# Synthesis of Novel L-2′,3′-Dideoxy-2′-trifluoromethyl-4′-thiocytidines from α-Trifluoromethyl-α,β-unsaturated Ester

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**Abstract:** A short and efficient synthesis of L-2′,3′-dideoxy-2′-trifluoromethyl-4′-thiocytidines is described. (2*R*,4*S*/2*S*,4*S*)-5-(*tert*-Butyldimethylsiloxy)-2-trifluoromethylpentan-4-olide (**3a** and **3b**) are prepared from α-trifluoromethyl-α,β-unsaturated ester (**1**) in three steps and converted to compounds **6a** and **6b**. The corresponding 1-*O*-acetyl derivatives **8a** and **8b** were obtained via the usual Pummerer rearrangement from **6a** and **6b** in two steps, which were in turn used to synthesize L-4′-thiocytidines **10a** and **10b**.

As of today, a number of modified nucleosides have been prepared in order to seek out new antiviral and anticancer agents.[1] Among these modified nucleosides, the 2′,3′-dideoxynucleosides (ddNs) are attractive compounds that have thus far proven to be the most effective therapeutic agents against human immunodeficiency virus (HIV)[2] and hepatitis B virus (HBV).[3] 3′-Azido-2′,3′-dideoxythymidine (AZT),[4] 2′,3′-dideoxyinosine (DDI),[5] and 2′,3′-dideoxycytidine (DDC)[6] have been approved for the treatment of AIDS. However, such ddNs have shown limited stability: the glycoside linkage of ddNs is susceptible to both acidic and enzymatic hydrolysis.[7]

Hoping to find better therapeutic agents for AIDS, a wide variety of sugar-modified nucleosides have been prepared. Thionucleosides in which the furanoside-oxygen of the sugar has been replaced by sulfur have shown interesting biological activities.[1] It has been demonstrated that the 4′-thionucleosides are resistant to hydrolytic cleavage of the glycosyl linkage that is catalyzed by nucleoside phosphorylase.[2] In addition, the potent antiviral activity and cytotoxicity of 4′-thionucleosides suggest that they are substrates of both viral and host cell kinases. The third important feature of 4′-thionucleosides is their antineoplastic activity.[3] Thus, the 4′-thionucleosides have received considerable attention as potential antiviral agents. Despite the unique biological activities of 4′-thionucleosides, the difficulty in synthesizing 4′-thionucleosides has impeded the investigation of structure−activity relationships (SAR)[4] and their development as clinical agents. Therefore, new synthetic methods are needed.

Currently the unnatural L-configuration has drawn considerable attention by medicinal chemists due to their unique potency, mechanism, and toxicity profile.[5] This has also been applied to the 4′-thionucleosides: e.g., L-2′,3′-dideoxy-didehydro-4′-thiocytidine (L-D4C) has potent antihuman immunodeficiency virus activity.[6] Recently a number of nucleosides with the fluorine incorporated into the sugar moiety have shown significant biological activities.[7] Whereas fluorine and trifluoromethyl groups have similar inductive effects, $\sigma = 0.5$ and 0.45, respectively, the lipophilicity of the trifluoromethyl group should improve the transport characteristics of the nucleoside and induce biological activities. But as far, only a few trifluoromethylated sugar nucleosides are known, which is probably due to the shortcoming of existing synthetic methods. Since we recently developed a new route to α-trifluoromethyl-α,β-unsaturated esters,[8] this induced us to prepare trifluoromethylated sugar nucleosides. In this paper we describe the synthesis of L-2′,3′-dideoxy-2′-trifluoromethyl-4′-thiocytidines by a short and efficient route.

In the preparation of L-2′,3′-dideoxy-2′-trifluoromethyl-4′-thiocytidines, the key step is the formation of a glycosidic bond at the α-methylene of the sulfide in the intermediate **6**[9] (Scheme 1). The Pummerer rearrangement could be suitable for introducing a base moiety at the 1-position of **6**.

Several years ago, Yoshimura and co-workers reported the elegant synthesis of D-2′-deoxy-2′,2′-disubstituted-4′-thiocytidines from D-glucose using the Pummerer rearrangement as the key step to form the glycosidic bond.[10] This encouraged us to synthesize the title compounds by using (*Z*)/(*E*)-ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-trifluoromethyl-2-propenoate **1** as a starting material.

