Synthesis and Anti-Human Immunodeficiency Virus Activity of 4′-Branched (±)-4′-Thiostavudines

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Motivated by our recent finding that 4′-ethynylstavudine (**4**) is a promising anti-human immunodeficiency virus type 1 (HIV-1) agent, we synthesized its 4′-thio analogue, as well as other 4′-thiostavudines having a carbon substituent at the 4′-position, as racemates in this study. Methyl 3-oxo-tetrahydrothiophen-2-carboxylate (**5**) was used as a starting material to construct the requisite 4-thiofuranoid glycal (**13**). Introduction of a thymine base was carried out by an electrophilic addition reaction to **13** using *N*-iodosuccinimide (NIS) and bis(trimethylsilyl)thymine. The desired β-anomer (**16**β) obtained as a major product in this reaction underwent ready elimination with activated Zn to give the 4′-carbomethoxy derivative (**18**). By using **18** as a common intermediate, 4′-carbon-substituted (CH_2OH, CO_2Me, $CONH_2$, $CH{=}CH_2$, CN, and $C{\equiv}CH$) 4′-thiostavudines were prepared. Among these six compounds, 4′-cyano (**28**) and 4′-ethynyl (**29**) analogues were found to show inhibitory activity against HIV-1 with ED_{50} values of 7.6 and 0.74 μM, respectively. The activity of **29** was comparable to that of stavudine, but **29** was not as active as **4**. Optical resolution of **29** was briefly examined.

Introduction

Nucleosides in which the furanose ring oxygen is replaced with a sulfur atom are called 4′-thionucleosides, and the first report dealing with this class of nucleosides appeared in 1964 for the synthesis of 4′-thioadenosine (**1**).[1] A renaissance of 4′-thionucleosides began in 1991 when potent antiviral and antitumor activities were found in 4′-thiothymidine (**2**) and 2′-deoxy-4′-thiocytidine (**3**) (Figure 1).[2] Extensive synthetic studies[3] carried out since then have led to the finding of several biologically interesting compounds.[4−6]

Meanwhile, our recent studies on the reaction of organoaluminum reagents with nucleosides bearing an epoxy-sugar structure[7,8] has disclosed that 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine (**4**, Figure 2) is more potent against human immunodeficiency virus (HIV) than the parent compound stavudine (d4T) and much less toxic to various cells and also to mitochondrial DNA synthesis.[8,9] This compound has several potential advantages as a promising anti-HIV agent: (1) it is a better substrate for human thymidine kinase than d4T, (2) it is very much resistant to catabolism by thymidine phosphorylase, and (3) its activity improves in the presence of a major mutation, K103N, known for nonnucleoside reverse transcriptase inhibitor resistant HIV.[9,10]

In this paper, as a study on the structure−activity relationship regarding **4**, we describe the synthesis and anti-HIV activity of the (±)-4′-thio-counterpart of **4**, as well as other 4′-thiostavudine analogues having carbon substituents at the 4′-position.

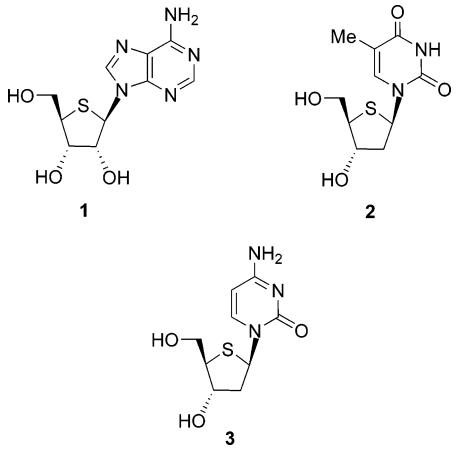

Figure 1. 4′-Thionucleosides **1**−**3**.

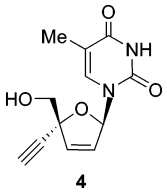

Figure 2. 4′-Ethynylstavudine (**4**).

