**<Supporting Information>**

# Synthesis and Anti-HIV Activity of 4′-Substituted 4′-Thiothymidines: A New Entry Based on Nucleophilic Substitution of 4′-Acetoxy Group

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**CONTENTS**



**Chemistry** Melting points are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded either at 400 MHz or at 500 MHz. Chemical sifts are reported relative to $Me_4Si$. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix. Column chromatography was carried out on silica gel. Thin-layer chromatography (TLC) was performed on silica gel. When necessary, analytical samples were purified by high performance liquid chromatography (HPLC). THF was distilled from benzophenone ketyl.

**1-[2-Deoxy-2-iodo-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-β-D-ribofuranosyl]thymine (8)**

To an $CH_3CN$ (30.0 mL) solution of bis-*O*-TMS-thymine, prepared from thymine (4.40 g, 34.88 mmol) and *N*,*O*-bis-trimethylsilylacetamide (17.21 mL, 69.75 mmol), was added an $CH_3CN$ (40 mL)/$CH_2Cl_2$ (20 mL) solution of **7** (8.71 g, 23.25 mmol). To the

mixtute was added *N*-iodosuccimide (7.85 g, 34.88 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 5 h, and was partitioned between $CHCl_3$/saturated aq $NaHCO_3$-0.2 M $Na_2S_2O_3$. Column chromatography (hexane/AcOEt = 3/1) of the organic layer gave **8** (10.86 g, 75%) as foam: UV (MeOH)$\lambda_{max}$ 270 nm (ε11500),$\lambda_{min}$ 236 nm (ε3000); $^1$H NMR ($CDCl_3$)δ0.96-1.12 (32H, m), 1.93 (3H, d, *J* = 1.2 Hz), 3.37 (1H, dd, *J* = 4.4 and *J* = 8.8 Hz), 3.68 (1H, ddd, *J* = 8.8, *J* = 2.0 and *J* = 3.2 Hz), 4.01 (1H, dd, *J* = 2.0 and *J* = 13.2 Hz), 4.12 (1H, dd, *J* = 3.2 and *J* = 13.2 Hz), 4.47 (1H, dd, *J* = 1.6 and *J* = 4.4 Hz), 6.07 (1H, d, *J* = 1.6 Hz), 8.07 (1H, d, *J* = 1.2 Hz), 8.44 (1H, br); NOE experiment: H-1′/H-4′ (1.0%), H-6/H-3′ (7.6%), H-6/H-5′a (0.3%) and H-6/H-2′ (1.7%); $^{13}$C NMR ($CDCl_3$)δ: 12.6, 12.7, 13.1, 13.2, 13.4, 16.91, 16.95, 16.97, 17.06, 17.3, 17.4, 17.5, 38.7, 54.0, 58.2, 67.2, 71.4, 76.7, 110.5, 136.3, 150.4, 163.3. FAB-MS (*m/z*) 627 ($M^+$+H). *Anal*. Calcd for $C_{22}H_{39}IN_2O_5SSi_2$: C, 42.16; H, 6.27; N, 4.47. Found: C, 42.25; H, 6.28; N, 4.42.

**1-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-β-D-ribo-furanosyl]thymine (9)**

To a toluene (70 mL) solution of **8** (10.76 g, 17.17 mmol) was added $Bu_3SnH$ (5.1 mL, 18.89 mmol) and $Et_3B$ (1 M THF solution) (1.7 mL, 1.7 mmol) at −70 °C under Ar atmosphere. The reaction mixture was stirred under $O_2$ atmosphere at −70 °C for 1.5 h. The reaction mixture was chromatographed on silica gel column (hexane/AcOEt = 2/1) to give **9** (8.56 g, 100%) as solid: mp 147-149 °C; UV (MeOH)$\lambda_{max}$ 271 nm (ε10900),λ

