz, HOCHaHb), 3.53 (qd, 1H, *J* = 6.0, 18.5 Hz, 5-H), 3.22 (t, 1H, *J* = 11.0 Hz, SCHaHb), 2.99 (ddd, 1H, *J* = 1.0, 8.0, 11.0 Hz, SCHaHb), 1.88 (d, 3H, *J* = 1.0 Hz, 5-CH<sub>3</sub>);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  166.4, 152.9, 140.3, 112.2, 95.9 (d, *J* = 187.3 Hz), 65.5 (d, *J* = 24.6 Hz), 64.5, 49.5 (d, *J* = 19.3 Hz), 27.6 (d, *J* = 8.3 Hz), 12.4;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  –186.80; LRMS(FAB) *m/z* 261 (M+H)<sup>+</sup>; Anal. Calcd for C<sub>10</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>S: C, 46.14; H, 5.03; N, 10.76; S, 12.32. Found: C, 45.82; H, 5.39; N, 10.62; S, 12.05.

#### 4.14. (–)-4-Amino-1-((3*S*,4*S*,5*R*)-4-fluoro-5-hydroxymethyl-tetrahydro-thiophen-3-yl)-1*H*-pyrimidin-2-one (**3**)

To a stirred solution of uracil nucleoside **1** (18 mg, 0.07 mmol) in anhydrous pyridine (1.5 mL) was added acetic anhydride (0.02 mL, 0.21 mmol) at room temperature, and the reaction mixture was stirred at the same temperature overnight. The reaction mixture was evaporated in vacuo and partitioned between ethyl acetate and dilute HCl aqueous solution. The organic layer was washed with saturated NaHCO<sub>3</sub> aqueous solution, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The resulting residue was used to the next reaction without further purification. To a stirred suspension of the acetylated residue **17** and 1,2,4-triazole (86 mg, 1.25 mmol) in anhydrous pyridine (2.5 mL) was added phosphorus oxychloride (0.08 mL, 0.83 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for overnight. 1,4-Dioxane (2 mL) and 28% ammonium hydroxide (2 mL) were added to the reaction mixture at 0 °C and stirred at room temperature overnight. After the volatiles were evaporated under reduced pressure, methanolic ammonia (3 mL) was added to the resulting residue, and the reaction mixture was stirred at room temperature overnight. After the volatiles were removed in vacuo, the resulting residue was purified by silica gel column chromatography using methylene chloride and methanol (7:1) as the eluent to give the final cytosine nucleoside **3** (9 mg, 54%) as a light brownish solid, which was recrystallized in ether and a small amount of methanol: hygroscopic; UV (MeOH)  $\lambda_{\max}$  271 nm;  $[\alpha]_{\text{D}}^{25}$  –26.1 (*c* 0.57, MeOH);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.72 (d, 1H, *J* = 7.5 Hz, H-6), 5.92 (d, 1H, *J* = 7.5 Hz, H-5), 5.42 (ddd, 1H, *J* = 6.0, 8.0, 54.0 Hz, 4-H), 5.08–5.00 (m, 1H, 3-H), 3.83 (dd, 1H, *J* = 6.5, 12.0 Hz, HOCHaHb), 3.71 (dd, 1H, *J* = 6.5, 11.5 Hz, HOCHaHb), 3.60–3.52 (m, 1H, 5-H), 3.30 (t, 1H, *J* = 11.0 Hz, SCHaHb), 3.04 (ddd, 1H, *J* = 1.0, 8.0, 11.0 Hz, SCHaHb);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  166.4, 157.4, 144.1, 95.3, 94.9 (d, *J* = 186.3 Hz), 66.3 (d, *J* = 25.0 Hz), 63.3 (d, *J* = 1.9 Hz), 48.8 (d, *J* = 19.5 Hz), 26.9 (d, *J* = 7.8 Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  –38.20; LRMS(FAB) *m/z* 246 (M+H)<sup>+</sup>; Anal. Calcd for C<sub>9</sub>H<sub>12</sub>FN<sub>3</sub>O<sub>2</sub>S: C, 44.07; H,

4.93; N, 17.13; S, 13.07. Found: C, 44.32; H, 5.03; N, 16.87; S, 12.99.