Compound **1** was synthesized from 1-(*R*)-glyceraldehyde acetonide in two steps by the procedure developed in our laboratory[8] (Scheme 2). Hydrogenation of **1** in the presence of palladium on activated carbon (10% Pd), followed by deprotection and ring closure in the presence of 2.0 mol % of 1 N HCl under reduced pressure, afforded lactone **2** as a mixture of the C-2 epimers (syn:anti = 1.67:1, determinded by $^{19}$F NMR) in 78% yield. Protection of the hydroxyl group of **2** with TBDMSCl gave **3a** and **3b**, which were readily separated by silica gel column chromatography.

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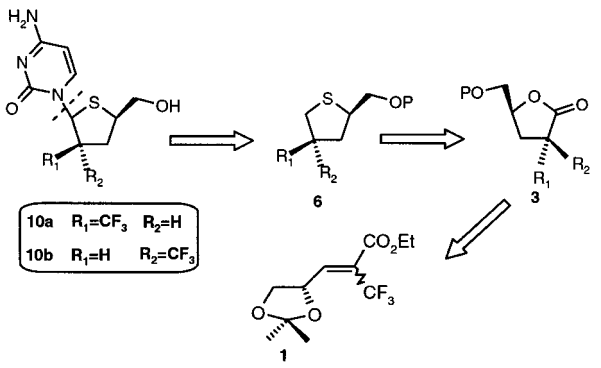
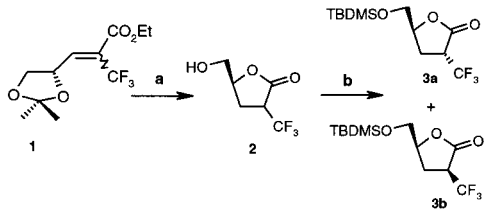
**Scheme 1**




**Scheme 2**[a]




[a] Reagents and conditions: (a) (1) $H_2$ (1 atm), Pd/C, $CH_2Cl_2$, rt, 24 h; (2) 2 mol % 1 N HCl, 60 mmHg, 50−55 °C, 24 h, 78%; (b) (1) TBDMSCl, imidazole, $CH_2Cl_2$, rt, 24 h; (2) column chromatography (hexane:ethyl acetate = 8:1), 90%.

Nucleophilic displacement with a sulfur-containing nucleophile followed by ring closure or ring contraction is a practicable method to prepare 4-thiofuranosides.[11] Furthermore, displacement with inversion of configuration resulted in the L-4-thiofuranosides. We were interested in exploring the feasibility of using **3** for the preparation of L-2-trifluoromethyl-4-thiofuranosides. The α-trifluoromethylated lactone **3a** was reduced by $NaBH_4$ in MeOH to provide compound **4a** in quantitative yield, which was not purified and was used directly in the next step. Compound **4a** was mesylated in anhydrous pyridine and then treated with sodium sulfide in DMF to give L-*β*-2-trifluoromethyl-4-thiofuranosides **6a** in 71% yield for the two steps (Scheme 3). Similarly, the *β*-trifluromethylated lactone **3b** was transformed into L-α-2-trifuoromethyl-4-thiofuranosides **6b** under the same reaction conditions, in 80% yield for the two steps. With these key intermediates **6a** and **6b** in hand, we could use the Pummerer reaction to form the glycosidic bond. The compound **6a** was oxidized to the sulfoxide with *m*-CPBA, and then the Pummerer rearangement of **7a** gave 1-*O*-acetate **8a** in 57% yield for the two steps, as an anomeric mixture. Under the same conditions, the 1-*O*-acetate **8b** was prepared in 62% yield for the two steps, also as an anomeric mixture. Coupling of **8a** with silylated $N^4$-benzoylcytosine under Vorbruggen conditions (glycosylation reactions)[12] gave mainly the α anomer **9aa** in a yield of 66% and the *β* anomer **9ab** in a yield of 8% (α/*β* = 89:11), which could be separated by column chromatography. The α-2-trifluoromethylated acetate **8b** was condensed with silylated $N^4$-benzoylcytosine, as described for **8a**, to afford mainly the *β* anomer **9bb** in 60% yield and the α anomer **9ba** in 21% yield (α/*β* = 26:74). This difference was presumably due to the steric interaction between trifluoromethyl group and $N^4$-benzoylcytosine. The removal of the 5′-silyl group and the $N^4$-benzoyl group with TBAF and a saturated solution of ammonia in methanol respectively gave L-2′,3′-dideoxy-2′*β*-trifluoromethyl-4′-thiocytidines (**10aa** and **10ab**) and L-2′,3′-dideoxy-2′α-trifluoromethyl-4′-thiocytidines (**10ba** and **10bb**).

