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SYNTHESIS OF *2'-DEOXY*-4'-*C*-HYDROXYMETHYL-4'-THIO-RIBONUCLEOSIDES AND THEIR *2',3'-DIDEOXY* AND *2',3'-DIDEHYDRO-2',3'-DIDEOXY* ANALOGUES

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Abstract - (±)- *2'-Deoxy*-4'-*C*-hydroxymethyl-4'-thioribonucleosides (**1**) and their *2',3'-dideoxy*- (**2**) and *2',3'-didehydro-2',3'-dideoxy*- (**3**) analogues have been prepared from hydrothiophene derivatives 2,2-bis(benzyloxymethyl)-3-benzyloxytetrahydrothiophene (**4**), 2,2-bis-(acetoxymethyl)tetrahydrothiophene (**5**) and 2,2-bis(acetoxym ethyl)-2,5-dihydrothiophene (**6**), respectively. Preparation of the com pound **1** has been carried out *via N*-glycosylation of the corresponding sulfoxide **9**, derived from **4** by *m*-CPBA oxidation, with trim ethylsilylated pyrimidines and trim ethylsilyl triflate (Kita-O 'Niel-Matsuda's m ethod; m odified Pummerer rearrangement). On the other hand, the compounds **2** and **3** have been obtained *via N*-glycosylation of the corresponding 4'-thiofuranoses **7** and **8** with trim ethylsilylated pyrim idines and $SnCl_4$, respectively, while the compounds **7** and **8** have been prepared from compounds **5** and **6** by an electrochemical 2-acetoxylation, respectively.

INTRODUCTION

Recently, a wide variety of sugar-m odified nucle osides have been prepared to search for effective antiviral agents in which thioribonucleosides have received much attention mostly

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

because of the reported anti-HIV activity of the 4'-thio-2',3'-dideoxy analogues.[1] Moreover, it has been reported that (±)-4'-thio-3'-oxa-2',3'-dideoxynucleosides, *cis*-5-fluorocytosine and adenine derivatives (BCH-1081 and BCH-371) exhibited a good anti-HIV activity in MT-4 cell, though all of the *trans* isomers were found to be inactive and non-toxic.[2] Here, we have focused our attention on the synthesis of (±)-4'-*C*-hydroxymethyl-4'-thioribonucleoside derivatives (**1**-**3**) which have both hydroxymethyl and nucleoside base substituents on thiofuranose ring in *cis* geometry, because (i) the *cis* geometry is essential for biological activities, (ii) many of 4'-substituted nucleosides have already been prepared and their biological activities have been investigated,[3] (iii) we are much interested in a structure-activity relationship of these compounds, although it has been reported that synthetic 4'-*C*-hydroxymethylcarbocyclic nucleosides do not have any biological activity.[4]

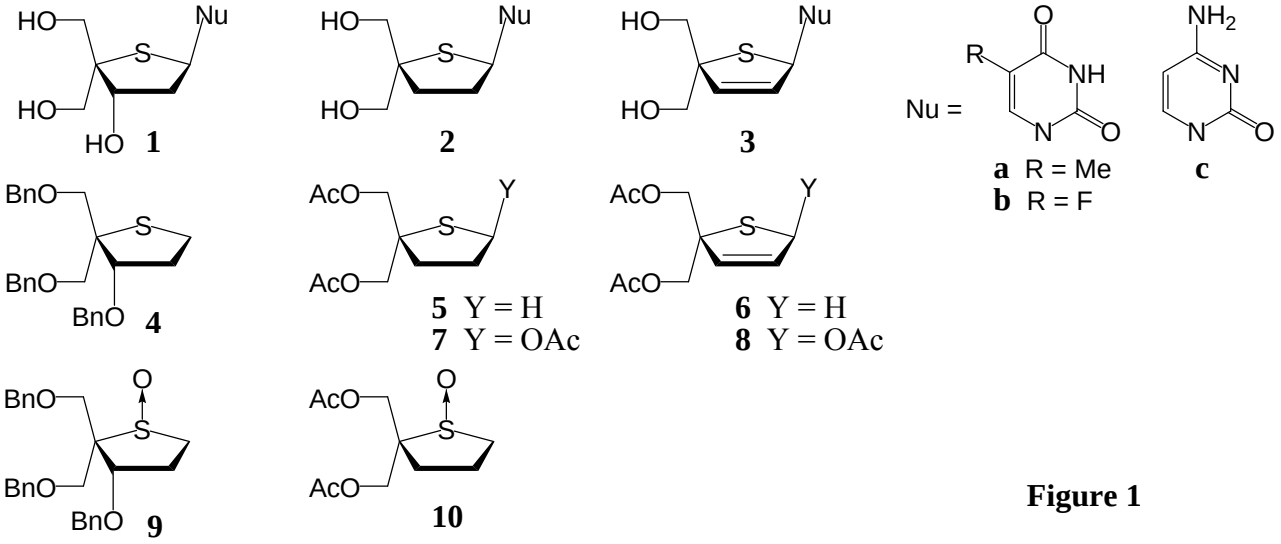
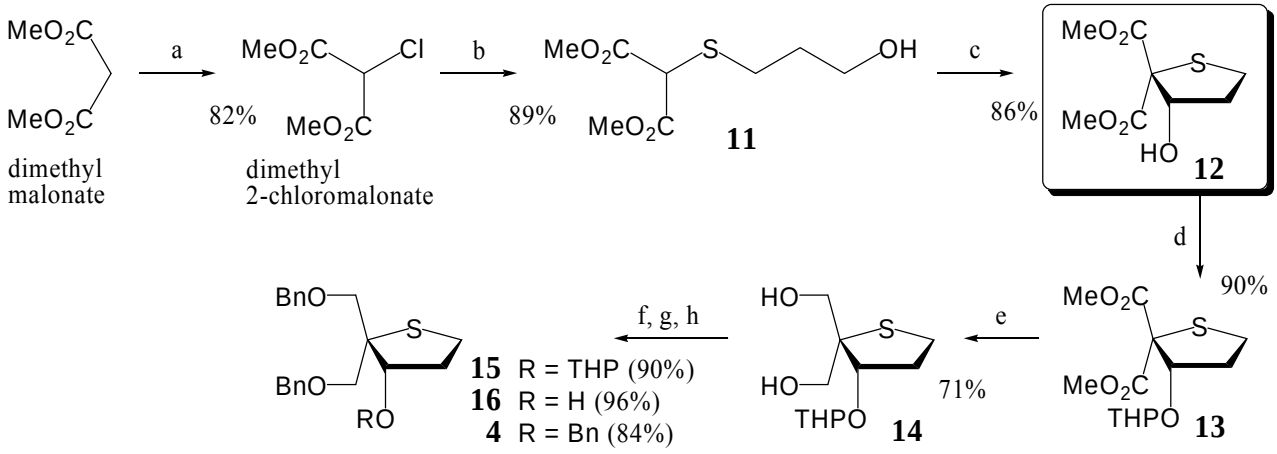


Figure 1

RESULTS AND DISCUSSION

2,2-Bis(benzyloxymethyl)-3-benzyloxytetrahydrothiophene (**4**) was prepared as follows. Dimethyl chloromalonate, derived from dimethyl malonate by chlorination with SO_2Cl_2, was treated with 3-hydroxypropanethiol and sodium carbonate in THF at 40-50 °C for 20 h to give the alcohol **11** in good yield. Treatment of **11** with PCC gave the corresponding aldol product 2,2-dimethoxycarbonyl-3-hydroxytetrahydrothiophene (**12**) directly in 86% yield. Protection of a hydroxy group of **12** was conducted under an acidic condition with DHP to give the THP-ether **13** avoiding a retroaldol reaction of **12** under basic reaction conditions. Two methoxycarbonyl groups in **13** were reduced by DIBAL-H to the diol **14**. The desired compound **4** was obtained in 72% overall yield *via* benzylation of hydroxy groups of **14** to the compound **15**, followed by its hydrolysis to the alcohol **16** and then its benzylation (Scheme 1).

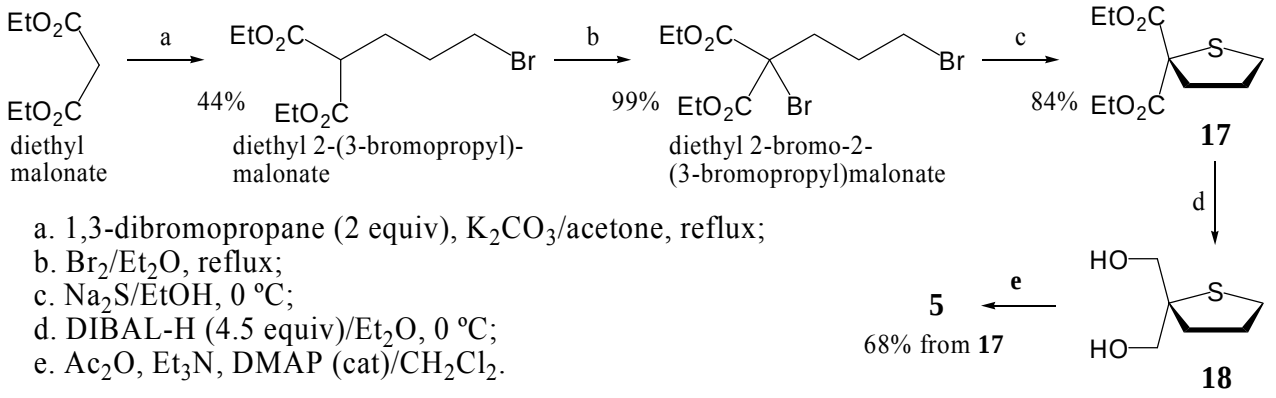
Scheme 1. Preparation of 2,2-bis(benzyloxymethyl)-3-benzyloxytetrahydrothiophene **4**



a. SO_2Cl_2/CH_2Cl_2, reflux for 3 days; b. $HS(CH_2)_3OH$/THF, 45 ºC for 20 h;
c. PCC (2 equiv)/4Å MS, CH_2Cl_2, rt; d. DHP, TsOH (cat.)/CH_2Cl_2, -30 ºC, 1 h;
e. DIBAL-H (4.2 equiv)/THF, 0 ºC, 1 h; f. NaH, BnCl (2.5 equiv)/DMF, -25 ºC (1 h)-rt (12 h);
g. TsOH (5 mol%)/MeOH, 0 ºC, 15 min; h. NaH, BnCl (2.4 equiv)/DMF, 0 ºC-rt (15 h).

2,2-Bis(acetoxymethyl)tetrahydrothiophene (**5**) was obtained easily *via* DIBAL-H reduction of 2,2-bis(ethoxycarbonyl)tetrahydrothiophene (**17**) followed by acetylation, where the compound **17** was prepared by Ikegami's method[5] (Scheme 2).

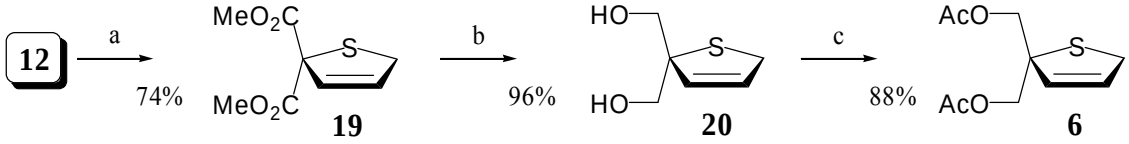
Scheme 2. Preparation of 2,2-bis(acetoxymethyl)tetrahydrothiophene **5**



a. 1,3-dibromopropane (2 equiv), K_2CO_3/acetone, reflux;
b. Br_2/Et_2O, reflux;
c. Na_2S/EtOH, 0 ºC;
d. DIBAL-H (4.5 equiv)/Et_2O, 0 ºC;
e. Ac_2O, Et_3N, DMAP (cat)/CH_2Cl_2.