Results and Discussion

A synthetic plan for the title compounds is depicted in Scheme 1 as a retrosynthetic analysis. The desired 4′-thiostavudine analogues **I** with a variety of 4′-carbon substituents can be prepared from **II** by manipulation of the 4′-carbomethoxy group. Two possible approaches were envisioned for the preparation of **II**: one is a Pd-catalyzed allylic substitution of **IV**, and the other is an electrophilic glycosylation followed by elimination of X and OR′ from **III** (**IV** → **III** → **II**). We anticipated that the known tetrahydrothiophene derivative **5** could be used for the preparation of **IV**.

Compound **5** used as the starting material was prepared according to the published procedure.[11] An aldol reaction between **5** and formaldehyde gave **6** (95%), which was then

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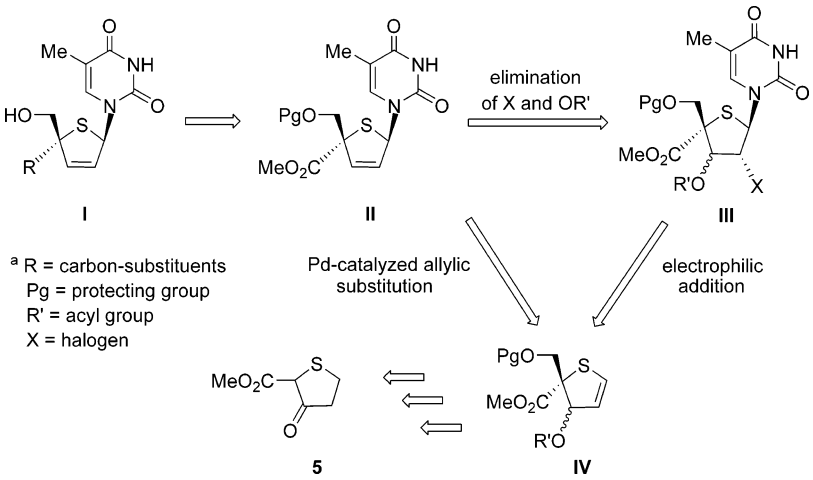
Scheme 1. Retrosynthesis of 4′-Substituted 4′-Thiostavudine Analogues



O-silylated to yield **7** (89%) (Figure 3). Transformation of **7** to the enone **8** (92%) was performed in CH_2Cl_2 by a Pummerer-type reaction using *N*-chlorosuccinimide (NCS). Treatment of **8** with $NaBH_4/CeCl_3$[12] in MeOH/THF (−50 °C, 1 h) followed by column chromatography gave a mixture of **9** and its epimer with a ratio of *ca.* 10/1 (89% combined yield) along with a minor byproduct (*ca.* 6%) that was assumed to be the 2-carbaldehyde (**10**) based on its ^{1}H NMR (δ 9.82, CHO) and FAB-MS (*m*/*z* 437, $M^+ + K$) spectra. The depicted stereochemistry of **9** was confirmed by NOE experiment, as well as X-ray crystallographic analysis, after introduction of thymine base. The stereoselectivity observed in 1,2-reduction of **8** has a precedent in the case of methyl 1-methyl-2-oxo-3-cyclopentenecarboxylate.[13] Conventional acylation of **9** gave the respective products (**11**−**14**).[14]

For the introduction of a thymine base, Pd-catalyzed allylic substitution[15] was first examined by using **11** as a substrate. However, attempts made by changing the catalyst [$Pd(Ph_3P)_4$, $Pd_2(dba)_3/Ph_3P$, $(\eta^3\text{-}C_3H_5PdCl)_2/Ph_3P$], the thymine derivative (N^3-benzoylthymine, bis(trimethylsilyl)thymine), or the solvent (THF, DMSO/THF, DMF) resulted in the recovery of **11**. The desired glycosylated product was formed only upon reacting the carbonate **14** with bis(trimethylsilyl)thymine in the presence of $Pd_2(dba)_3/Ph_3P$ (in THF at 60 °C), but the yield was only 8%. These results led us to apply the second approach, electrophilic glycosylation and subsequent elimination.