Stereochemical assignments of the final compounds were made on the basis of 1D and 2D NMR spectroscopy. The configuration of the anomeric center was assigned mainly by $^1$H NMR, in which the anomers with H4′ at lower field were assigned as the α anomers, and the ones at higher field were assigned as the *β* anomers on the basis of the deshielding effect of the base moiety.[13] This assignments was further confirmed by the NOESY experiment of **10aa**, **10ab**, **10ba**, and **10bb**. (Figure 1).

In conclusion, we have first synthesized this new class of L-2′,3′-dideoxy-2′-trifluoromethyl-4′-thiocytidines. Furthermore, work is in progress to utilize the intermediate **8a** and **8b** for the syntheses of other nucleosides with the natural as well as the unnatural heterocyclic moieties. Antiviral activity and cytotoxicity evalulations of compound **10aa**, **10ab**, **10ba**, and **10bb** are in progress.

## Experimental Section

**(2*R*,4*S*/2*S*,4*S*)-5-Hydroxy-2-trifluoromethylpentan-4-olide (2).** Pd/C (10%) (2.00 g, 1.88 mmol) was added to a solution of (*Z*)/(*E*)-**1** (7.10 g, 26.49 mmol) in ethanol (150 mL) at room temperature under 1 atm of hydrogen. After stirring for 24 h, the reaction mixture was filtered and the solvent removed to give a colorless oil that was used in the next step. The oil and 1 N HCl (2 mL) were stirred at 50−55 °C under atmospheric pressure for 2 h and then under a reduced pressure at 60 mmHg overnight. The excess water was removed by stirring at that temperature under high vacuum for 3 h. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give 3.80 g (78% yield for the two steps) of a mixture of the (2*R*/2*S*)-trifluoromethyl lactones **2**: $^1$H NMR (300 MHz, $CDCl_3$) *δ* 4.70−4.62 (m, 1H), 3.95 (m, 1H), 3.65−3.60 (m, 2H), 3.27 (s, 1H), 2.53 (m, 1H), 2.32 (m, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.78 (d, *J* = 8.7 Hz, 1.88F), −8.10 (d, *J* = 8.7 Hz, 1.12F);[14] IR (thin film) $\nu_{max}$ 3422, 1779, 1374 cm$^{-1}$; MS *m*/*z* 185 ($M^+ + 1$, 29), 77 (100). Anal. Calcd for $C_6H_7O_3F_3$: C, 39.14; H, 3.83. Found: C, 39.49; H, 3.77.

**(2*R*,4*S*/2*S*,4*S*)-5-(*tert*-Butyldimethylsiloxy)-2-trifluoromethylpentan-4-olide (3a and 3b).** To a solution of lactone **2** (3.73 g, 20.29 mmol) in $CH_2Cl_2$ (50 mL) were added *tert*-butyldimethylsilyl chloride (8.84 g, 40.57 mmol) and imidazole (4.14 g, 60.86 mmol) in $CH_2Cl_2$ (30 mL) with stirring. After being stirred for 50 min at room temperature, the reaction mixture was poured onto water. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated to give a yellowish oil, which was purified by silica gel column chromatography (hexane:ethyl acetate = 8:1) to give 3.21 g (53% yield) of compound **3a** as a white solid and 2.23 g (37% yield) of compound **3b** as a white solid. **3a**: mp 40−42 °C; $^1$H NMR (300 MHz, $CDCl_3$) *δ* 4.68 (m, 1H), 3.93 (dd, *J* = 11.5 Hz, 2.2 Hz, 1H), 3.69 (dd, *J* = 11.5 Hz, 2.0 Hz, 1H), 3.55 (m, 1H), 2.50 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.80 (d, *J* = 8.8 Hz); IR (KBr) $\nu_{max}$ 1775, 1369 cm$^{-1}$; MS *m*/*z* 299 ($M^+ + 1$, 18), 298 ($M^+$, 2), 77 (100). Anal. Calcd for $C_{12}H_{21}O_3F_3Si$: C, 48.30; H, 7.03. Found: C, 48.15; H, 7.16. **3b**: mp 84−85 °C; $^1$H NMR (300 MHz, $CDCl_3$) *δ* 4.54 (m, 1H), 3.93 (dd, *J* = 11.6 Hz, 3.4 Hz, 1H), 3.75 (dd, *J* = 11.6 Hz, 3.4 Hz, 1H), 3.46 (m, 1H), 2.49 (m, 2H), 0.89 (s, 9H), 0.09 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ*