2,2-Bis(acetoxymethyl)-2,5-dihydrothiophene (**6**) was very conveniently prepared from **12** as shown in Scheme 3. Dehydration of **12** to **19** was performed by treating of **12** with 2 equivalents of trifluoromethanesulfonic anhydride and an excess amount of *N*,*N*-dimethylaminopyridine (DMAP). The desired compound **6** was obtained *via* DIBAL-H reduction of two methoxycarbonyl groups of **19** to the corresponding diol **20**, followed by its acetylation (Scheme 3).

Scheme 3. Preparation of 2,2-bis(acetoxymethyl)-2,5-dihydrothiophene **6**



a. Tf_2O (2.2 equiv), DMAP (5 equiv)/CH_2Cl_2, -30 ºC (1 h)-rt (15 h);
b. DIBAL-H (4.2 equiv)/THF, 0 ºC, 1 h;
c. Ac_2O (3 equiv), Et_3N (3 equiv), DMAP (cat.)/$ClCH_2CH_2Cl$, 0 ºC-rt (30 min).

4'-Thioribonucleosides (**1**-**3**) were successfully obtained from the corresponding hydrothiophene derivatives (**4**-**6**) mainly by two methods, (A) and (B), as shown in Figure 2. (A) A very convenient method for the *N*-thioglycosylation *via* the corresponding sulfoxide (**SO**), in which the C-N bond formation may take place by a nucleophilic addition of nitrogen atom (silylated nucleoside base) to an *in situ* generated stable cation (**SC**), formed by Pummerer type rearrangement of **SO** *via* a transition state **TS1**.[1r,1u,6] (B) A traditional method which has been generally used for *N*- and *O*-glycosylation by glycosyl donor such as α-acetoxy sulfide (**AS**) together with an activator (Lewis acid such as $SnCl_4$), in which glycosylation may take place similarly as above with the stable cation (**SC**) formed from **AS** *via* a transition state **TS2**.[1o,7]

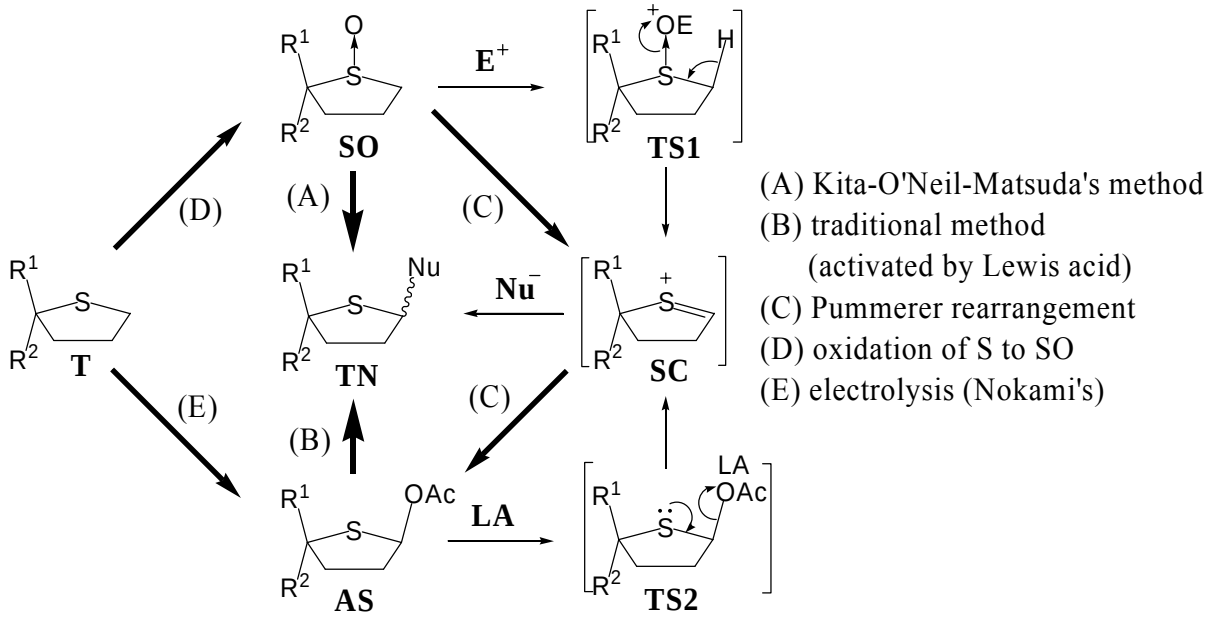
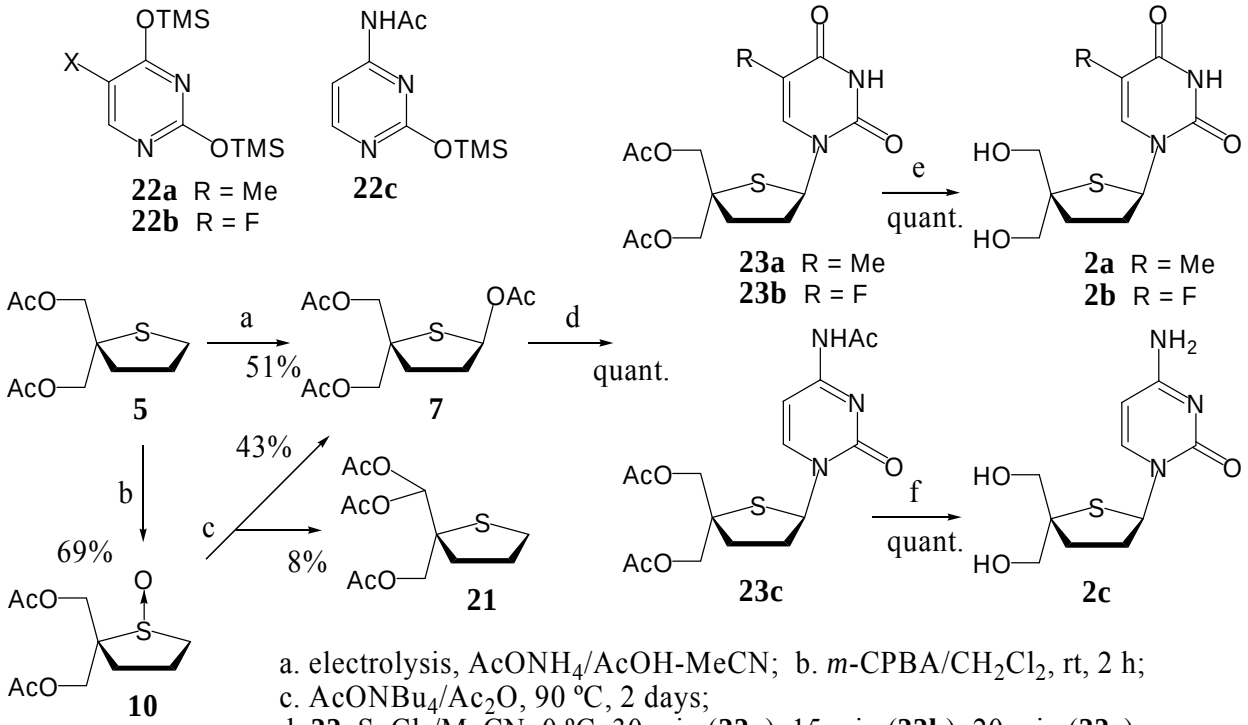


Figure 2. Synthesis of 4'-thioribonucleosides (TN) from tetrahydrothiophenes (T)

First, we investigated a conversion of the tetrahydrothiophene derivative **5** to the corresponding 4'-thioribonucleoside **2** *via* pass (B) in Figure 2, in which 2-acetoxy-4,4-bis(acetoxymethyl)tetrahydrothiophene (**7**; acetyl 4-*C*-acetoxymethyl-2,3-dideoxy-5-*O*-acetyl-

4-thioribose) served as a glycosyl donor for *N*-glycosylation of silylated nucleoside bases **22**. The glycosyl donor **7** was derived from **5** *via* direct acetoxylation by electrolysis [pass (E) in Figure 2][8] or *via* acetoxylation by Pummerer rearrangement of the corresponding sulfoxide **9** [pass (D) and (C) in Figure 2]. We observed that electrochemical 2-acetoxylation of the sulfide **5** gave 2-acetoxytetrahydrothiophene derivative **7** in better yield than the process *via* Pummerer rearrangement of the corresponding sulfoxide **10**.[9] In the latter case, the conversion of the sulfide **5** to the sulfoxide **10** by *m*-CPBA oxidation as well as that of **10** to **7** by Pummerer rearrangement gave unsatisfactory yields. By-product **21**, which may be formed *via* thermolysis of **10**, was isolated in 8% yield after column chromatography on silica gel. *N*-Glycosylation of trimethylsilylated pyrimidines **22a-c** was performed with **7** in the presence of anhydrous $SnCl_4$ in acetonitrile to give **23** in quantitative yields. 2',3'-Dideoxy-4'-*C*-hydroxymethyl-4'-thiothymidine (**2a**), 2',3'-dideoxy-5-fluoro-4'-*C*-hydroxymethyl-4'-thiouridine (**2b**) and 2',3'-dideoxy-4'-*C*-hydroxymethyl-4'-thiocytidine (**2c**) were obtained *via* hydrolysis of **23a-c**, respectively, using aq. ammonia or aq. dimethylamine in 1,4-dioxane, although it took a long reaction time (Scheme 4).

Scheme 4. Preparation of 2',3'-dideoxy-4'-*C*-hydroxymethyl-4'-thioribonucleosides **2a-c**

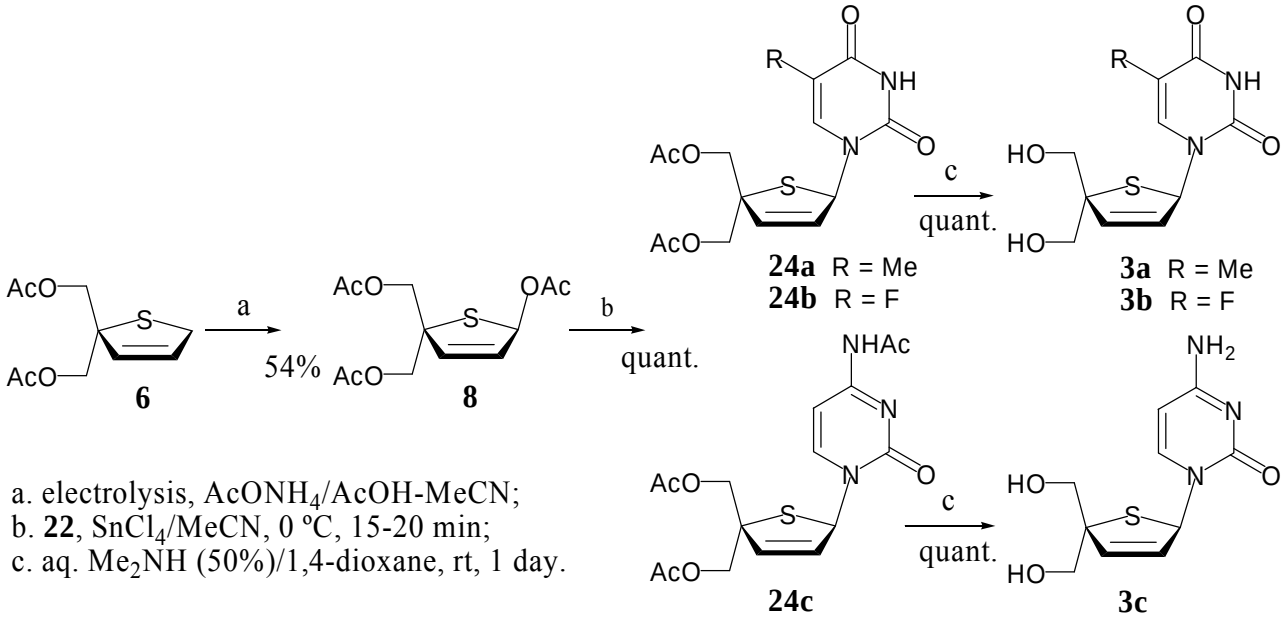


a. electrolysis, $AcONH_4$/AcOH-MeCN; b. *m*-CPBA/CH_2Cl_2, rt, 2 h;
c. $AcONBu_4/Ac_2O$, 90 ºC, 2 days;
d. **22**, $SnCl_4$/MeCN, 0 ºC, 30 min (**22a**), 15 min (**22b**), 20 min (**22c**);
e. aq. NH_3 (30%)/1,4-dioxane, rt, 1 day (**23a**), 5 days (**23b**).
f. aq. Me_2NH/1,4-dioxane, 3 weeks.