Electrophilic glycosylation using thiofuranoid glycals has previously been reported from our laboratory.[16] As shown in Scheme 2, when the acetylated thiofuranoid glycal **11** was reacted with bis(trimethylsilyl)thymine (1.5 equiv) in the presence of *N*-iodosuccinimide (NIS) (1.5 equiv) as an electrophile in CH_3CN (at rt, overnight), a mixture of the β-anomer (**15**β) and α-anomer (**15**α) [NOE data **15**β, H-1′/H-3′ (7.8%) and H-6/H-2′ (11.6%); **15**α, H-2′/H-6 (12.3%) and H-2′/H-3′ (11.8%)][17] was formed in 40% combined yield. The diastereomeric ratio of **15**β/**15**α = 5/1 was determined on the basis of ^{1}H NMR spectroscopy by comparing integration of H-2′. One might expect that the presence of a more bulky acyl protecting group would encourage the more efficient iodonium formation at the α-face of the thioglycal **11**, thus leading to a higher ratio of the desired β-anomer. This appeared, however, not to be the case. When the pivalate **12** was subjected to the glycosylation under the same reaction conditions as described above, equal amounts of **16**β and **16**α [NOE data **16**β, H-2′/H-6 (13.9%) and H-2′/H-5′ (1.7%); **16**α, H-2′/H-6 (13.9%) and H-2′/H-3′ (10.3%)] were formed in 88% combined yield. The highest β-selectivity (**17**β/**17**α = 10/1) and combined yield (98%) were seen in the case of the benzoate **13**. Moreover, in this particular case, the desired β-anomer (**17**β) was isolated from the anomeric mixture simply by crystallization. The stereochemistry of **17**β was confirmed on the basis of its NOE data [H-2′/H-5′ (1.2%) and H-3′/H-1′ (2.9%)], while that of the α-anomer (**17**α) was determined by X-ray crystallographic analysis.[18]

Compound **17**β was found to readily undergo elimination with activated Zn.[19] Thus, treatment of **17**β with the activated Zn in THF/AcOH at rt for 1 h gave the 4′-carbomethoxy derivative (**18**) of 4′-thiostavudine in 99% yield (Scheme 2). Attempted direct transformation of **18** to its 4′-formyl derivative (*e.g.*, *i*-Bu_2AlH in CH_2Cl_2 or THF) all met with concomitant formation of the 4′-hydroxymethyl derivative (**19**). Therefore, **18** was converted to **19** (98%) by reacting with an excess amount of $NaBH_4$ in MeOH/THF, and then the resulting **19** was oxidized with $(CF_3CO)_2O$/DMSO in CH_2Cl_2 at −80 °C to give the aldehyde **20** in 97% yield.

Preparation of the 4′-ethynyl derivative (**21**) from **20** was examined. The reaction between **20** and Me_3SiCHN_2/lithium diisopropyl amide (LDA)[20] gave several unknown byproducts, and the desired **21** was isolated only in 20% yield. This result presumably originates in the highly basic nature of LDA, which is needed to generate an anionic species from Me_3SiCHN_2. In fact, the use of dimethyl 1-diazo-(2-oxopropyl)phosphonate[21] in combination with K_2CO_3 in MeOH gave **21** in a higher yield of 85% (Scheme 2). To generate the Wittig reagent $Ph_3P{=}CH_2$ from methyltriphenylphosphonium bromide required for the preparation of the 4′-vinyl derivative **22**, methylsulfinyl carbanion was found to be an appropriate base to give **22** in 98%