$_{min}$ 242 nm (ε5200); $^1$H NMR ($CDCl_3$)δ1.00-1.15 (32H, m), 1.93 (3H, d, *J* = 1.2 Hz), 2.26 (1H, dd, *J* = 13.6 and *J* = 6.0 Hz), 2.48 (1H, ddd, *J* = 8.0, *J* = 13.6 and *J* = 12.0 Hz), 3.33 (1H, ddd, *J* = 9.2, *J* = 1.6 and *J* = 3.2 Hz), 3.96 (1H, dd, *J* = 1.6 and *J* = 12.8 Hz), 4.13 (1H, dd, *J* = 3.2 and *J* = 12.8 Hz), 4.46 (1H, ddd, *J* = 6.0, *J* = 12.0 and *J* = 9.2 Hz), 6.05 (1H, d, *J* = 8.0 Hz), 7.89 (1H, d, *J* = 1.2 Hz), 8.42 (1H, br); $^{13}$C NMR ($CDCl_3$)δ: 12.4, 12.5, 12.9, 13.2, 13.4, 16.89, 16.97, 17.06, 17.14, 17.3, 17.4, 17.5, 43.0, 54.9, 57.1, 58.1, 70.9, 110.8, 136.6, 150.6, 163.5. FAB-MS (*m/z*) 501 ($M^+$+H). *Anal*. Calcd for $C_{22}H_{40}N_2O_5SSi_2$: C, 52.76; H, 8.05; N, 5.59. Found: C, 52.58; H, 8.17; N, 5.51.

**1-[2-Deoxy-3,5-di-*O*-acetyl-4-thio-β-D-ribofuranosyl]thymine (10)**

To a THF (70 mL) solution of **9** (8.52 g, 17.01 mmol) was added $Ac_2O$ (8.0 mL, 85.05 mmol) and $Bu_4NF$ (1 M THF solution) (51 mL, 51.03 mmol) at 0 °C under Ar atmosphere. After stirring for 5 h at rt, the reaction mixture was partitioned between $CHCl_3$/saturated aq $NaHCO_3$. Silica gel column chromatography (hexane/AcOEt = 1/2) of the organic layer gave **10** (5.41 mg, 93%) as foam: UV (MeOH)$\lambda_{max}$ 270 nm (ε9900), $\lambda_{min}$ 236 nm (ε2500); $^1$H NMR ($CDCl_3$)δ1.98 (3H, d, *J* = 1.2 Hz), 2.13 and 2.15 (6H, each as s), 2.20 (1H, ddd, *J* = 9.2 and *J* = 13.6 and *J* = 4.4 Hz), 2.54 (1H, ddd, *J* = 6.4, *J* = 13.6 and *J* = 2.4 Hz), 3.71 (1H, ddd, *J* = 2.0, *J* = 7.6 and *J* = 6.0 Hz), 4.20 (1H, dd, *J* = 7.6 and *J* = 11.6 Hz), 4.37 (1H, dd, *J* = 6.0 and *J* = 11.6 Hz), 5.38 (1H, ddd, *J* = 4.4, *J* = 2.4 and *J* = 2.0 Hz), 6.56 (1H, dd, *J* = 9.2 and *J* = 6.4 Hz), 7.53 (1H, d, *J* = 1.2 Hz), 8.66 (1H, br); $^{13}$C NMR ($CDCl_3$)δ12.7, 20.8, 21.0, 39.4, 52.6, 61.1, 64.9, 76.4, 112.3, 135.4,

150.7, 163.2, 170.1, 170.5. FAB-MS (*m/z*) 343 ($M^+$+H). *Anal*. Calcd for $C_{14}H_{18}N_2O_6S$: C, 49.11; H, 5.30; N, 8.18. Found: C, 49.14; H, 5.33; N, 7.93.

**1-[-2,5-Dideoxy-5-iodo-4-thio-β-D-ribofuranosyl]thymine (11)**

Compound **10** (5.94 g, 17.35 mmol) was treated with $NH_3$/MeOH (200 mL) at rt for 12 h. The reaction mixture was evaporated to dryness and the residue was dried in vacuo overnight. To a dioxane (120 mL) solution of the residue was added pyridine (3.5 mL, 43.38 mmol), $PPh_3$ (9.1 g, 34.7 mmol) and iodine (8.81 g, 34.7 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred at rt for 10 h and chromatographed on silica gel (4% MeOH in $CH_2Cl_2$) to give **11** (5.16 g, 81%) as solid: mp 184-186 °C; UV (MeOH)$\lambda_{max}$ 269 nm (ε11300),$\lambda_{min}$ 236 nm (ε4800); $^1$H NMR ($CDCl_3$)δ1.91 (3H, d, *J* = 1.2 Hz), 2.29–2.38 (2H, m), 3.58 (1H, br), 3.58 (2H, br), 4.56 (1H, dd, *J* = 2.4 and *J* = 3.6), 6.48 (1H, dd, *J* = 8.0 and *J* = 7.6 Hz), 7.74 (1H, d, *J* = 1.2 Hz), 8.66 (1H, br); $^{13}$C NMR (DMSO-$d_6$)δ: 11.0, 12.0, 58.3, 61.2, 75.7, 95.4, 110.3, 136.7, 150.6, 163.4. FAB-MS (*m/z*) 369 ($M^+$+H). *Anal*. Calcd for $C_{10}H_{13}IN_2O_3S$: C, 32.62; H, 3.56; N, 7.61. Found: C, 32.91; H, 3.36; N, 7.23.