Next, 2',3'-didehydro-2',3'-dideoxy-4'-*C*-hydroxymethyl-4'-thioribonucleosides **3a-c** were

similarly prepared from the compound **6** *via* several steps as shown in Scheme 5: electrolysis of **6** to the corresponding glycosyl donor **8**, *N*-glycosylation of **22** with **8** to give **24**, and its hydrolysis.

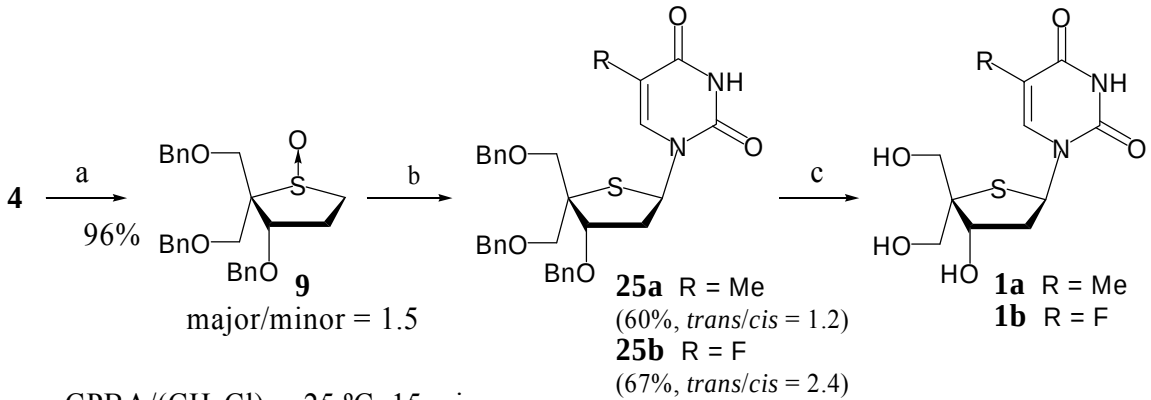
Scheme 5. 2',3'-Didehydro-2',3'-dideoxy-4'-*C*-hydroxymethyl-4'-thioribonucleosides **3a-c**



a. electrolysis, $AcONH_4$/AcOH-MeCN;
b. **22**, $SnCl_4$/MeCN, 0 ºC, 15-20 min;
c. aq. Me_2NH (50%)/1,4-dioxane, rt, 1 day.

On the other hand, the conversion of **4** to 2'-deoxy-4'-*C*-hydroxymethyl-4'-thioribonucleosides (**1a,b**) was carried out by Kita-O'Neil-Matsuda's method[6] *via* pass (A) in Figure 2, in which the corresponding sulfoxide **9** served as a glycosyl donor for *N*-glycosylation of thymine and 5-fluorouracil to give **25** in satisfactory yield. Debenzylation of **25** by hydrogenation in the presence of $Pd(OH)_2$ (30 mol%) gave **1** in good yield (Scheme 6).

Scheme 6. Preparation of 2'-deoxy-4'-*C*-hydroxymethyl-4'-thioribonucleosides **1a**,**b**



a. *m*-CPBA/$(CH_2Cl)_2$, -25 ºC, 15 min;
b. thymine or 5-fluorouracil (3.5 equiv), Et_3N (10 equiv), TMSOTf (10 equiv)/ CH_2Cl_2, rt, 5 min; and ZnI_2 (0.3 equiv) at 0 ºC, rt, 19 h;
c. H_2/$Pd(OH)_2$-C (30 mol%)/EtOH, rt, 3 days.

Among the compounds **2a-c** and **3a-c**, where their anti-HIV activity was evaluated, **3b** showed a weak activity against HIV (MT-4) (50% inhibitory concentration: 2.73 μg/mL), although other compounds did not show any activity at a concentration of 100 μg/mL.

EXPERIMENTAL

General

TLC was performed on aluminum-backed plates coated with silica gel 60 with F_{254} indicator. Column chromatography was carried out on silica gel BW-300 (200-400 mesh, Fuji Silysia Chemical Ltd.). Infrared spectra were recorded on a Nicolet Series II Magna-IR system 550 spectrometer. ^{1}H NMR (300, 400, 500 MHz) and ^{13}C NMR (75, 100, 125 MHz) spectra were measured on a JEOL JNM-400 and LAMBDA-300 and 500 spectrometers. High-resolution mass spectra were obtained with a JEOL JMS-700 mass spectrometer. Elemental analyses were obtained on a Perkin-Elmer PE-2400 Series II CHN analyzer.

Dimethyl 2-(3-hydroxypropylthio)malonate (11). To a solution of dimethyl 2-chloromalonate (4.43 g, 26.0 mmol) and 3-mercapto-1-propanol (1.76 mL, 20.0 mmol) in THF (50 mL) was added a finely powdered Na_2CO_3 (6.35 g, 60.0 mmol). After stirring at 40-50 °C for 20 h, the reaction mixture was filtered off under reduced pressure and the filtrate was concentrated *in vacuo*. The crude residue was column chromatographed on silica gel (Et_2O/hexane = 1:1) to afford **11** (3.76 g, 85%) as colorless oil; R_f 0.46 (Et_2O/hexane = 1:3); IR (neat) 3419, 1732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (brs, 1H), 1.85 (tt, J = 6.1, 7.0 Hz, 2H), 2.87 (t, J = 7.0 Hz, 2H), 3.76 (t, J = 6.1 Hz, 2H), 3.81 (s, 6H), 4.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 31.3, 50.5, 53.3, 60.9, 167.4. HRMS *m*/*z* calcd for $C_8H_{14}O_5S$ 222.0562, found 222.0558.

2,2-Dimethoxycarbonyl-3-hydroxytetrahydrothiophene (12). To a suspension of pyridinium chlorochromate (915 mg, 4.24 mmol) and molecular sieves (5Å) (powder, 610 mg) in dry dichloromethane (CH_2Cl_2, 16 mL) was added a solution of **11** (470 mg, 2.12 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under argon atmosphere. After stirring at room temperature (rt) for 6 h, the solvent was removed *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1:1) to afford 404 mg (86%) of **12** as colorless oil. R_f = 0.37 (EtOAc/hexane= 1:1); IR (neat) 3541, 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33-2.41 (m, 2H), 2.95-3.03 (m, 2H), 3.13-3.22 (m, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (dd, J = 4.9, 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 35.9, 53.3, 53.4, 69.1, 78.7, 169.2, 169.9. Anal. Calcd for $C_8H_{12}O_5S$: C, 43.63; H, 5.49. Found: C, 43.93; H, 5.35.

2,2-Dimethoxycarbonyl-3-(tetrahydropyranyloxy)tetrahydrothiophene (13). To a solution of **12** (893 mg, 4.06 mmol) and dihydropyran (DHP, 0.55 mL, 6.09 mmol) in CH_2Cl_2 was added *p*-

toluenesulfonic acid monohydrate (TSA·H_2O, ca. 40 mg) at 0 °C. After stirring for 15 min at 0 °C, the reaction was quenched with saturated aq. $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1:5) to afford 1.10 g (90%) of a diastereoisomeric mixture (ca. 1:1) of **13** as white solid. R_f = 0.39 and 0.33 (EtOAc/hexane = 1:3); mp (mixture) 50-51 °C; [less polar **13** (R_f = 0.39)] IR (Nujol mull) 1768, 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48-1.61 (m, 5H), 1.72-1.79 (m, 1H), 2.31-2.38 (m, 1H), 2.48-2.53 (m, 1H), 2.95 (ddd, *J* = 3.1, 7.1, 10.1 Hz, 1H), 3.26 (dt, *J* = 5.8, 10.1 Hz, 1H), 3.52-3.56 (m, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 3.85 (ddd, *J* = 3.3, 7.9, 11.2 Hz, 1H), 4.73 (t, *J* = 4.0 Hz, 1H), 4.85 (t, *J* = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 25.1, 30.5, 37.2, 52.9, 52.9, 62.6, 70.2, 85.0, 100.7, 167.7, 169.8; and [polar **13** (R_f = 0.33)] IR (Nujol mull) 1768, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50-1.68 (m, 6H), 2.18-2.31 (m, 1H), 2.49 (dddd, *J* = 3.4, 3.4, 9.5, 23.2 Hz, 1H), 2.92 (ddd, *J* = 3.1, 11.9, 15.6 Hz, 1H), 3.16 (ddd, *J* = 9.3, 16.3, 19.0 Hz, 1H), 3.50-3.57 (m, 1H), 3.75 (s, 3H), 3.75-3.82 (m, 1H), 3.82 (s, 3H), 4.80 (brs, 1H), 5.00 (t, *J* = 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 25.1, 30.0, 30.4, 33.1, 52.9, 53.0, 61.2, 70.4, 79.1, 93.5, 167.2, 169.7; Anal. Calcd for $C_{13}H_{20}O_6S$ (mixture): C, 51.30; H, 6.62. Found: C, 51.10; H: 6.65.