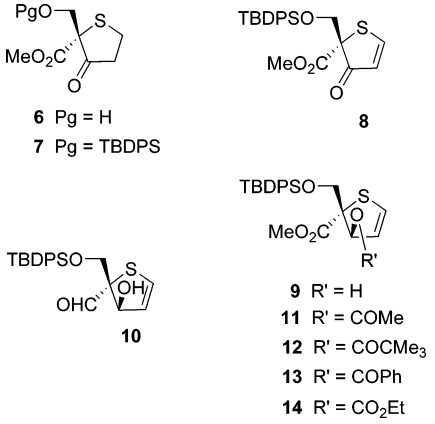
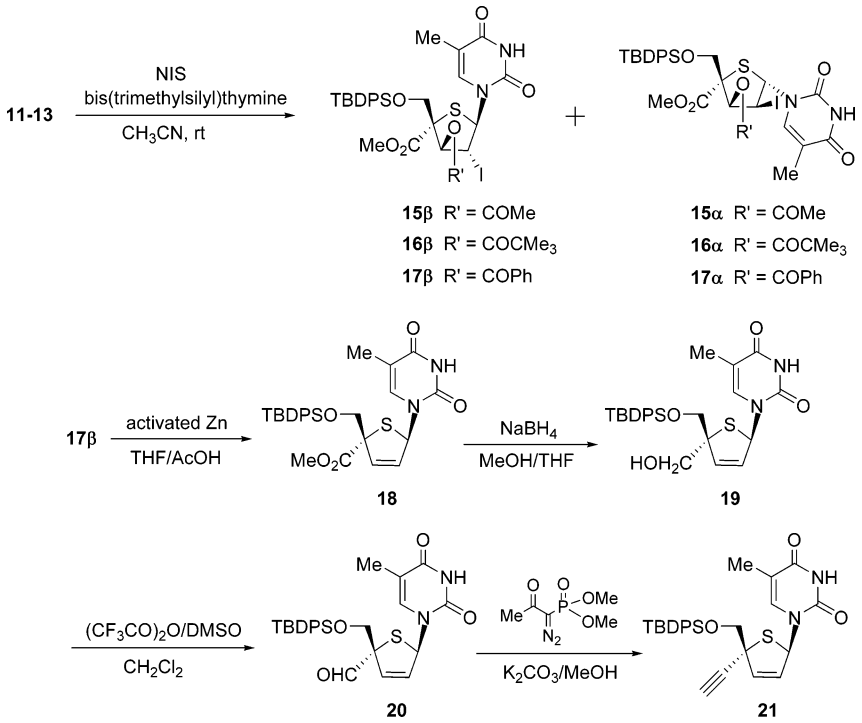


Figure 3. Compounds **6**−**14**.

Scheme 2. Electrophilic Glycosylation by Using Thiofuranoid Glycals **11**−**13** and Transformation of **17**β to the 4′-Ethynyl Analogue **21**



yield. When **20** was converted to its oxime and then reacted with MsCl in pyridine, spontaneous formation of the 4′-cyano derivative **23** was observed (Figure 4).

The 4′-carbon-substituted derivatives thus far prepared were deprotected to yield the corresponding free (±)-4′-thiostavudines (**24**−**29**). Compound **26**, 4′-carbamoyl-4′-thiostavudine, was prepared from **18** by a conventional reaction sequence: desilylation, acetylation, and ammonolysis. Table 1 summarizes anti-HIV-1 activity and cytotoxicity of **24**−**29**, together with those of stavudine and 4′-ethynylstavudine (**4**). It is consistent with our previous observation[8,9,22,23] that only compounds having an sp-hybridized 4′-carbon substituent (**28** and **29**) show inhibitory activity against HIV-1. The fact that the 4′-ethynyl analogue (**29**) is more inhibitory than the 4′-cyano analogue (**28**) also follows our previous observation in the case of 4′-substituted stavudines.[22]