#### 4.15. (–)-9-[(3*S*,4*S*,5*R*)-5-(*tert*-Butyl-diphenyl-silanyl-oxy-methyl)-4-fluoro-tetrahydro-thiophen-3-yl]-6-chloro-9*H*-purine (**18**)

Compound **12** (65 mg, 0.17 mmol) was converted to **18** (78 mg, 88%) as a colorless sticky oil according to the similar procedure used in the preparation of compound **13**: UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  264 nm;  $[\alpha]_{\text{D}}^{25}$  –12.4 (*c* 0.56, CHCl<sub>3</sub>);  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.75 (s, 1H, H-8), 8.23 (s, 1H, H-2), 8.68–7.39 (m, 10H, 2× Ar), 5.74 (ddd, 1H, *J* = 1.5, 8.0, 52.5 Hz, 4-H), 5.32–5.24 (m, 1H, 3-H), 3.92 (dd, 1H, *J* = 5.5, 11.0 Hz, TBDP-SOCHaHb), 3.84 (dd, 1H, *J* = 6.0, 10.5 Hz, TBDP-CHaHb), 3.75 (qd, 1H, *J* = 6.0, 20.0 Hz, 5-H), 3.71 (t, 1H, *J* = 11.5 Hz, SCHaHb), 3.28 (dd, 1H, *J* = 7.5, 11.0 Hz, SCHaHb), 1.10 (s, 9H, *t*-Bu);  $^{13}\text{C}$  NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  151.9, 151.5, 151.4, 141.8, 135.5, 135.4, 132.5, 132.7, 132.0, 129.8, 127.7, 127.6, 94.8 (d, *J* = 191.0 Hz), 64.7 (d, *J* = 1.7 Hz), 62.9 (d, *J* = 24.3 Hz), 48.3 (d, *J* = 19.5 Hz), 28.4 (d, *J* = 7.1 Hz), 26.6, 19.2;  $^{19}\text{F}$  NMR (470 MHz, CDCl<sub>3</sub>)  $\delta$  –187.66; LRMS(FAB) *m/z* 527 (M+H)<sup>+</sup>; Anal. Calcd for C<sub>26</sub>H<sub>28</sub>ClFN<sub>4</sub>OSSi: C, 59.24; H, 5.35; N, 10.63; S, 6.08. Found: C, 59.51; H, 5.40; N, 10.44; S, 5.91.

#### 4.16. (–)-[(2*R*,3*S*,4*S*)-4-(6-Amino-purin-9-yl)-3-fluoro-tetrahydro-thiophen-2-yl]-methanol (**4**)

A solution of 6-chloropurine nucleoside **18** (78 mg, 0.15 mmol) in methanolic ammonia (6 mL) was heated to 80 °C in a glass bomb overnight. After cooling, the volatiles were removed in vacuo and the resulting residue was purified by silica gel column chromatography using methylene chloride and methanol (10:1) to give adenine nucleoside **4** (27 mg, 68%) as a colorless sticky oil, which was crystallized in ether and a small amount of methanol to afford a white solid: mp = 159.4–160.7 °C; UV (MeOH)  $\lambda_{\max}$  259 nm;  $[\alpha]_{\text{D}}^{25}$  –32.5 (*c* 1.49, MeOH);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.30 (s, 1H, H-8), 8.24 (s, 1H, H-2), 5.61 (ddd, 1H, *J* = 6.5, 8.5, 52.5 Hz, 3-H), 5.39–5.31 (m, 1H, 4-H), 3.79 (dd, 1H, *J* = 6.0, 11.0 Hz, HOCHaHb), 3.72 (dd, 1H, *J* = 6.0, 11.0 Hz, HOCHaHb), 3.72–3.62 (m, 1H, 2-H), 3.61 (t, 1H, *J* = 10.5 Hz, SCHaHb), 3.24 (ddd, 1H, *J* = 1.5, 7.5, 11.0 Hz, SCHaHb);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  156.7, 152.7, 150.9, 142.1, 120.7, 96.9 (d, *J* = 189.1 Hz), 64.5 (d, *J* = 1.4 Hz), 63.5 (d, *J* = 24.1 Hz), 49.9 (d, *J* = 19.1 Hz), 29.0 (d, *J* = 7.4 Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  –186.41; LRMS(FAB) *m/z* 270 (M+H)<sup>+</sup>; Anal. Calcd for C<sub>10</sub>H<sub>12</sub>FN<sub>5</sub>OS: C, 44.60; H, 4.49; N, 26.01; S, 11.91. Found: C, 44.84; H, 4.51; N, 25.77; S, 12.18.

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