2,2-Di(hydroxymethyl)-3-(tetrahydropyranyloxy)tetrahydrothiophene (14). To a hexane solution of DIBAL-H (44.0 mL, 0.95 M, 41.8 mmol) was added dropwise a dry THF (49 mL) solution of **13** (a diastereoisomeric mixture; 3 g, 9.87 mmol) at 0 °C under argon atmosphere. After stirring at 0 °C for 15 min, the reaction was quenched with EtOAc (4.2 mL) and then with H_2O (1.8 mL) at 0 °C. The mixture was stirred for 30 min and the solvent was removed by filtration through a glass frit. The residue was stirred in MeOH (30 mL) for 24 h and filtrated off under a reduced pressure. The combined filtrate was concentrated *in vacuo* to give a crude product. The crude product was column chromatographed on silica gel (from Et_2O/hexane = 1:3 to Et_2O) to afford **14** in 71% (2.40 g) yield as a mixture of diastereoisomers. R_f = 0.36 (Et_2O); mp (mixture) 63-63.5 °C. A small portion of the crystal was again carefully column chromatographed on silica gel (Et_2O/hexane = 1:3) to obtain the spectra of both diastereoisomers separately; [less polar **14** (from faster eluent)] IR (Nujol mull) 3298 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52-1.60 (m, 4H), 1.71-1.82 (m, 2H), 2.25-2.31 (m, 1H), 2.38-2.44 (m, 1H), 2.56 (t, *J* = 6.1 Hz, 1H), 2.77 (ddd, *J* = 6.2, 9.8, 10.7 Hz, 1H), 2.85 (ddd, *J* = 4.5, 7.0, 11.2 Hz, 1H), 3.00-3.04 (m, 1H), 3.53-3.57 (m, 1H), 3.67 (dd, *J* = 8.9, 10.4 Hz, 1H), 3.73 (dd, *J* = 4.6, 11.6 Hz, 1H), 3.83 (dd, *J* = 7.4, 11.6 Hz, 1H), 3.91 (ddd, *J* = 3.4, 7.4, 10.9 Hz, 1H), 4.10 (dd, *J* = 3.7, 11.9 Hz, 1H), 4.34 (dd, *J* = 5.1, 8.4 Hz, 1H), 4.74 (dd, *J* = 2.6, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 25.1, 26.4, 30.7, 35.2, 62.9, 63.3, 66.0, 83.5, 100.9 and [polar **14** (from later eluent)] IR (Nujol mull) 3301 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 1.48-1.53 (m, 4H), 1.74-1.87 (m, 2H), 2.13-2.23 (m, 2H), 2.81 (ddd, *J* = 3.0, 6.9, 10.1 Hz, 1H), 3.03 (dt, *J* = 6.3, 10.2 Hz, 1H), 3.49-3.54 (m, 2H), 3.66-3.71 (m, 2H), 3.85 (dd, *J* = 3.4, 11.6 Hz, 1H), 4.00-4.02 (m, 1H), 4.22-4.26 (m, 2H), 4.48 (dd, *J* = 2.4, 7.6 Hz, 1H), 4.60 (t, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 24.9, 28.6, 31.6, 35.3, 64.4, 66.0, 66.1, 69.2, 81.0, 100.7. Anal. Calcd for $C_{13}H_{20}O_6S$ (a diastereoisomeric mixture): C, 53.20; H, 8.12. Found: C, 53.32; H, 8.22.

2,2-Di(benzyloxymethyl)-3-(tetrahydropyranyloxy)tetrahydrothiophene (15). To a suspension of NaH, prepared from 60 wt% of oil dispersion of NaH (400 mg, 10 mmol) by rinsing with dry hexane (2 x 10 mL), in DMF (25 mL) was added dropwise dry DMF (12 mL) solution of **13** (1.00 g, 4.04 mmol) at -25 °C under argon atmosphere. After stirring for 30 min, benzyl chloride (1.2 mL, 10.4 mmol) was added to a pale yellowish reaction mixture and the mixture was allowed to stir at -25 °C for 1 h and at rt overnight, and then the reaction was quenched by careful addition of H_2O (50 mL) on an ice-water bath. The organic layer was separated and the aqueous layer was extracted twice with a mixed solvent (EtOAc/hexane = 1/1, 2 x 20 mL). The combined extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (Et_2O/hexane = 1/1) to give **15** (1.48 g, 87% yield) as a mixture of diastereoisomers. R_f = 0.70 (Et_2O/hexane = 3/1); mp (mixture) 68-69 °C. [less polar **15** (from faster eluent)] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42-1.61 (m, 5H), 1.73-1.80 (m, 1H), 2.08-2.15 (m, 1H), 2.30-2.36 (m, 1H), 2.80 (ddd, *J* = 3.7, 6.9, 10.5 Hz, 1H), 3.03 (dt, *J* = 5.8, 9.9 Hz, 1H), 3.47 (ddd, *J* = 4.9, 4.9, 9.8 Hz, 1H), 3.52 (d, *J* = 9.5 Hz, 1H), 3.60 (d, *J* = 9.4 Hz, 1H), 3.69 (d, *J* = 8.6 Hz, 1H), 3.82-3.87 (m, 1H), 3.93 (d, *J* = 9.2 Hz, 1H), 4.23 (t, *J* = 1.33 Hz, 1H), 4.49-4.59 (m, 4H), 4.64 (t, *J* = 3.7 Hz, 1H), 7.25-7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 25.2, 28.3, 30.4, 36.6, 62.5, 63.1, 70.7, 73.0, 73.1, 83.5, 100.2, 127.1, 127.2, 127.2, 127.3, 127.9, 128.0, 128.0, 138.2, 138.3 and [polar **15** (from later eluent)] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43-1.56 (m, 4H), 1.66 (ddt, *J* = 3.3, 3.3, 11.5 Hz, 1H), 1.72-1.79 (m, 1H), 1.93-2.00 (m, 1H), 2.25 (ddd, *J* = 2.8, 2.8, 5.6, 13.4 Hz, 1H), 2.78 (ddd, *J* = 2.8, 7.3, 10.1 Hz, 1H), 2.95 (dt, *J* = 6.0, 10.5 Hz, 1H), 3.42-3.46 (m, 1H), 3.46 (d, *J* = 9.5 Hz, 1H), 3.67 (d, *J* = 9.5 Hz, 1H), 3.77-3.82 (m, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 4.12 (d, *J* = 9.2 Hz, 1H), 4.49 (t, *J* = 3.1 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 12.5 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.71 (t, *J* = 3.2 Hz, 1H), 7.23-7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 25.2, 28.1, 30.6, 32.3, 61.6, 63.6, 71.0, 72.9, 73.2, 77.9, 94.5, 127.1, 127.2, 127.3, 128.0, 128.0, 138.4, 138.6. HRMS *m*/*z* calcd for $C_{25}H_{22}O_4S$ (a diastereoisomeric mixture) 428.2021, found 428.2048.

2,2-Di(benzyloxymethyl)-3-hydroxytetrahydrothiophene (16). To a suspension of **15** (2.89 g, 6.74 mmol) in methanol (67 mL) was added TSA·H_2O (ca. 60 mg) at 0 °C. After stirring for 15 min, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and washed with saturated aq. Na_2CO_3 (10 mL) and brine (50 mL). The aqueous layer was extracted with EtOAc (3 x

10 mL). The combined extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (Et_2O/hexane = 1/1) to afford **16** (2.22 g, 95%) as colorless oil. R_f = 0.36 (Et_2O/hexane = 1/1); IR (neat) 3453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09-2.27 (m, 2H), 2.80 (dt, *J* = 6.7, 10.5 Hz, 1H), 2.94 (dt, *J* = 6.9, 10.5 Hz, 1H), 3.05 (d, *J* = 4.6 Hz, 1H), 3.57 (d, *J* = 9.0 Hz, 1H), 3.75 (d, *J* = 9.0 Hz, 1H), 3.79 (d, *J* = 9.4 Hz, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 4.22 (dd, *J* = 5.1, 10.9 Hz, 1H), 4.50 (d, *J* = 12.3 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 7.25-7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 36.4, 60.9, 71.1, 73.3, 73.4, 74.1, 78.5, 127.4, 127.5, 127.5, 127.6, 128.2, 128.3, 137.7, 138.0. HRMS (FAB) *m*/*z* calcd for $C_{13}H_{17}O_2S$ [M-BnO]$^+$ 237.0950, found 237.0917.

3-Benzyloxy-2,2-di(benzyloxymethyl)tetrahydrothiophene (4). To a suspension of NaH, prepared from 60 wt% of oil dispersion of NaH (35 mg) by rinsing with dry hexane (2 x 5 mL), in DMF (5 mL) was added dropwise a solution of **16** (128 mg, 0.37 mmol) in dry DMF (5 mL) at -25 °C under argon atmosphere. After stirring for 15 min at 0 °C, benzyl chloride (0.1 mL, 0.87 mmol) was added to a pale yellowish reaction mixture and then the mixture was allowed to stir at 0 °C for 1 h and at rt over night, and then the reaction was quenched by careful addition of H_2O (30 mL) on an ice-water bath. The organic layer was separated and the aqueous layer was extracted twice with a mixed solvent (EtOAc/hexane = 1/1, 2 x 20 mL). The combined extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (Et_2O/hexane = 1/1) to give **4** (135 mg, 84% yield) as colorless oil. R_f = 0.57 (Et_2O/hexane = 3/1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.94-2.05 (m, 1H), 2.28 (dddd, *J* = 3.1, 3.1, 6.2, 13.4 Hz, 1H), 2.78 (ddd, *J* = 3.2, 7.1, 10.3 Hz, 1H), 3.01 (dt, *J* = 5.9, 10.3 Hz, 1H), 3.46 (d, *J* = 9.5 Hz, 1H), 3.65 (d, *J* = 9.5 Hz, 1H), 3.81 (d, *J* = 9.0 Hz, 1H), 4.04 (d, *J* = 9.2 Hz, 1H), 4.14 (t, *J* = 3.4 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 2H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 7.24-7.33 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 33.7, 63.6, 71.1, 71.7, 73.1, 73.3, 83.6, 127.3, 127.4, 127.4, 128.2, 128.3, 138.4, 138.7. HRMS *m*/*z* calcd for $C_{27}H_{30}O_3S$ 434.1916, found 434.1892.

Diethyl 2-(3-bromopropyl)malonate. To a suspension of finely powdered K_2CO_3 (22.1 g, 161 mmol) in acetone (200 mL) were added 1,3-dibromopropane (21.7 mL, 214 mmol) and diethyl malonate (16.2 mL, 107 mmol), and the reaction mixture was refluxed with stirring for 4 days. After cooling down to rt, an insoluble solid was removed by filtration and the filtrate was concentrated *in vacuo*. To the residue was added water (50 mL) and extracted twice with EtOAc (2 x 50 mL). The combined extract was dried over $MgSO_4$ and distilled under reduced pressure to give colorless oil (145-147 °C/1.5-1.6 mmHg, 3.3g, 44%), which was column chromatographed on silica gel (Et_2O/hexane = 1/5) to give diethyl 2-(3-bromopropyl)malonate (12.7 g, 42%). R_f = 0.58 (Et_2O/hexane = 1/1); IR (neat) 1732 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 6H), 1.91 (m, 2H), 2.05 (m, 2H), 3.35 (t, *J* = 7.2 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.3, 30.3, 32.6, 51.1, 61.5, 169.1. Anal. Calcd for $C_{10}H_{17}O_4Br$: C, 42.72; H, 6.09. Found: C, 42.98; H. 5.88.

Diethyl 2-bromo-2-(3-bromopropyl)malonate. To a solution of diethyl 2-(3-bromopropyl)malonate (8.90 g, 31.6 mmol) in Et_2O (32 mL) was added bromine (1.63 mL, 31.6 mmol) at 0 °C, and the reaction mixture was refluxed for 70 min. The mixture was added with saturated aq. $NaHCO_3$ solution at 0 °C and extracted twice with ether (2 x 30 mL). The combined extract was dried and concentrated *in vacuo*. The residue was column chromatographed on silica gel to give diethyl 2-bromo-2-(3-bromopropyl)malonate (11.3 g, 99%). R_f = 0.59 (Et_2O/hexane = 1/1); IR (neat) 1742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 6H), 2.02 (m, 2H), 2.44 (m, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 28.7, 32.4, 36.9, 62.4, 63.2, 166.6. Anal. Calcd for $C_{10}H_{16}O_4Br_2$: C, 33.36; H, 4.48. Found: C, 33.66; H, 4.41.