Since (±)-4′-ethynyl-4′-thiostavudine (**29**) was almost as active as stavudine, its optical resolution was carried out. After esterification of **29** with (−)-camphanic chloride, HPLC separation ($CHCl_3$/MeOH = 200/1) enabled us to isolate the two diastereomers. Each diastereomer was then treated with K_2CO_3/MeOH to give the respective optically active **29**.[24] From the anti-HIV assay of the separated enantiomers, it was concluded that the observed activity of **29** derived from (−)-**29**. Although the actual configuration of (−)-**29** is not known at the moment, it may be possible to assume that this compound has D-configuration, since the L-isomer of stavudine has been reported not to be inhibitory against HIV-1.[25]

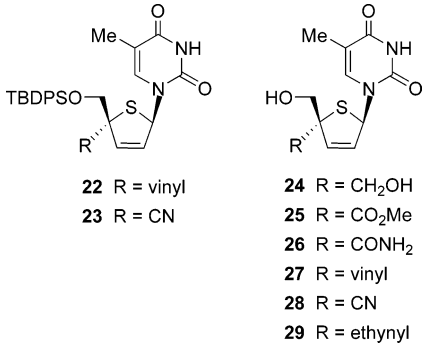


Figure 4. Compounds **22**−**29**.

Table 1. Anti-HIV-1 Activity of **24**−**29** in MT-4 Cells

compound	4′-substituent	EC_{50}[a] (μM)	CC_{50}[b] (μM)
24	CH_2OH	>100	>100
25	CO_2Me	>100	>100
26	$CONH_2$	>100	>100
27	$CH{=}CH_2$	>100	>100
28	CN	7.6	>100
29	C≡CH	0.74	>100
(−)−29	C≡CH	0.37	>100
(+)−29	C≡CH	>20	>100
stavudine		0.51	>100
4′-ethynyl-stavudine **(4)**		0.060	>100

[a] Inhibitory concentration required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 IIIB. [b] Cytotoxic concentration required to reduce the viability of mock-infected MT-4 cells by 50%.

Conclusion

Our recent finding that 4′-ethynylstavudine is a highly promising anti-HIV agent led us to carry out the present study. Synthesis of (±)-4′-ethynyl-4′-thiostavudine (**29**) and its analogues having a carbon substituent at the 4′-position was accomplished based on stereoselective electrophilic addition of NIS/bis(trimethylsilyl)thymine to the 4-thiofuranoid glycal **13**. The resulting major product (**16**β), upon reaction with activated Zn, gave the elimination product **18** in almost quantitative yield. Manipulation of the carbomethoxy group in **18** allowed the preparation of other 4′-carbon-substituted 4′-thiostavudines. Among six 4′-carbon-substituted (±)-4′-thiostavudines synthesized in the present study, the 4′-cyano (**28**) and 4′-ethynyl (**29**) analogues showed inhibitory activity against HIV-1, suggesting that the presence of an sp-hybridized carbon substituent at the

4′-position is crucial for the activity. It should be noted that 4′-thiostavudine itself has been reported not to be inhibitory against HIV.[26] The most active compound, (±)-4′-ethynyl-4′-thiostavudine (**29**), showed EC_{50} of 0.74 μM, which is almost comparable to that of stavudine. Optical resolution of **29** revealed that its *levo*-enantiomer is the active component.

Experimental Section

Chemistry. Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were measured on a JEOL JNM-LA 500 (500 MHz). Chemical shifts are reported relative to Me_4Si. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix on a JEOL JMS-700. Ultraviolet spectra (UV) were recorded on a JASCO V-530 spectrophotometer. Column chromatography was carried out on silica gel (Micro Bead Silica Gel PSQ 100B, Fuji Silysia Chemical Ltd.). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck). Where necessary, analytical samples were purified by high-performance liquid chromatography (HPLC). HPLC was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H)′KIT column (2 cm × 25 cm).