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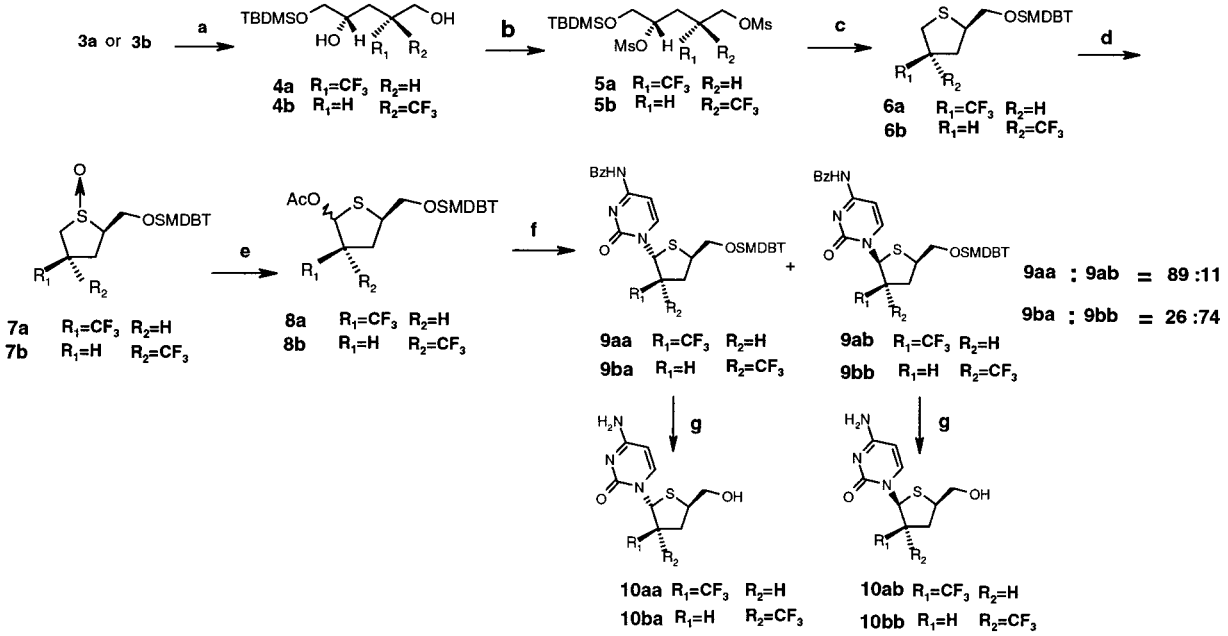
(14) $^{19}$F NMR spectra were obtained on 282 MHz spectrometer using $CF_3CO_2H$ as external standard, downfield shifts being designed as negative.

**Scheme 3**[a]




[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 1.5 h,; (b) MsCl, pyr,0 °C−rt., 12 h; (c) $Na_2S{\cdot}9H_2O$, DMF, 100 °C, 4 h; (d) m-CPBA, $CH_2Cl_2$, −78 °C, 3 h; (e) $(Ac)_2O$, 100 °C, 4.5 h; (f) (1) $N^4$-benzoylcytosine, *N*,*O*-bis(trimethylsilyl)acetamide, $CH_3CN$, reflux, 0.5 h, then TMSOTf, 0 °C-rt., 24 h; (2) column chromatography; (g) (1) TBAF, THF, rt, 1 h; (2) satd $NH_3$/MeOH, rt, 24 h.

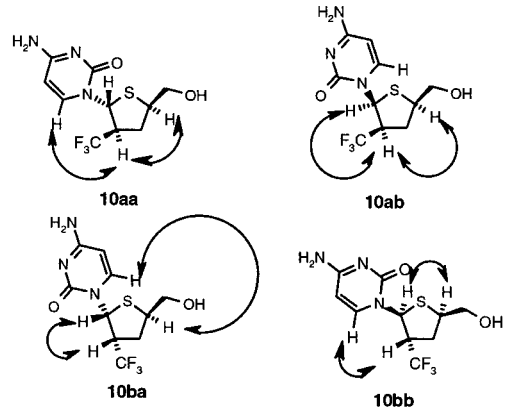



**Figure 1.** NOE correlations from NOESY spectra of **10aa, 10ab**, **10ba**, and **10bb**.

−8.34 (d, $J$ = 8.39); IR (KBr) $\nu_{max}$ 1760, 1263, 1127 $cm^{-1}$; MS *m*/*z* 241 (2), 77 (100).