**1-[3-*O*-Acetyl-2,5-dideoxy-β-D-*glycero*-4-eno-4-thiofuranosyl]thymine (12)**

To an $CH_3CN$ (30 mL) suspension of **11** (5.16 g, 14.01 mmol) was added *i*-$Pr_2NEt$ (7.3 mL, 42.03 mmol), $Ac_2O$ (2.6 mL, 28.02 mmol) and DMAP (856.4 mg, 7.01 mmol) at 0°C under Ar atmosphere. After stirring for 18 h at rt, the reaction mixture was partitioned between $CHCl_3$/saturated aq $NaHCO_3$. Silica gel column chromatography

(5% MeOH in $CH_2Cl_2$) of the organic layer gave the 5'-*O*-acetate. To an $CH_3CN$ (35 mL) solution of the acetate was added DBN (4.1 mL, 33.48 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred at rt for 24 h, neutralized with acetic acid, and partitioned between $CHCl_3$/sat. $NaHCO_3$. The organic layer was chromatographed on a silica gel column (3% MeOH in $CH_2Cl_2$) to give **12** (3.29 g, 83%) as foam: $^1$H NMR ($CDCl_3$)δ1.97 (3H, d, *J* = 0.8 Hz), 2.12 (3H, s), 2.20 (1H, ddd, *J* = 8.4, *J* = 13.6 and *J* = 4.8 Hz), 2.57 (1H, ddd, *J* = 6.4, *J* = 13.6 and *J* = 3.2 Hz), 5.26 (1H, s), 5.52 (1H, s), 5.85 (1H, dd, *J* = 4.8 and *J* = 2.4 Hz), 6.77 (1H, dd, *J* = 8.4 and *J* = 6.4 Hz), 7.35 (1H, d, *J* = 0.8 Hz), 9.31 (1H, br); $^{13}$C NMR ($CDCl_3$)δ: 12.1, 20.9, 61.3, 77.0, 108.9, 110.7, 136.3, 145.6, 150.6, 163.4, 169.6, 170.3. FAB-MS (*m/z*) 283 ($M^+$+H). High resolution FAB-MS (*m/z*): calcd for $C_{12}H_{15}N_2O_4S$ : 283.0753 ($M^+$ + H). Found: 283.0745.

**1-[3-*O*-(*t*-Butyldimethylsilyl)-2,5-dideoxy-β-D-*glycero*-4-eno-4-thiofuranosyl]thymine (13)**

Compound **12** (3.5 g, 12.40 mmol) was treated with $NH_3$/MeOH (80 mL) for 10 h at rt. The reaction mixture was evaporated and dried in vacuo overnight. To a DMF (40 mL) solution of the residue was added imidazole (2.5 g, 37.2 mmol) and *t*-butyldimethylsilyl chrolide (3.7 g, 24.8 mmol) at 0 °C under Ar atmosphere. After stirring for 10 h at rt, the reaction mixture was partitioned between AcOEt/$H_2O$. Silica gel column chromatography (hexane/AcOEt = 3/1) of the organic layer to give **13** (3.15 g, 72%) as foam: UV (MeOH)$\lambda_{max}$ 268 nm (ε11000),$\lambda_{min}$ 251 nm (ε300). $^1$H NMR ($CDCl_3$)δ0.11

(6H, s), 0.91 (9H, s), 1.96 (3H, d, *J* = 1.2 Hz), 2.04 (1H, ddd, *J* = 7.0, *J* = 13.0 and *J* = 4.4 Hz), 2.40 (1H, ddd, *J* = 6.2, *J* = 13.0 and *J* = 4.8 Hz), 4.76 (1H, dd, *J* = 4.4 and *J* = 4.8 Hz), 5.12 (1H, d, *J* = 1.2 Hz), 5.32 (1H, d, *J* = 1.2 Hz), 6.62 (1H, dd, *J* = 7.0 and *J* = 6.2 Hz), 7.37 (1H, d, *J* = 1.2 Hz), 8.47 (1H, br); $^{13}$C NMR ($CDCl_3$)δ: −4.7, −4.6, 12.7, 18.0, 25.7, 44.2, 61.4, 76.6, 106.2, 111.9, 135.8, 149.1, 150.5, 163.4. FAB-MS (*m/z*) 355 ($M^+$+H). *Anal*. Calcd for $C_{16}H_{26}N_2O_3SSi$: C, 54.20; H, 7.39; N, 7.90. Found: C, 54.28; H, 7.52; N, 7.79.