Methyl 2-Hydroxymethyl-3-oxotetrahydrothiophen-2-carboxylate (6). A mixture of **5** (10.0 g, 62.4 mmol), 38% aqueous solution of HCHO (60 mL, 759 mmol), and AcOH (7.15 mL, 125 mmol) was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **6** (11.2 g, 95%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.74 (2H, m, H-4 or H-5), 2.80 (1H, br, OH), 2.95 (1H, m, H-4 or H-5), 3.04 (1H, m, H-4 or H-5), 3.79 (3H, s, CO_2Me), 4.04 (2H, m, CH_2OH); ^{13}C NMR ($CDCl_3$) δ 23.7 (C-4 or C-5), 40.0 (C-4 or C-5), 53.1 (CO_2*Me*), 62.8 (C-2), 64.0 (C-5), 170.3 (*C*O_2Me) 209.2 (C-3); FAB-MS (*m*/*z*) 191 ($M^+ + H$). Anal. Calcd for $C_7H_{10}O_4S$: C, 44.20; H, 6.07; N, 5.30. Found: C, 44.19; H, 6.00; N, 5.26.

Methyl 2-(*tert*-Butyldiphenylsilyloxy)methyl-3-oxotetrahydrothiophen-2-carboxylate (7). A mixture of **6** (500 mg, 2.62 mmol), imidazole (269 mg, 3.94 mmol), and *tert*-butyldiphenylsilyl chloride (TBDPSCl; 0.75 mL, 2.89 mmol) in DMF (5.0 mL) was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 20/1) of the organic layer gave **7** (1.00 g, 89%) as a solid. Crystallization from hexane−Et_2O gave an analytical sample: mp 85−88 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, SiBu-*t*), 2.78 and 2.92 (2H, each as m, H-5), 3.16 (3H, s, CO_2Me), 3.95 and 4.27 (2H, each as d, J_{gem} = 10.3 Hz, CH_2OSi), 7.37−7.45 (6H, m, Ph), 7.66−7.73 (4H, m, Ph); ^{13}C NMR($CDCl_3$) δ 19.2 (Si*C*Me_3), 24.2 (C-4), 26.6 (SiC*Me*$_3$), 40.7 (C-5), 52.9 (CO_2*Me*), 64.0 (C-2), 64.9 (*C*H_2OSi), 127.7, 127.8, 129.8, 129.9, 135.6 and 135.7 (Ph-tertiary), 132.5 and 132.6 (Ph-quaternary), 169.6 (*C*O_2Me) 208.9 (C-3); FAB-MS (*m*/*z*) 429 ($M^+ + H$). Anal. Calcd for $C_{23}H_{28}O_4SSi$: C, 64.45; H, 6.59. Found: C, 64.37; H, 6.55.

Methyl 2-(*tert*-Butyldiphenylsilyloxy)methyl-3-oxo-2,3-dihydrothiophen-2-carboxylate (8). To a solution of **7** (2.66 g, 6.19 mmol) in CH_2Cl_2 (12.5 mL) was added NCS (860 mg, 6.44 mmol) at 0 °C under positive pressure of dry Ar. The reaction mixture was stirred at rt for 2.5 h and then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 10/1) of the organic layer gave **8** (2.43 g, 92%) as a solid. Crystallization from hexane−Et_2O gave an analytical sample: mp 102−106 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (9H, s, SiBu-*t*), 3.71 (3H, s, CO_2Me), 4.21 and 4.30 (2H, each as d, J_{gem} = 10.3 Hz, CH_2OSi), 6.19 (1H, d, $J_{4,5}$ = 5.7 Hz, H-4), 7.38−7.45 (6H, m, Ph), 7.62−7.63 (4H, m, Ph), 8.45 (1H, d, $J_{4,5}$ = 5.7 Hz, H-5); ^{13}C NMR($CDCl_3$) δ 19.5 (Si*C*Me_3), 26.5 (SiC*Me*$_3$), 53.3 (CO_2*Me*), 65.2 (*C*H_2OSi) 47.5 (C-2), 121.8 (C-4), 127.7, 127.8, 129.9 and 135.6 (Ph-tertiary), 132.4 and 132.6 (Ph-quaternary), 163.3 (C-5), 166.7 (*C*O_2Me), 199.3 (C-3); FAB-MS (*m*/*z*) 427 ($M^+ + H$). Anal. Calcd for $C_{23}H_{26}O_4SSi$: C, 64.76; H, 6.14. Found: C, 64.60; H, 6.13.