**(2*R*,4*S*)-5-(*tert*-Butyldimethylsiloxy)-2-trifluoromethylpentane-1,4-diol (4a).** To a solution of **3a** (1.086 g, 3.64 mmol) in MeOH (7 mL) was added $NaBH_4$ (0.277 g, 7.28 mmol) in small portions at 0 °C with stirring. After the reaction mixture was stirred for 1.5 h, the solvent was removed, and the residue was washed with 2 mL of water. The aqueous layer was extracted with ethyl acetate The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, and concentrated to give compound **4a** in quantitative yield as a colorless oil that was used in the next step: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.94 (m, 1H), 3.90 (d, $J$ = 4.9 Hz, 2H), 3.65 (dd, $J$ = 9.9 Hz, 3.7 Hz, 1H), 3.45 (dd, $J$ = 9.9 Hz, 7.4 Hz, 1H), 2.62 (m, 3H), 1.77 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −7.50 (d, $J$ = 9.8 Hz); IR (thin film) $\nu_{max}$ 3370, 1258 $cm^{-1}$; MS *m*/*z* 302 ($M^+$, 6), 153 (99), 139 (100). Anal. Calcd for $C_{12}H_{25}O_3F_3Si$: C, 47.66; H, 8.33. Found: C, 47.67; H, 8.01.

**(2*S*,4*S*)-5-(*tert*-Butyldimethylsiloxy)-2-trifluoromethylpentane-1,4-diol (4b).** Compound **4b** (1.314 g, 87%) was prepared as a colorless oil from compound **3b** (1.490 g, 5.00 mmol) using the same procedure as for **4a**: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.95 (dd, $J$ = 11.8 Hz, 3.7 Hz, 1H), 3.79 (m, 1H), 3.75 (dd, $J$ = 11.8 Hz, 6.4 Hz, 1H), 3.65 (dd, $J$ = 9.6 Hz, 3.7 Hz, 1H), 3.43 (dd, $J$ = 9.6 Hz,8.0 Hz, 1H), 2.43 (m, 1H), 1.84 (ddd, $J$ = 14.7 Hz, 4.0 Hz, 2.0 Hz, 1H), 1.62 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −6.51 (d, $J$ = 9.3 Hz); IR (thin film) $\nu_{max}$ 3362, 1257 $cm^{-1}$; MS *m*/*z* 227 (100), 75 (100). Anal. Calcd for $C_{12}H_{25}O_3F_3Si$: C, 47.66; H, 8.33. Found: C, 47.66; H, 7.85.

**(2*R*,4*S*)-*tert*-Butyldimethyl-(4-trifluoromethyl-tetrahydro-thiophen-2-ylmethoxy)silane (6a).** To a solution of compound **4a** in anhydrous pyridine (11 mL) was added MsCl (1.16 mL, 14.56 mmol) at 0 °C with stirring. After the reaction mixture was stirred at room-temperature overnight, water was added to the mixture. Then the mixture was extracted with ethyl acetate. The combined oil layer was washed with brine and dried over $Na_2SO_4$. After concentration, the residue was dissolved in DMF (40 mL), and $Na_2S{\cdot}9H_2O$ (1.309 g, 5.46 mmol) was added. Then the mixture was kept at 100 °C for 4 h. Water was added to the mixture. The resulting mixture was extracted with ethyl acetate. The combined oil layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellowish oil. The oil was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 100:1) to give 0.775 g (71% yield, two steps) of **6a** as a colorless oil: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.72 (d, $J$ = 6.4 Hz, 2H), 3.65 (m, 1H), 2.97−2.90 (m, 3 H), 2.50 (m, 1H), 1.70 (m, 1H), 0.93 (s, 9H), 0.10 (s, 6H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −6.84 (d, $J$ = 5.8 Hz); IR (thin film) $\nu_{max}$ 1384, 1266 $cm^{-1}$; MS *m*/*z* 243 (68), 99 (100). Anal. Calcd for $C_{12}H_{23}OF_3SSi$: C, 47.97; H, 7.72; S, 10.67. Found: C, 47.98; H, 7.69, S, 11.40.

**(2*R*,4*R*)-*tert*-Butyldimethyl-(4-trifluoromethyl-tetrahydro-thiophen-2-ylmethoxy)silane (6b).** Compound **6b** (491 mg, 80% yield, two steps) was prepared as a colorless oil from compound **4b** (618 mg, 2.05 mmol) using the same conditions as for compound **6a**: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.60−3.51 (m, 3H), 3.00−2.92 (m, 3H), 2.37 (m, 1H), 2.05 (m, 1H), 0.89 (s, 9H), 0.08 (s, 6H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −7.23 (d, $J$ = 6.2 Hz); IR (thin film) $\nu_{max}$ 1382, 1270 $cm^{-1}$; MS *m*/*z* 243 (95), 169 (100). Anal. Calcd for $C_{12}H_{23}OF_3SSi$: C, 47.97; H, 7.72; S, 10.67; Found: C, 48.05; H, 7.73; S, 11.01.