2,2-Di(methoxycarbonyl)tetrahydrothiophene (17). To a solution of diethyl 2-bromo-2-(3-bromopropyl)malonate (5.67 g, 15.7 mmol) in EtOH (20 mL) was added a suspension of sodium sulfide (Na_2S, 1.50 g, 17.3 mmol) in EtOH (40 mL) and the mixture was stirred for 1 h. It (a yellow suspension) was filtrated and concentrated *in vacuo* to remove ethanol, and the residue was diluted with EtOAc (50 mL) and washed with brine. The water layer was extracted twice with EtOAc (2 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel to give **17** as colorless oil (3.05 g, 84%). R_f = 0.59 (Et_2O/hexane = 1/1); IR (neat) 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 6H), 2.19 (tt, *J* = 6.4, 6.4, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 30.9, 34.1, 38.4, 62.2, 66.0, 170.3. Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.71; H, 6.94. Found: C, 51.55; H. 6.84.

2,2-Di(hydroxymethyl)tetrahydrothiophene (18). To a solution of **17** (422 mg, 1.81 mmol) in EtOH (4 mL) was added a suspension of sodium borohydride ($NaBH_4$, 206 mg, 5.43 mmol) in EtOH (2 ml) at 0 °C and the reaction mixture was stirred at rt for 1 day. The mixture was added with saturated aq. ammonium chloride and then concentrated *in vacuo*. The residue was diluted with EtOAc (30 mL) and washed with brine. The water layer was extracted twice with EtOAc (2 x 30 mL). The combined extract was dried over $MgSO_4$ and concentrated to give crude **18** (246 mg, 92%) as white crystal which was pure enough to use for acetylation. The following characterization data of **18** was obtained after further purification by column chromatography on silica gel (Et_2O). R_f = 0.53 (Et_2O); mp 68-72 °C; IR (Nujol mull) 3296 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 6H), 2.19 (tt, *J* = 6.4, 6.4, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6,

33.0, 35.2, 65.3, 67.7. Anal. Calcd for $C_6H_{12}O_2S$: C, 48.62; H, 8.16. Found: C, 48.81; H. 7.89.

2,2-Di(acetoxymethyl)tetrahydrothiophene (5). To a solution of crude **18** (278 mg, 1.68 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (1.41 mL, 10.1 mmol), acetic anhydride (0.97 mL, 5.04 mmol) and a small amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) at 0 °C and the mixture was stirred at rt for 100 min. It was then concentrated *in vacuo*, and the residue was diluted with EtOAc (30 mL) and successively washed with saturated aq. tartaric acid (10mL), saturated aq. $NaHCO_3$ and brine (10 mL). The water layers were also extracted twice with EtOAc (2 x 30 mL). The combined extract was dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was column chromatographed on silica gel (Et_2O/hexane = 2/1) to afford **5** (366 mg, 93%). R_f = 0.46 (Et_2O/hexane = 2/1); IR (neat) 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (t, *J* = 6.4 Hz, 2H), 2.00-2.22 (m, 2H), 2.08 (s, 6H), 2.91 (t, *J* = 6.4 Hz, 2H), 4.09 (d, *J* = 11.2 Hz, 2H), 4.27 (d, *J* = 11.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 29.4, 32.6, 35.6, 67.0, 170.7. Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.71; H, 6.94. Found: C, 51.70; H. 6.92.

2,2-Di(methoxycarbonyl)-2,5-dihydrothiophene (19). To a solution of DMAP (3.16 g, 25.9 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise a solution of **12** (1.14 g, 5.18 mmol) in dry CH_2Cl_2 (10 mL) at -25 °C under argon atmosphere. After stirring for 30 min, trifluoromethanesulfonic anhydride (Tf_2O, 1.9 mL 11.4 mmol) was added dropwise to the mixture for over 15 min at -25 °C and the stirring was continued overnight at rt. To the reaction mixture was added water (30 mL), and then aqueous layer was separated and extracted twice with Et_2O (2 x 30 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1:3 and then Et_2O) to afford 778 mg (74%) of **19** as white solid. R_f = 0.73 (EtOAc/hexane = 1:1); mp 42.0-42.5 °C; IR (neat) 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 6H), 3.88 (t, *J* = 2.5 Hz, 2H), 5.98 (dt, *J* = 2.3, 6.3 Hz, 1H), 6.11 (dt, *J* = 2.6, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.7, 53.5, 73.0, 128.4, 132.6, 169.3. HRMS *m*/*z* calcd for $C_8H_{10}O_4S$ 202.0300, found 202.0307.

2,2-Di(hydroxymethyl)-2,5-dihydrothiophene (20). To a solution of diester **19** (125 mg, 0.62 mmol) in dry THF (3 mL) was added dropwise a hexane solution of DIBAL-H (1.4 mL, 0.95 M, 1.33 mmol) at 0 °C under argon atmosphere. After stirring for 30 min, the reaction mixture was added dropwise with EtOAc (0.1 mL), saturated aq. NaCl (10 mL) and tetrabutylammonium fluoride (0.92 mL, 1.0 M, 0.92 mmol). The mixture was filtrated off under reduced pressure and washed with $CHCl_3$ (20 mL). The filtrate was washed with saturated aq. NaCl (40 mL). The aqueous layer was extracted twice with $CHCl_3$. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1:3 and then EtOAc) to afford 87 mg (96%) of **20** as white crystal. R_f = 0.54 (EtOAc/hexane = 4:1); mp 73-74 °C; IR (neat) 3310 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.14 (t, *J* = 6.6 Hz, 2H), 3.70-3.75 (m, 4H), 3.77 (t, *J* = 2.5 Hz, 2H), 5.67 (dt, *J* = 2.3, 6.2 Hz,

1H), 5.96 (dt, J = 2.6, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.4, 66.9, 73.1, 130.1, 132.0. HRMS m/z calcd for $C_6H_{10}O_2S$ 146.0402, found 146.0409.

2,2-Di(acetoxymethyl)-2,5-dihydrothiophene (6). To a solution of crude **20** (320 mg, 2.19 mmol) in CH_2Cl_2 (22 mL) were added Et_3N (0.91 mL, 6.58 mmol), acetic anhydride (0.62 mL, 6.56 mmol) and a small amount of DMAP at 0 °C and the mixture was stirred at rt for 30 min. It was then concentrated *in vacuo*, and the residue was diluted with EtOAc (30 mL) and successively washed with saturated aq. tartaric acid (10 mL), saturated aq. $NaHCO_3$ (10 mL) and brine (10 mL). The water layers were also extracted twice with EtOAc (2 x 30 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was column chromatographed on silica gel (Et_2O/hexane = 1/3) to afford **4** (443 mg, 88%) as colorless oil. R_f = 0.62 (Et_2O/hexane = 2/1); IR (neat) 1744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 6H), 3.73 (t, J = 2.2 Hz, 2H), 4.24 (d, J = 11.2 Hz, 1H), 4.28 (d, J = 11.2 Hz, 1H), 5.70 (dt, J = 2.4, 6.4 Hz, 1H), 5.98 (d, J = 2.4, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 38.5, 65.5, 67.4, 130.5, 131.2, 170.6. Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13. Found: C, 52.18; H. 6.30.

2-Acetoxy-4,4-di(acetoxymethyl)tetrahydrothiophene (7; Acetyl 4-*C*-acetoxymethyl-5-*O*-acetyl-2,3-dideoxy-4-thioribose). Electrolysis of the thiophene derivative **5** to the thioribose derivative **7** was carried out as follows. A solution of **5** (465 mg, 2.0 mmol) and ammonium acetate (102 mg, 1.32 mmol) in a mixed solvent of acetic acid (0.7 mL) and MeCN (1.5 mL) was electrolyzed at a constant current of 50 mA/cm^2 at two platinum foil electrodes (1 cm^2), placed parallel to each other 4 mm apart, in an undivided cell without cooling. During the electrolysis, the applied voltage was maintained at ca. 5.7 V. After passage of 2.5 F/mol of electricity, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to give the corresponding α-acetoxy sulfide **7** as colorless oil (295 mg, 51%). R_f = 0.33 (Et_2O/hexane = 2/1); IR (neat) 1742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89-2.18 (m, 2H), 2.06 (s, 3H), 2.08 (s, 6H), 2.20-2.36 (m, 2H), 4.09 (d, J = 11.2 Hz, 1H), 4.13 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 11.2 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 6.12 (brd, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.2, 32.8, 35.3, 65.0, 68.3, 82.4, 170.3, 170.6. Anal. Calcd for $C_{12}H_{18}O_6S$: C, 49.64; H, 6.25. Found: C, 49.88; H. 6.10.

2,2-Di(acetoxymethyl)tetrahydrothiophene-*S*-oxide (10) and Pummerer rearrangement of 10 to 7. To a solution of **5** (100 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) was added dropwise a suspension of *m*-CPBA (121 mg 0.56 mmol) in CH_2Cl_2 (2 mL) at 0 ºC and the reaction mixture was stirred at rt for 2 h. The reaction was quenched with saturated aq. $Na_2S_2O_3$ (1 mL) and the mixture was washed with saturated aq. $NaHCO_3$ (5 mL). The aqueous layer was extracted twice with $CHCl_3$ (2 x 10 mL). The

combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (Et_2O) to give **10** (73.3 mg, 69%) [R_f = 0.33 (EtOAc/hexane = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (dt, J = 6.8, 13.6 Hz, 1H), 2.04–2.12 (m, 1H), 2.10 (s, 6H), 2.22 (m, 1H), 2.56 (m 1H), 4.16 (d, *J* = 11.8 Hz, 1H), 4.24 (d, *J* = 11.8 Hz, 1H), 4.40 (s, 2H)]. A mixture of **10** (73.3 mg, 0.295 mmol), tetrabutylammonium acetate (98.0 mg, 0.325 mmol, 1.1 equiv.) and acetic anhydride (2.5 mL) was stirred at 90 °C for 24 h under argon atmosphere. The mixture was concentrated under reduced pressure and the residue was column chromatographed on silica gel to give **7** (37.1 mg, 43%) and by-product **21** (8%). **21**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-2.03 (m, 2H), 2.03-2.20 (m, 2H), 2.095 (s, 3H), 2.097 (s, 3H), 2.12 (s, 3H), 2.89 (t, *J* = 6.6 Hz, 2H), 4.20 (d, *J* = 11.4 Hz, 1H), 4.26 (d, *J* = 11.4 Hz, 1H), 7.01 (s, 1H).

4'-*C*-Acetoxymethyl-5'-*O*-acetyl-2',3'-dideoxy-4'-thiothymidine (23a). To a solution of **7** (171 mg 0.59 mmol) and bis(trimethylsilyl)thymine **22a** (0.40 mL, 1.47 mmol) in dry MeCN (3.9 mL) was added $SnCl_4$ (0.105 mL, 0.88 mmol) at rt under nitrogen atmosphere. After stirring for 15 min, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL) at 0 °C and the mixture was extracted three times with $CHCl_3$ (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1/1) to afford **23a** (209 mg, 99%) as white crystal. R_f = 0.25 (EtOAc/hexane = 4/1); mp 177-178 °C; IR (Nujol mull) 3172, 3045, 1735, 1697, 1683, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86-2.23 (m, 3H), 1.98 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.52 (dt, *J* = 6.3, 13.0 Hz, 1H), 4.13 (d, *J* = 11.4, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 6.39 (t, *J* = 6.4 Hz, 1H), 7.60 (s, 1H), 9.50 (s; 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 20.8, 20.9, 33.1, 35.6, 60.1, 63.1, 66.0, 66.7, 111.6, 135.9, 150.8, 163.6, 170.4, 170.6. Anal. Calcd for $C_{15}H_{20}N_2O_6S$: C, 50.55; H, 5.66; N, 7.86. Found: C, 50.64; H, 5.81; N, 8.03.