Methyl 2-(*tert*-Butyldiphenylsilyloxy)methyl-(*trans*-3-hydroxy)-2,3-dihydro-thiophen-2-carboxylate (9) and 2-(*tert*-Butyldiphenylsilyloxy)methyl-(*trans*-3-hydroxy)-2,3-dihydrothiophen-2-carbaldehyde (10). A solution of **8** (9.0 g, 21.1 mmol) and $CeCl_3$·$7H_2O$ (7.76 g, 21.1 mmol) in MeOH (225 mL)/THF (75 mL) was cooled to −50 °C under positive pressure of dry Ar. To this was added $NaBH_4$ (1.20 g, 31.6 mmol) by portions over 0.5 h. After being stirred for 1.5 h, the reaction mixture was quenched by addition of AcOH and acetone and then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography of the organic layer gave **9** (eluted with hexane/EtOAc = 10/1, 7.92 g, 89%, containing its epimer) and **10** (eluted with hexane/EtOAc = 5/1, 500 mg, 6%). An analytically pure **9** was obtained by crystallization from hexane−Et_2O.

Physical data for **9**: mp 53−57 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (9H, s, SiBu-*t*), 2.48 (1H, d, $J_{3,OH}$ = 6.1 Hz, OH), 3.72 (3H, s, CO_2Me), 4.18 and 4.26 (2H, each as d, J_{gem} = 9.8 Hz, CH_2OSi), 5.65 (1H, ddd, $J_{3,OH}$ = 6.1 Hz, $J_{3,4}$ = 2.9 Hz, $J_{3,5}$ = 0.7 Hz, H-3), 5.76 (1H, dd, $J_{4,5}$ = 6.1 Hz and $J_{3,4}$ = 2.9 Hz, H-4), 6.25 (1H, dd, $J_{4,5}$ = 6.1 Hz and $J_{3,5}$ = 0.7 Hz, H-5), 7.38−7.45 (6H, m, Ph), 7.63−7.67 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2 (Si*C*Me_3), 26.7 (SiC*Me*$_3$), 52.7 (CO_2*Me*), 64.3 (*C*H_2OSi) 65.3 (C-2), 79.9 (C-3), 124.5 (C-4), 127.7 (C-5), 127.8, 130.0, 135.5 and 135.6 (Ph-tertiary), 132.4 and 132.5 (Ph-quaternary), 172.1 (*C*O_2Me); FAB-MS (*m*/*z*) 467 ($M^+ + K$). Anal. Calcd for $C_{23}H_{28}O_4SSi$: C, 64.45; H, 6.59. Found: C, 64.20; H, 6.61.

Physical data for **10**: ^{1}H NMR ($CDCl_3$) δ 1.07 (9H, s, SiBu-*t*), 2.44 (1H, d, $J_{3,OH}$ = 8.5 Hz, OH), 3.96 and 4.07 (2H, each as d, J_{gem} = 10.5 Hz, CH_2OSi), 5.29 (1H, ddd, $J_{3,OH}$ = 8.5 Hz and $J_{3,4}$ = 2.4 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 5.76 (1H, dd, $J_{4,5}$ = 6.0 Hz and $J_{3,4}$ = 2.4 Hz, H-4), 6.26 (1H, dd, $J_{4,5}$ = 6.0 Hz and $J_{3,5}$ = 1.5 Hz, H-5), 7.38−7.47 (6H, m, Ph), 7.63−7.69 (4H, m, Ph), 9.82 (1H, s, CHO); FAB-MS (*m*/*z*) 437 ($M^+ + K$).