**(3*S*,5*R*)-5-(*tert*-Butyldimethyl-silanyloxymethyl)-3-trifluoromethyl-tetrahydrothiophen-2-yl Acetate (8a).** To a solution of compound **6a** (273 mg, 0.91 mmol) in $CH_2Cl_2$ (7 mL) was added *m*-CPBA (70−75%, 220 mg, 0.91 mmol) in $CH_2Cl_2$ (7 mL) at −78 °C. After the reaction mixture was stirred at the same temperature for 3h, the reaction was quenched with

saturated aqueous $NaHCO_3$. The resulting mixture was extracted with $CHCl_3$. The organic layer was washed with a 10% sodium thiosulfate solution, saturated aqueous $NaHCO_3$, and brine and dried over $Na_2SO_4$. After concentration, the residue was dissolved in $Ac_2O$ (10 mL), and the mixture was kept at 100 °C for 4.5 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$. This was stirred for 10 min. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with saturated aqueous $NaHCO_3$, water, and brine, dried over $Na_2SO_4$, and concentrated to give a oil. The oil was purified by silica gel column chromatography (petroleum ether:dichloromethane = 2:1) to give α anomer **8a** 49 mg (15% yield, two steps), *β* anomer **8a** 137 mg (42% yield, two steps) as a light yellowish oil: α anomer **8a** $^1$H NMR (300 MHz, $CDCl_3$) *δ* 6.24 (d, *J* = 6.0 Hz, 1H), 3.77−3.67 (m, 3H), 3.13 (m, 1H), 2.49 (m, 2H), 2.09 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −6.93 (d, *J* = 8.5 Hz); *β* anomer **8a** $^1$H NMR (300 MHz, $CDCl_3$) *δ* 6.22 (d, *J* = 4.1 Hz, 1H), 3.72 (dd, *J* = 6.4 Hz, 1.3 Hz, 2H), 3.64 (m, 1H), 2.96 (m, 1H), 2.49 (m, 1H), 2.12 (m, 1H), 2.07 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −11.20 (d, *J* = 7.2 Hz); IR (thin film) $\nu_{max}$1752, 1261, 1228 cm$^{-1}$; MS *m*/*z* 301 ($M^+ - t$-Bu, 4), 167 (100), 43 (100). HRMS Calcd for $C_{10}H_{16}O_3F_3SSi$ ($M^+ - t$-Bu): 301.05416. Found: 301.05320.

**(3*R*,5*R*)-5-(*tert*-Butyldimethyl-silanyloxymethyl)-3-trifluoromethyl- tetrahydrothiophen-2-yl Acetate (8b).** Compound **8b** (222 mg, 62% yield, two steps) was prepared as a light yellowish oil from compound **6b** (300 mg, 1.00 mmol) using the same conditions as for compound **8a**: $^1$H NMR (300 MHz, $CDCl_3$) *δ* 6.23 (d, *J* = 4.6 Hz, 0.38 H), 6.22 (d, *J* = 4.3 Hz, 0.62 H), 3.71−3.50 (m, 3H), 3.22−3.08 (m, 1H), 2.46−2.30 (m, 2H), 2.08 (s, 3H), 0.91 (s, 3.42 H), 0.90 (s, 5.58 H), 0.08 (s, 2.28 H), 0.06 (s, 3.72 H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −11.69 (d, *J* = 6.9 Hz, 1.87 F), −7.04 (d, *J* = 9.0 Hz, 1.13 F); IR (thin film) $\nu_{max}$ 1755, 1261, 1227 cm$^{-1}$; MS *m*/*z* 301 ($M^+ - t$-Bu, 6), 43 (100). HRMS Calcd for $C_{10}H_{16}O_3F_3SSi$ ($M^+ - t$-Bu): 301.05415. Found: 301.05366.