4'-*C*-Acetoxymethyl-5'-*O*-acetyl-2',3'-dideoxy-5-fluoro-4'-thiouridine (23b). To a solution of **7** (38 mg 0.131 mmol) and bis(trimethylsilyl)-5-fluorouracil **22b** (0.09 mL, 0.33 mmol) in dry MeCN (1.0 mL) was added $SnCl_4$ (0.023 mL, 0.197 mmol) at rt under nitrogen atmosphere. After stirring for 15 min, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL) at 0 °C and the mixture was extracted three times with $CHCl_3$ (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc) to afford **23b** (46 mg, 98%) as white solid. R_f = 0.31 (EtOAc/hexane = 2/1); mp 168-169 °C; IR (Nujol mull) 3160, 3101, 1738, 1716, 1693, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (μ, 2H), 2.11 (s, 3H), 2.17 (s, 3H), 2.14-2.28 (m, 1H), 2.56 (dt, *J* = 7.2, 14.0 Hz, 1H), 4.12 (d, *J* = 11.4, 1H), 4.26 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 6.30 (t, *J* = 4.8

Hz, 1H), 8.18 (d, J = 12.0 Hz, 1H), 9.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.8, 32.3, 36.2, 60.8, 64.7, 66.1, 66.6, 125.1 (d, $^2J_{CF}$ = 34.8 Hz), 140.2 (d, $^1J_{CF}$ = 235.9 Hz), 149.3, 156.8 (d, $^2J_{CF}$ = 27.4 Hz), 170.4, 170.5. Anal. Calcd for $C_{14}H_{17}FN_2O_6S$: C, 46.66; H, 4.75; N, 7.77. Found: C, 46.68; H, 4.50; N, 7.70.

4'-*C*-Acetoxymethyl-4-*N*,5'-*O*-diacetyl-2',3'-didehydro-2',3'-dideoxy-4'-thiouridine (23c). To a solution of **7** (277 mg 0.954 mmol) and 4-*N*-acetyl-2-*O*-(trimethylsilyl)cytosine **22c** (0.537 mL, 2.39 mmol) in dry MeCN (6.4 mL) was added $SnCl_4$ (0.17 mL, 1.43 mmol) at rt under nitrogen atmosphere. After stirring for 20 min, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL) at 0 °C and the mixture was extracted three times with $CHCl_3$ (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (MeOH/EtOAc = 1/10) to afford **23c** (344 mg, 94%) as white solid. R_f = 0.25 (MeOH/EtOAc = 1/10); mp 187.5-188.5 °C; IR (Nujol mull) 3232, 3125, 3070, 1734, 1712, 1656, 1643, 1620, 1608, 1565 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.11 (s, 3H), 2.31 (s, 3H), 4.27 (d, J = 11.4, 1H), 4.31 (d, J = 11.4 Hz, 2H), 4.37 (d, J = 11.4 Hz, 1H), 5.97 (dd, J = 2.6, 6.2 Hz, 1H), 6.15 (dd, J = 1.8, 6.2 Hz, 1H), 7.14 (brs, 1H), 7.49 (d, J = 7.4 Hz, 1H), 7.96 (d, J = 7.4 Hz, 1H), 10.1 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.775, 20.845, 24.9, 32.2, 36.4, 60.7, 66.06, 66.148, 66.4, 96.9, 145.5, 155.5, 162.7, 170.4, 170.4, 171.2. Anal. Calcd for $C_{16}H_{21}N_3O_6S$: C, 50.12; H, 5.52; N, 10.96. Found: C, 50.11; H, 5.44; N, 10.76.

2',3'-Dideoxy-4'-*C*-hydroxymethyl-4'-thiothymidine (2a). To a solution of **23a** (150 mg, 0.420 mmol) in 1,4-dioxane (2.1 mL) was added aq. NH_3 (29%, 4.2 mL) and the mixture was stirred at rt for 22 h and then concentrated *in vacuo*. The residue was heated at 50 °C to remove acetamide and then recrystallized from $CHCl_3$ to afford **2a** as white solid (110 mg, 97%). R_f = 0.46 (MeOH/$CHCl_3$ = 1/5); mp 179.0-180.0 °C; IR (Nujol mull) 3260, 3190, 1706, 1665 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75-1.84 (m, 1H), 1.80 (s, 3H), 1.94 (m, 1H), 2.16 (dt, J = 6.0, 13.5 Hz, 1H), 2.29 (dt, J = 7.1, 13.5 Hz, 1H), 3.39 (dd, J = 5.4, 10.8 Hz, 1H), 3.49 (dd, J = 5.4, 10.8 Hz, 1H), 3.61 (dd, J = 5.4, 11.2 Hz, 1H), 3.72 (dd, J = 5.4, 11.2 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 5.20 (t, J = 5.4 Hz, 1H), 6.06 (t, J = 6.0 Hz, 1H), 8.02 (s, 1H), 11.3 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.2, 30.9, 34.9, 62.1, 64.0, 64.9, 66.3, 109.1, 137.1, 150.5, 163.5.

2',3'-Dideoxy-5-fluoro-4'-*C*-hydroxymethyl-4'-thiouridine (2b). To a solution of **23b** (120 mg, 0.333 mmol) in 1,4-dioxane (1 mL) was added aq. NH_3 (29%, 2.2 mL) and the mixture was stirred at rt for 120 h and then concentrated *in vacuo* at 50 °C. The residue was column chromatographed on silica gel (MeOH/$CHCl_3$ = 1/8) to afford **2b** in 98% (90 mg) as white solid. R_f = 0.53 (MeOH/$CHCl_3$ = 1/5); mp 179.5-180.5 °C; IR (Nujol mull) 3367, 3127, 1714, 1697, 1647

cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (dt, *J* = 6.7, 13.8 Hz, 1H), 1.93 (dt, *J* = 6.7, 13.8 Hz, 1H), 2.18 (m, 1H), 2.33 (ddt, *J* = 3.2, 6.7, 13.6 Hz, 1H), 3.27-3.43 (m, 1H), 3.47 (dd, *J* = 4.8, 10.8 Hz, 1H), 3.63 (dd, *J* = 4.8, 11.0 Hz, 1H), 3.70 (d, *J* = 4.8, 11.0 Hz, 1H), 5.04 (t, *J* = 4.8 Hz, 1H), 5.35 (t, *J* = 4.8 Hz, 1H), 6.00 (brs, 1H), 8.65 (d, *J* = 7.6 Hz, 1H), 11.8 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 35.4, 63.5, 63.9, 65.1, 66.7, 126.2 (d, $^2J_{CF}$ = 35.0 Hz), 139.2 (d, $^1J_{CF}$ = 227.7 Hz), 149.2, 156.9 (d, $^2J_{CF}$ = 26.2 Hz).

2',3'-Dideoxy-4'-*C*-hydroxymethyl-4'-thiocytidine (2c). To a solution of **23c** (101 mg 0.263 mmol) in 1,4-dioxane (1.3 mL) was added 50% aq. Me_2NH (1.3 mL) and the mixture was stirred at rt for 3 weeks and then concentrated *in vacuo* at 50 °C to remove 1,4-dioxane and *N*,*N*-dimethylacetamide. The residue was recrystallized from MeOH to afford **2c** quantitatively (67 mg) as white solid. R_f = 0.34 (MeOH/$CHCl_3$ = 1/2); mp 211.0-212.0 °C; IR (Nujol mull) 3331, 3138, 1680, 1634, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (m, 2H), 2.,04 (dt, *J* = 6.0, 13.0 Hz, 1H), 2.31 (dt, *J* = 6.0, 13.0 Hz, 1H), 3.25-3.45 (m, 1H), 3.50 (dd, *J* = 5.2, 10.8 Hz, 1H), 3.58 (dd, *J* = 5.2, 10.8 Hz, 1H), 3.70 (dd, *J* = 5.2, 10.8 Hz, 1H), 4.97 (t, *J* = 5.2 Hz, 1H), 5.10 (t, *J* = 5.2 Hz, 1H), 1H), 5.77 (s, 1H), 6.12 (brs, 1H), 7.12 (brs, 2H), 8.10 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 35.2, 62.9, 64.2, 64.6, 65.9, 142.1, 142.1, 155.2, 165.2.

2-Acetoxy-4,4-di(acetoxymethyl)-2,5-dihydrothiophene (8; Acetyl 4-*C*-acetoxymethyl-5-*O*-acetyl-2,3-didehydro-2,3-dideoxy-4-thioribose). A solution of **6** (229 mg, 1.0 mmol) and ammonium acetate (102 mg, 1.32 mmol) in a mixed solvent of acetic acid (0.7 mL) and MeCN (1.5 mL) was electrolyzed at a constant current of 50 mA/cm^2 at two platinum foil electrodes (1 cm^2), placed parallel to each other 4 mm apart, in an undivided cell without cooling. During the electrolysis, the applied voltage was maintained at ca. 5.7 V. After passage of 2.5 F/mol of electricity, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to give the corresponding α-acetoxy sulfide **7** as colorless oil (137 mg, 54%). R_f = 0.39 (Et_2O/hexane = 2/1); IR (neat) 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 6H), 2.09 (s, 3H), 2.20-2.36 (m, 2H), 4.26 (s, 2H), 4.29 (d, *J* = 4.8 Hz, 2H), 6.03 (dd, *J* = 2.8, 6.4 Hz, 1H), 6.10 (d, *J* = 6.4 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.8, 21.0, 65.1, 66.4, 67.2, 84.8, 130.3, 136.4, 170.4, 170.4. Anal. Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59. Found: C, 50.02; H. 5.56. HRMS *m*/*z* calcd for $C_{12}H_{16}O_6S$: 288.0668, found 288.0575.

4'-*C*-Acetoxymethyl-5'-*O*-acetyl-2',3'-didehydro-2',3'-dideoxy-4'-thiothymidine (24a). To a solution of **8** (154 mg 0.53 mmol) and bis(trimethylsilyl)thymine **22a** (0.35 mL, 1.33 mmol) in dry MeCN (3.5 mL) was added $SnCl_4$ (0.10 mL, 0.80 mmol) at rt under nitrogen atmosphere. After stirring for 15 min, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL) at 0 °C and the mixture was extracted three times with $CHCl_3$ (3 x 20 mL). The combined extracts

were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1/1 and then MeOH/EtOAc = 1/4) to afford **24a** (137 mg, 73%) as white crystal. R_f = 0.32 (EtOAc/hexane = 4/1); mp 160-161 °C; IR (Nujol mull) 3169, 3047, 1746, 1693, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 4.24 (d, *J* = 11.6, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 5.88 (dd, *J* = 2.4, 6.2 Hz, 1H), 6.12 (dd, *J* = 1.6, 6.2 Hz, 1H), 7.10 (dd, *J* = 2.1, 2.1 Hz, 1H), 7.23 (s, 1H), 9.52 (s; 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 20.8, 20.9, 66.1, 66.7, 67.2, 67.5, 112.3, 130.8, 135.6, 136.5, 150.7, 170.3, 170.4. Anal. Calcd for $C_{15}H_{18}N_2O_6S$: C, 50.84; H, 5.12; N, 7.91. Found: C, 50.89; H, 5.12; N, 8.05.