*Microanalytical Data*

| no | Empirical Formula | Calcd. | | | Found | | |
|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N |
| 8 | $C_{22}H_{39}IN_2O_5SSi_2$ | 42.16 | 6.27 | 4.47 | 42.25 | 6.28 | 4.42 |
| 9 | $C_{22}H_{40}N_2O_5SSi_2$ | 52.76 | 8.05 | 5.59 | 52.58 | 8.17 | 5.51 |
| 10 | $C_{14}H_{18}N_2O_6S$ | 49.11 | 5.30 | 8.18 | 49.14 | 5.33 | 7.93 |
| 11 | $C_{10}H_{13}IN_2O_3S$ | 32.62 | 3.56 | 7.61 | 32.91 | 3.36 | 7.23 |
| 13 | $C_{16}H_{26}N_2O_3SSi$ | 54.20 | 7.39 | 7.90 | 54.28 | 7.52 | 7.79 |
| 14 | $C_{20}H_{32}N_2O_7SSi$ | 50.83 | 6.82 | 5.93 | 50.93 | 6.86 | 5.87 |
| 15 | $C_{20}H_{32}N_2O_7SSi$ | 50.83 | 6.82 | 5.93 | 50.83 | 6.88 | 5.83 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 16 | $C_{16}H_{26}N_2O_4SSi$ | 51.86 | 7.07 | 7.56 | 51.98 | 7.15 | 7.49 |
| 17a | $C_{24}H_{34}N_2O_5S_2Si$ | 55.14 | 6.56 | 5.36 | 54.79 | 6.54 | 5.32 |
| 20b | $C_{17}H_{30}N_2O_5SSi$ | 50.72 | 7.51 | 6.96 | 50.81 | 7.60 | 6.81 |
| 21a | $C_{21}H_{34}N_2O_5SSi$ | 55.48 | 7.54 | 6.16 | 55.68 | 7.75 | 5.99 |
| 23 | $C_{28}H_{46}N_2O_4S_2Si_2$ | 56.52 | 7.79 | 4.71 | 56.47 | 7.85 | 4.66 |
| 24 | $C_{24}H_{44}N_2O_6SSi_2$ | 52.91 | 8.14 | 5.14 | 53.06 | 8.28 | 5.14 |
| 26a | $C_{23}H_{41}N_3O_4SSi_2$ | 53.97 | 8.07 | 8.21 | 54.26 | 8.30 | 7.85 |
| 27 | $C_{22}H_{40}N_2O_4SSi_2$ | 54.50 | 8.32 | 5.78 | 54.87 | 8.55 | 5.84 |
| 28a | $C_{15}H_{17}N_3O_6S$ | 49.04 | 4.66 | 11.44 | 49.00 | 4.53 | 11.04 |

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|---|---|---|---|---|---|---|---|
| 29 | $C_{23}H_{42}N_2O_5SSi_2$ | 53.66 | 8.22 | 5.44 | 53.85 | 8.37 | 5.40 |
| 31 | $C_{16}H_{18}N_3O_6S\cdot1/2AcOEt$ | 62.67 | 5.40 | 6.83 | 53.02 | 5.55 | 6.94 |
| 32 | $C_{16}H_{18}N_2O_4S_2$ | 52.44 | 4.95 | 7.64 | 52.71 | 5.08 | 7.48 |
| 33 | $C_{10}H_{13}N_5O_4S\cdot1/2AcOMe$ | 41.07 | 4.79 | 20.82 | 41.00 | 4.44 | 21.22 |
| 34 | $C_{11}H_{16}N_2O_5S$ | 45.82 | 5.59 | 9.72 | 45.95 | 5.57 | 9.41 |
| 35 | $C_{13}H_{19}N_2O_4S$ | 52.33 | 6.08 | 9.39 | 52.10 | 5.98 | 9.05 |
| 36 | $C_{11}H_{13}N_3O_4S$ | 46.63 | 4.63 | 14.83 | 46.70 | 4.60 | 14.47 |
| 37 | $C_{12}H_{14}N_2O_4S\cdot1/4H_2O$ | 50.25 | 5.10 | 9.77 | 50.21 | 4.96 | 9.90 |