**(2′*S*)-L-*N*$^4$-Benzoyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-dideoxy-2′trifluoromethyl-4′-thiocytidine (9aa and 9ab).** To a stirred solution of compound **8a** (150 mg, 0.42 mmol) and *N*$^4$-benzoylcytosine (252 mg, 1.17 mmol) in anhydrous acetonitrile (15 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (0.57 mL, 2.43 mmol). The reaction mixture was stirred at reflux for 30 min. After cooling to 0 °C, trimethylsilyl triflate (0.21 mL, 0.96 mmol) was added dropwise, and the solution was stirred for 24 h at room temperature. Saturated aqueous $NaHCO_3$ was added to the reaction mixture. The resulting mixture was filtered, and the solid was washed with $CHCl_3$ three times. The filtrate was extracted with $CHCl_3$. Then the organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated to give a yellowish oil. The oil was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 2:1 to 5:4) to give 141 mg (65.6% yield) of α anomer **9aa** as a white solid, and 18 mg (8.4% yield) of *β* anomer **9ab** as a white foam. **9aa:** $[\alpha]^{20}_D = -25.4°$ (*c* 0.385, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) *δ* 7.92 (m, 3H), 7.64−7.54 (m, 4H), 6.35 (d, *J* = 7.9 Hz, 1H), 4.21 (m, 1H), 3.82 (dd, *J* = 10.2 Hz, 5.8 Hz, 1H), 3.72 (dd, *J* = 10.2 Hz, 6.7 Hz, 1H), 3.46 (m, 1H), 2.62 (m, 1H), 2.05 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.18 (d, *J* = 6.3 Hz); IR (KBr) $\nu_{max}$ 3422, 1686, 1666, 1626, 1549 cm$^{-1}$; MS *m*/*z* 456 ($M^+$ - *t*-Bu, 89), 272 (21),105 (100). Anal. Calcd for $C_{23}H_{30}O_3N_3F_3SSi$: C, 53.78; H, 5.89; N, 8.18. Found: C, 53.90; H, 6.05; N, 8.12. HRMS Calcd for $C_{19}H_{21}O_3N_3F_3SSi$ ($M^+ - t$-Bu): 456.10250. Found: 456.10305. **9ab:** $[\alpha]^{20}_D = -27.2°$ (*c* 0.570, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) *δ* 8.72 (d, *J* = 7.19 Hz, 1H), 7.93 (d, *J* = 7.19 Hz, 1H), 7.63−7.53 (m, 5H), 6.94 (d, *J* = 6.0 Hz, 1H), 3.97 (d, *J* = 3.2 Hz, 2H), 3.83 (m, 1H), 3.28 (m, 1H), 2.40 (m, 2H), 0.99 (s, 9H), 0.19 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −11.7 (d, *J* = 7.7 Hz); IR (KBr) $\nu_{max}$ 3422, 1668, 1627, 1553 cm$^{-1}$; MS *m*/*z* 456 ($M^+ - t$-Bu, 100), 105 (86). HRMS Calcd for $C_{19}H_{21}O_3N_3F_3SSi$ ($M^+ - t$-Bu): 456.10250. Found: 456.10059.

**(2′*R*)-L-*N*$^4$-Benzoyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-dideoxy-2′trifluoromethyl-4′-thiocytidine (9ba and 9bb).** Compound **9ba** (59 mg, 20.5%) and **9bb** (172 mg, 59.5%) were prepared as a white foam respectively from compound **8b** (200 mg, 0.559 mmol) using the same procedure as for compounds **9aa** and **9ab. 9ba:** $[\alpha]^{20}_D = -8.4°$ (*c* 0.215, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) *δ* 8.15 (d, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 1H), 7.64−7.53 (m, 5H), 6.85 (d, *J* = 6.0 Hz, 1H), 3.97 (m, 1H), 3.69 (m, 2H), 3.49 (m, 1H), 2.45 (m, 2H), 0.93 (s, 9H), 0.11 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −11.89 (d, *J* = 8.6 Hz); IR (KBr) $\nu_{max}$ 3400, 1693, 1660, 1619, 1544 cm$^{-1}$; MS *m*/*z* 514 ($M^+ + 1$, 2), 513 ($M^+$, 3), 456 ($M^+ - t$-Bu, 30),105 (100). HRMS calcd for $C_{19}H_{21}O_3N_3F_3SSi$ ($M^+ - t$-Bu): 456.10250. Found: 456.10096. **9bb:** $[\alpha]^{20}_D = -1.2°$ (*c* 0.215, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) *δ* 8.62 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.61−7.52 (m, 5H), 6.65 (d, *J* = 6.3 Hz, 1H), 3.93 (m, 2H), 3.76 (m, 1H), 3.33 (m, 1H), 2.39 (m, 2H), 0.96 (s, 9H), 0.18 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.23 (d, *J* = 8.5 Hz); IR (KBr) $\nu_{max}$ 3400, 3069, 1675, 1626, 1554 cm$^{-1}$; MS *m*/*z* 456 ($M^+ - t$-Bu, 34), 105 (100). Anal. Calcd for $C_{23}H_{30}O_3N_3F_3SSi$: C, 53.78; H, 5.89; N, 8.18. Found: C, 53.70; H, 5.69; N, 8.02. HRMS Calcd for $C_{19}H_{21}O_3N_3F_3SSi$ ($M^+ - t$-Bu): 456.10250. Found: 456.10060.