4'-*C*-Acetoxymethyl-5'-*O*-acetyl-2',3'-didehydro-2',3'-dideoxy-5-fluoro-4'-thiouridine (24b). To a solution of **8** (62 mg 0.21 mmol) and bis(trimethylsilyl)-5-fluorouracil **22b** (0.14 mL, 0.53 mmol) in dry MeCN (1.4 mL) was added $SnCl_4$ (0.04 mL, 0.32 mmol) at rt under nitrogen atmosphere. After stirring for 15 min, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL) at 0 °C and the mixture was extracted three times with $CHCl_3$ (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc and then MeOH/EtOAc = 1/10) to afford **24b** (74 mg, 99%) as white solid. R_f = 0.28 (EtOAc/hexane = 2/1); mp 163-165 °C; IR (Nujol mull) 3172, 1741, 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.15 (s, 3H), 4.23 (d, *J* = 11.4 Hz, 1H), 4.31 (d, *J* = 11.2 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.2 Hz, 1H), 5.88 (dd, *J* = 2.4, 6.2 Hz, 1H), 6.12 (dd, *J* = 2.0, 6.2 Hz, 1H), 7.11 (brd, *J* = 2.4 Hz, 1H), 7.76 (d, *J* = 5.6 Hz, 1H), 9.61 (s; 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.7, 66.6, 66.8, 68.07, 68.11, 124.5 (d, $^2J_{CF}$ = 34.7 Hz), 130.3, 137.3, 140.8 (d, $^1J_{CF}$ = 237.7 Hz), 149.2, 156.6 (d, $^2J_{CF}$ = 28.4 Hz), 170.2, 179.3. Anal. Calcd for $C_{14}H_{15}FN_2O_6S$: C, 46.93; H, 4.22; N, 7.82. Found: C, 46.70; H, 4.32; N, 7.63.

4'-*C*-Acetoxymethyl-4-*N*,5'-*O*-diacetyl-2',3'-didehydro-2',3'-dideoxy-4'-thiouridine (24c). To a solution of **8** (107 mg 0.37 mmol) and 4-*N*-acetyl-2-*O*-(trimethylsilyl)cytosine **22c** (0.21 mL, 0.93 mmol) in dry MeCN (2.5 mL) was added $SnCl_4$ (0.07 mL, 0.56 mmol) at rt under nitrogen atmosphere. After stirring for 20 min, the reaction was quenched with saturated aq. $NaHCO_3$ (20 mL) at 0 °C and the mixture was extracted three times with $CHCl_3$ (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (MeOH/EtOAc = 1/10) to afford **24c** (132 mg, 94%) as white solid. R_f = 0.36 (MeOH/EtOAc = 1/10); mp 177.5-178.5 °C; IR (Nujol mull) 3259, 3077, 1747, 1727, 1661, 1632, 1554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.11 (s, 3H), 2.31 (s, 3H), 4.27 (d, *J* = 11.4, 1H), 4.31 (d, *J* = 11.4 Hz, 2H), 4.37 (d, *J* = 11.4 Hz, 1H), 5.97 (dd, *J* = 2.6, 6.2 Hz,

1H), 6.15 (dd, *J* = 1.8, 6.2 Hz, 1H), 7.14 (brs, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 1H), 10.1 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 25.0, 66.2, 66.8, 67.6, 68.8, 98.0, 130.5, 137.0, 145.0, 155.5, 162.9, 170.3, 170.3, 171.2. Anal. Calcd for $C_{16}H_{19}N_3O_6S$: C, 50.39; H, 5.02; N, 11.02. Found: C, 50.51; H, 5.06; N, 10.84.

2',3'-Didehydro-2',3'-dideoxy-4'-*C*-hydroxymethyl-4'-thiothymidine (3a). To a solution of **24a** (107 mg, 0.30 mmol) in 1,4-dioxane (3 mL) was added 50% aq. Me_2NH (6.0 mL) and the mixture was stirred at rt for 29 h and then concentrated *in vacuo* at 50 °C. The residue was column chromatographed on silica gel (MeOH/$CHCl_3$ = 1/7) to afford **3a** quantitatively as a white solid (82 mg). R_f = 0.44 (MeOH/$CHCl_3$ = 1/5); mp 200.0-201.0 °C; IR (Nujol mull) 3471, 3427, 3140, 3067, 1697, 1682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75, (d, *J* = 1.0 Hz, 3H), 3.53 (dd, *J* = 6.4, 10.4, 1H), 3.57 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.66 (dd, *J* = 5.2, 11.2 Hz, 1H), 3.77 (dd, *J* = 5.2, 11.2 Hz, 1H), 5.14 (t, *J* = 5.2 Hz, 1H), 5.27 (t, *J* = 5.2 Hz, 1H), 5.84 (dd, *J* = 2.4, 6.4 Hz, 1H), 6.12 (dd, *J* = 2.0, 6.4 Hz, 1H), 6.79 (brs, 1H), 7.73 (d, *J* = 1.0 Hz, 1H), 11.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 64.6, 66.2, 66.3, 73.1, 109.6, 128.4, 136.9, 139.0, 150.5, 163.6. HRMS (FAB) *m*/*z* calcd for $C_{11}H_{15}N_2O_4S$ $[MH]^+$ 271.0753, found 271.0773.

2',3'-Didehydro-2',3'-dideoxy-5-fluoro-4'-*C*-hydroxymethyl-4'-thiouridine (3b). To a solution of **24b** (59 mg, 0.16 mmol) in 1,4-dioxane (3 mL) was added 50% aq. Me_2NH (3.0 mL) and the mixture was stirred at rt for 29 h and then concentrated *in vacuo* at 50 °C. The residue was column chromatographed on silica gel (MeOH/$CHCl_3$ = 1/7) to afford **3b** in 98% (43 mg) as a white solid. R_f = 0.39 (MeOH/$CHCl_3$ = 1/5); mp 171.0-172.0 °C; IR (Nujol mull) 3174, 3050, 1723, 1658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (d, *J* = 10.6 Hz, 1H), 3.58 (d, *J* = 10.6 Hz, 1H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.82 (d, *J* = 11.2 Hz, 1H), 5.20 (s, 1H), 5.40 (s, 1H), 5.84 (dd, *J* = 2.4, 6.4 Hz, 1H), 6.12 (dd, *J* = 1.2, 6.4 Hz, 1H), 6.78 (brd, *J* = 2.0 Hz, 1H), 8.31 (d, *J* = 6.8 Hz, 1H), 11.9 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.5, 66.7, 66.9, 73.4, 125.7 (d, $^2J_{CF}$ = 35.0 Hz), 128.2, 139.5, 139.7 (d, $^1J_{CF}$ = 229.1 Hz), 149.1, 156.9 (d, $^2J_{CF}$ = 26.3 Hz). HRMS (FAB) *m*/*z* calcd for $C_{10}H_{12}FN_2O_4S$ $[MH]^+$ *m*/*z* 275.0502, found 275.0501.

2',3'-Didehydro-2',3'-dideoxy-4'-*C*-hydroxymethyl-4'-thiocytidine (3c). To a solution of **24c** (101 mg 0.27 mmol) in 1,4-dioxane (2.6 mL) was added 50% aq. Me_2NH (5.2 mL) and the mixture was stirred at rt for 28 h and then concentrated *in vacuo* at 50 °C to remove 1,4-dioxane and *N*,*N*-dimethylacetamide. The residue was recrystallized from MeOH to afford **3c** in 94% (65 mg) as a white crystal. R_f = 0.11 (MeOH/$CHCl_3$ = 1/5); mp 204.0-205.0 °C; IR (Nujol mull) 3353, 3146, 1665, 1591, 1518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (dd, *J* = 6.4, 10.6 Hz, 1H), 3.58 (dd, *J* = 5.2, 10.6 Hz, 1H), 3.64 (dd, *J* = 5.2, 11.2 Hz, 1H), 3.69 (dd, *J* = 5.2, 11.2 Hz, 1H), 5.09 (t, *J*

= 5.2 Hz, 1H), 5.11 (t, *J* = 5.2 Hz, 1H), 1H), 5.75 (dd, *J* = 7.6 Hz, 1H), 5.81 (dd, *J* = 2.4, 6.4 Hz, 1H), 6.11 (dd, *J* = 1.6, 6.4 Hz, 1H), 6.83 (brs, 1H), 7.20 (brd, *J* = 12.8 Hz, 2H), 7.69 (d, *J* = 7.2 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.8, 65.9, 66.9, 72.3, 94.7, 128.8, 138.5, 141.8, 155.2, 165.4. HRMS (FAB) *m*/*z* calcd for $C_{10}H_{14}N_3O_3S$ $[MH]^+$ 256.0756, found 256.0799.

3-Benzyloxy-2,2-di(benzyloxymethyl)tetrahydrothiophene-*S*-oxide (9). To a solution of **4** (1.20 g, 2.77 mmol) in CH_2Cl_2 (29.0 mL) was added dropwise a suspension of *m*-CPBA (889 mg, 80 wt%, 4.13 mmol) in CH_2Cl_2 (6 mL) at -25 °C and the mixture was stirred for 25 min. The reaction was quenched with saturated aq. $Na_2S_2O_3$ (5 mL) and the reaction mixture was washed with saturated aq. Na_2CO_3 (10 mL). The aqueous layer was extracted twice with $CHCl_3$ (2 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was column chromatographed on silica gel (EtOAc/hexane = 1/1 and then EtOAc) to afford 1.20 g (96%) of a diastereoisomeric mixture (1/1.5) of **9**. R_f = 0.56 (EtOAc); **less polar isomer**: IR (neat) 1099 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (dt, *J* = 5.5, 18.9 Hz, 1H), 2.46 (ddt, *J* = 6.7, 10.2, 13.5 Hz, 1H), 2.87 (dt, *J* = 6.5, 12.5 Hz, 1H), 2.97 (ddd, *J* = 6.4, 10.5, 13.o Hz, 1H), 3.71 (d, *J* = 9.8 Hz, 1H), 3.81 (d, *J* = 10.7 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 4.04 (d, *J* = 10.7 Hz, 1H), 4.21 (dd, *J* = 5.7, 6.9 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 7.20-7.33 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 49.3, 65.1, 70.6, 72.3, 73.0, 73.6, 73.7, 82.2, 127.4, 127.5, 127.7, 127.8, 128.2, 128.3, 128.4, 137.5, 137.9, 138.3; **polar isomer**: IR (neat) 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30-2.38 (m, 1H), 2.59-2.70 (m, 2H), 3.26-3.36 (m, 1H), 3.56 (d, *J* = 10.1 Hz, 1H), 3.90 (d, *J* = 10.1 Hz, 1H), 3.91 (d, *J* = 10.4 Hz, 1H), 4.03 (d, *J* = 10.1 Hz, 1H), 4.27 (t, *J* = 5.7 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 7.21-7.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 50.4, 67.0, 67.2, 72.5, 72.9, 73.6, 73.8, 82.4, 127.5, 127.6, 127.6, 127.8, 128.3, 128.4, 137.8, 137.9, 138.0. HRMS *m*/*z* calcd for $C_{27}H_{30}O_4S$ (diastereoisomeric mixture) 450.1865, found 450.1892.