**α-L-(2′*S*)-2′,3′-Dideoxy-2′-trifluoromethyl-4′-thiocytidine (10aa).** A stirred solution of protected nucleoside **9aa** (119 mg, 0.232 mmol) in anhydrous THF (10 mL) was treated with a 1.0 M solution of TBAF in THF (0.69 mL, 0.69 mmol) at room temperature. After stirring for 1 h, the solvent was removed, and the residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:4) to give crude desilylated cytosine derivative, which was dissolved in saturated methanolic ammonia (13 mL). The resulting reaction mixture was stirred for 12 h. After removed the volatile materials, the residue was purified by silica gel column chromatography ($CH_2Cl_2$:MeOH = 5:1) to give 64 mg (94% yield) of **10aa** as a white solid: mp 109−111 °C; $[\alpha]^{20}_D = -75.2°$ (*c* 0.340, MeOH); $^1$H NMR (300 MHz, MeOH-$d_4$) *δ* 8.11 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 1H), 6.17 (d, *J* = 7.5 Hz, 1H), 4.29 (m, 1H), 3.94 (dd, *J* = 11.2 Hz, 5.4 Hz, 1H), 3.78 (dd, *J* = 11.2 Hz, 6.9 Hz, 1H), 3.71 (m, 1H), 2.77 (m, 1H), 2.11 (m, 1H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) *δ* −9.51 (d, *J* = 6.9 Hz); IR (KBr) $\nu_{max}$ 3346, 3207, 1653, 1613, 1526 cm$^{-1}$; MS *m*/*z* 295 ($M^+$, 4), 112 (100). HRMS Calcd for $C_{10}H_{12}O_2N_3F_3S$: 295.06024. Found: 295.05950. Anal. Calcd for $C_{10}H_{12}O_2N_3F_3S$: C, 40.86; H, 4.10. Found: C, 40.33; H, 4.60.

***β*-L-(2′*S*)-2′,3′-Dideoxy-2′-trifluoromethyl-4′-thiocytidine (10ab).** Compound **10ab** (8 mg, 72% yield) was prepared as a white solid from **9ab** (20 mg, 0.039 mmol) using the same conditions as for compound **10aa**: mp 114−117 °C; $[\alpha]^{20}_D = -23.6°$ (*c* 0.125, MeOH); $^1$H NMR (300 MHz, MeOH-$d_4$) *δ* 8.53 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 5.6 Hz, 1H), 6.11 (d, *J* = 7.6 Hz, 1H), 4.08−4.01 (m, 3H), 3.69 (m, 1H), 2.61 (m, 1H), 2.46 (m, 1H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) *δ* −14.14 (d, *J* = 8.3 Hz).

**α-L-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethyl-4′-thiocytidine (10ba).** Compound **10ba** (24 mg, 77% yield) was prepared as a white solid from **9ba** (54 mg, 0.105 mmol) using the same conditions as for compound **10aa**: mp 65−67 °C; $[\alpha]^{20}_D = -38.8°$ (*c* 0.955, MeOH); $^1$H NMR (300 MHz, MeOH-$d_4$) *δ* 8.13 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 6.5 Hz, 1H), 6.13 (s, 1H), 4.14 (m, 1H), 3.77 (d, *J* = 6.5 Hz, 2H), 3.73 (m, 1H), 2.64 (m, 2H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) *δ* −14.43 (d, *J* = 8.6 Hz); IR (KBr) $\nu_{max}$ 3344, 3206, 1653, 1612, 1526 cm$^{-1}$; MS *m*/*z* 295 ($M^+$, 9), 2112 (100).

***β*-L-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethyl-4′-thiocytidine (10bb).** Compound **10bb** (63 mg, 76% yield) was prepared as a white solid from **9bb** (144 mg, 0.281 mmol) using the same conditions as for compound **10aa**: mp 95−97 °C; $[\alpha]^{20}_D = +38.0°$ (*c* 0.225, MeOH); $^1$H NMR (300 MHz, MeOH-$d_4$) *δ* 8.39 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.17 (d, *J* = 7.5 Hz, 1H), 3.99 (d, *J* = 5.2 Hz, 2H), 3.82 (m, 1H), 3.69 (m, 1H), 2.62 (m, 2H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) *δ* −9.72 (d, *J* = 8.5 Hz); IR (KBr) $\nu_{max}$ 3342, 3205, 1651, 1612, 1527 cm$^{-1}$; MS *m*/*z* 295 ($M^+$, 11), 112 (100). HRMS Calcd for $C_{10}H_{12}O_2N_3F_3S$: 295.06024. Found: 295.06109. Anal. Calcd for $C_{10}H_{12}O_2N_3F_3S$: C, 40.86; H, 4.10. Found: C, 40.33; H, 4.65.

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