3'-*O*-Benzyl-4'-*C*-benzyloxymethyl-2'-deoxy-4'-thiothymidine (25a). To a suspension of thymine (236 mg, 1.87 mmol) in CH_2Cl_2 (5.5 mL) were added dropwise triethylamine (0.73 mL, 5.30 mmol) and TMSOTf (0.96 mL, 5.30 mmol) at 0 °C under argon atmosphere. After stirring at rt for 5 min, **9** (241 mg, 0.53 mmol) in CH_2Cl_2 (10 mL) solution and ZnI_2 (51 mg, 0.16 mmol) were added to the reaction mixture at 0 °C. The mixture was stirred at rt for 4 h and then poured into saturated aq. $NaHCO_3$ (20 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted twice with EtOAc (2 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1/2) to afford **25a** (179 mg) in 60% yield as a

mixture of *cis* and *trans* isomers (*trans*/*cis* = 1.2/1). The isomers were separated by column chromatography on silica gel (EtOAc/hexane = 1/5→1/3) followed by recrystallization (MeOH/$CHCl_3$) to give *trans*-**25a** and *cis*-**25a**. *trans*-**24a**: R_f = 0.44 (EtOAc/hexane = 3/1); mp 138-142 ºC, IR (neat) 3163, 1708, 1677, 1460 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.60 (d, *J* = 0.9 Hz, 3H), 2.31 (ddd, *J* = 4.3, 8.0, 13.3 Hz, 1H), 2.58 (ddd, *J* = 4.4, 6.5, 13.5 Hz, 1H), 3.72 (t, *J* = 9.2 Hz, 2H), 3.88 (t, *J* = 8.7 Hz, 2H), 4.24 (t, *J* = 4.1 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 6.41 (t, *J* = 7.2 Hz, 1H), 7.26-7.36 (m, 15H), 7.84 (d, *J* = 1.2 Hz, 1H), 8.30 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 40.3, 60.2, 65.1, 71.9, 72.2, 73.5, 73.6, 73.8, 82.1, 111.1, 127.5, 127.6, 127.8, 128.0, 128.3, 128.4, 128.6, 137.1, 137.6, 137.6, 138.0, 150.5, 163.4; HRMS *m*/*z* calcd for $C_{32}H_{35}N_2O_5S$ $[MH]^+$ 559.2267, found 559.2285. *cis*-**24a**: R_f = 0.43 (EtOAc/hexane = 3/1); mp 115-116 ºC, IR (neat) 3231, 1708, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (d, *J* = 0.9 Hz, 3H), 2.42 (ddd, *J* = 3.2, 3.2, 14.5 Hz, 1H), 2.57 (ddd, *J* = 4.2, 7.7, 14.6 Hz, 1H), 3.43 (d, *J* = 9.5 Hz, 1H), 3.69 (d, *J* = 9.5 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 4.08 (d, *J* = 9.4 Hz, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 4.42 (s, 2H), 4.49 (d, *J* = 9.5 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.62 (s, 2H), 6.26 (dd, *J* = 3.1, 7.7 Hz, 1H), 7.26-7.35 (m, 15H), 7.95 (d, *J* = 1.3 Hz, 1H), 7.96 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 40.4, 60.6, 66.7, 70.4, 72.0, 72.8, 73.4, 73.5, 82.8, 110.0, 127.6, 127.6, 127.6, 127.7, 127.8, 128.0, 128.4, 128.4, 128.5, 137.1, 137.8, 137.9, 138.7, 150.8, 163.5; HRMS *m*/*z* calcd for $C_{32}H_{35}N_2O_5S$ $[MH]^+$ 559.2267, found 559.2248.

3'-*O*-Benzyl-4'-*C*-benzyloxymethyl-2'-deoxy-5-fluoro-4'-thiouridine (25b). To a suspension of 5-fluorouracil (215 mg, 1.71 mmol) in CH_2Cl_2 (5 mL) were added dropwise triethylamine (0.65 mL, 4.70 mmol) and TMSOTf (0.85 mL, 4.70 mmol) at 0 °C under argon atmosphere. After stirring at rt for 5 min, **9** (213 mg, 0.47 mmol) in CH_2Cl_2 (10 mL) solution and ZnI_2 (45 mg, 0.14 mmol) were added to the reaction mixture at 0 °C. The mixture was stirred at rt for 19 h and then poured into saturated aq. $NaHCO_3$ (20 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted twice with EtOAc (2 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was column chromatographed on silica gel (EtOAc/hexane = 1/2) to afford **25b** (179 mg) in 67% yield as a mixture of *cis* and *trans* isomers (*trans*/*cis* = 2.4/1). The isomers were separated by column chromatography on silica gel (EtOAc/hexane = 1/5→1/3) followed by recrystallization (MeOH/$CHCl_3$) to give *trans*-**25b** and *cis*-**25b**. *trans*-**25b**: R_f = 0.60 (EtOAc/hexane = 3/1); mp 46-47 ºC, IR (neat) 3169, 1718, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.27 (ddd, *J* = 4.3, 7.5, 13.1 Hz, 1H), 2.57 (ddd, *J* = 4.4, 6.3, 13.4 Hz, 1H), 3.67 (d, *J* = 9.2 Hz, 1H), 3.74 (d, *J* = 10.1 Hz, 1H), 3.83 (t, *J* = 10.1 Hz, 1H), 3.83 (d, *J* = 9.2 Hz, 1H), 4.19 (t, *J* = 4.4 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 6.31 (t, *J* = 6.9 Hz, 1H), 7.23-7.37

(m, 15H), 8.30 (brd, *J* = 4.3 Hz, 1H), 8.36 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5, 61.1, 65.1, 68.0, 71.8, 72.2, 73.5, 73.5, 73.7, 81.9, 125.6, 125.9, 127.4, 127.6, 127.8, 128.0, 128.1, 128.3, 128.3, 128.5, 137.0, 137.4, 137.8, 139.0, 149.4, 156.8, 157.0; HRMS *m*/*z* calcd for $C_{31}H_{31}FN_2O_5SNa$ $[MNa]^+$ 585.1835, found 585.1866. ***cis*-25b**: R_f = 0.60 (EtOAc/hexane = 3/1); mp 118-120 ºC, IR (neat) 3231, 1720, 1712, 1458 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (ddd, *J* = 2.9, 2.9, 14.6 Hz, 1H), 2.56 (ddd, *J* = 4.4, 7.9, 14.7 Hz, 1H), 3.40 (d, *J* = 9.8 Hz, 1H), 3.66 (d, *J* = 9.85 Hz, 1H), 3.95 (d, *J* = 9.2 Hz, 1H), 4.04 (d, *J* = 9.2 Hz, 1H), 4.16 (d, *J* = 3.7 Hz, 1H), 4.42 (d, J = 11.3 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.58 (d, J = 12.4 Hz, 1H), 4.61 (d, J = 12.2 Hz, 1H), 6.18 (t, *J* = 7.3 Hz, 1H), 7.17-7.35 (m, 15H), 8.35 (d, *J* = 4.2 Hz, 1H), 8.52 (brd, J = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6, 61.8, 67.0, 70.2, 72.3, 72.6, 73.4, 73.6, 82.5, 127.1, 127.5, 127.7, 127.7, 127.8, 128.1, 128.4, 128.4, 128.6, 136.8, 137.7, 137.9, 141.0, 149.6, 156.6, 157.0; HRMS *m*/*z* calcd for $C_{31}H_{31}FN_2O_5S$ $[MH]^+$ 562.1938, found 562.1945.

***trans*-2'-Deoxy-4'-*C*-hydroxymethyl-4'-thiothymidine (*trans*-1a).** To a solution of ***trans*-25a** (199 mg, 0.34 mmol) in EtOH (7 mL) was added $Pd(OH)_2$ on carbon (299 mg), and the mixture was stirred at rt for 3 days under hydrogen (balloon). The mixture was filtered off and concentrated *in vacuo*. The residue was column chromatographed on silica gel (MeOH/$CHCl_3$ = 1/5) to give white solid, which could be recrystallized from MeOH/$CHCl_3$ for further purification (85 mg, 83%). ***trans*-1a**; R_f = 0.55 (MeOH/$CHCl_3$ = 1/5); HRMS (FAB) *m*/*z* calcd for $C_{11}H_{17}N_2O_5S$ $[MH]^+$ 289.0858, found 289.0818.

***cis*-2'-Deoxy-4'-*C*-hydroxymethyl-4'-thiothymidine (*cis*-1a).** To a solution of ***cis*-25a** (160 mg, 0.29 mmol) in EtOH (6 mL) was added $Pd(OH)_2$ on carbon (240 mg), and the mixture was stirred at rt for 3 days under hydrogen (balloon). The mixture was filtered off and concentrated *in vacuo*. The residue was column chromatographed on silica gel (MeOH/$CHCl_3$ = 1/5) to give white solid, which could be recrystallized from MeOH/$CHCl_3$ for further purification (75 mg, 91%). ***cis*-1a**; R_f = 0.55 (MeOH/$CHCl_3$ = 1/5); HRMS (FAB) *m*/*z* calcd for $C_{11}H_{17}N_2O_5S$ $[MH]^+$ 289.0858, found 289.0854.

***trans*-2'-Deoxy-5-fluoro-4'-*C*-hydroxymethyl-4'-thiothymidine (*trans*-1b).** To a solution of ***trans*-25b** (101 mg, 0.18 mmol) in EtOH (4 mL) was added $Pd(OH)_2$ on carbon (152 mg), and the mixture was stirred at rt for 3 days under hydrogen (balloon). The mixture was filtered off and concentrated *in vacuo*. The residue was column chromatographed on silica gel (MeOH/$CHCl_3$ = 1/5) to give white solid, which could be recrystallized from MeOH/$CHCl_3$ for further purification (46 mg, 88%). ***trans*-1b**; R_f = 0.32 (MeOH/$CHCl_3$ = 1/5); HRMS (FAB) *m*/*z* calcd for $C_{10}H_{14}FN_2O_5S$ $[MH]^+$ 293.0607, found 293.0628.

***cis*-2'-Deoxy-5-fluoro-4'-*C*-hydroxymethyl-4'-thiothymidine (*cis*-1b).** To a solution of ***cis*-25b** (56 mg, 0.10 mmol) in EtOH (2 mL) was added $Pd(OH)_2$ on carbon (84 mg), and the mixture was stirred at rt for 3 days under hydrogen (balloon). The mixture was filtered off and concentrated *in vacuo*. The

residue was column chromatographed on silica gel (MeOH/$CHCl_3$ = 1/5) to give white solid, which could be recrystallized from MeOH/$CHCl_3$ for further purification (26 mg, 89%). ***cis*-1b**; R_f = 0.32 (MeOH/$CHCl_3$ = 1/5); HRMS (FAB) *m/z* calcd for $C_{10}H_{14}FN_2O_5S$ $[MH]^+$ 293.0607, found 293.0565.

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9. In our preliminary experiments, we have obtained some following results. Electrochemical 2-acetoxylation of a sulfide bearing an acetoxy functionality, such as **5** and **6**, gave the desired products, such as **7** and **8**, more easily than that of the corresponding benzyloxy derivatives. However, Pummerer reaction of sulfides bearing a benzyloxy functionality, such as **4**, gave the

corresponding 2-substituted sulfides, such as **25a**,**b** (*via m*-CPBA oxidation of **4** to **9**), in better yield rather than that of the corresponding acetoxy derivative, although 30 mol% of $Pd(OH)_2$-C (expensive catalyst) was required for debenzylation of tri-benzyloxy compounds **25a**,**b** to afford triols **1a**,**b** in good yield.