Methyl *trans*-3-Benzoyloxy-2-(*tert*-butyldiphenylsilyloxy)-methyl-2,3-dihydro-thiophen-2-carboxylate (13). To a mixture of **9** (3.43 g, 8.01 mmol), 4-dimethylaminopyridine (DMAP; 1.27 g, 10.41 mmol), and *i*-Pr_2NEt (1.4 mL, 10.41 mmol) was added BzCl (1.21 mL, 10.41 mmol) at rt. The reaction mixture was stirred at rt overnight and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 4/1) of the organic layer gave **13** (3.93 g, 94%) as an oil, which was crystallized from Et_2O−hexane: mp 111−114 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s, SiBu-*t*), 3.73 (3H, s, CO_2Me), 4.21 and 4.37 (2H, each as d, J_{gem} = 9.7 Hz, CH_2OSi), 5.90 (1H, dd, $J_{4,5}$ = 5.7 Hz and $J_{3,4}$ = 2.9 Hz, H-4), 6.46 (1H, d, $J_{4,5}$ = 5.7 Hz, H-5), 6.74 (1H, dd, $J_{3,4}$ = 2.9 Hz, H-3), 7.07−7.10 (2H, m, Ph), 7.26−7.31 (1H, m, Ph), 7.33−7.43 (7H, m, Ph), 7.55−7.58 (3H, m, Ph), 7.90−7.92 (2H, m, Ph); ^{13}C NMR($CDCl_3$) δ 19.0 (Si*C*Me_3), 26.5 (SiC*Me*$_3$), 52.9 (CO_2*Me*), 63.2 (*C*H_2OSi) 66.3 (C-2), 79.1 (C-3), 121.9 (C-4), 131.1 (C-5), 127.5, 127.6, 128.4, 129.8, 130.0, 133.0, 135.4 and 135.7 (Ph-tertiary), 129.6, 132.5 and 132.6 (Ph-quaternary), 165.0 (*C*OPh), 171.4 (*C*O_2Me); FAB-MS (*m*/*z*) 533 ($M^+ + K$). Anal. Calcd for $C_{30}H_{32}O_5SSi$: C, 67.64; H, 6.05. Found: C, 67.51; H, 5.96.

1-[[(*cis*-3-Benzoyloxy)-[*cis*-2-(*tert*-butyldiphenylsilyloxy)methyl]-(*trans*-4-iodo)-(*trans*-2-carbomethoxy)tetrahydrothiophen-5-yl]]-thymine (17β) and 1-[[(*trans*-3-Benzoyloxy)-[*trans*-2-(*tert*-butyldiphenylsilyloxy)methyl]-(*trans*-4-iodo)-(*cis*-2-carbomethoxy)-tetrahydrothiophen-5-yl]thymine (17α). A mixture of thymine (1.78 g, 14.1 mmol), $(Me_3Si)_2NH$ (150 mL), and $(NH_4)_2SO_4$ (88 mg) was refluxed with stirring. After complete dissolution of the thymine was confirmed (*ca.* 7 h), the mixture was evaporated to remove excess $(Me_3Si)_2NH$. The resulting syrupy residue was dissolved in CH_3CN (50 mL). To this were added a solution of **13** (5.0 g, 9.39 mmol) in CH_3CN (50 mL) and NIS (3.2 g, 14.1 mmol). The reaction mixture was stirred at rt overnight and partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ containing a small amount of $Na_2S_2O_3$. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave a mixture of **17**β and **17**α (7.29 g, 98%) as a solid. Crystallization of this mixture from CH_2Cl_2−hexane gave an analytically pure **17**β. Compound **17**α was isolated by HPLC

(hexane/EtOAc = 1/1) purification and crystallized from Et_2O−hexane to give a sample for X-ray analysis.

Physical data for **17**β: mp 178−180 °C; UV (MeOH) λ_{max} 265 nm (ϵ 12 300), λ_{min} 249 nm (ϵ 8000); ^{1}H NMR (CD_2Cl_2) δ 1.13 (9H, s, SiBu-*t*), 1.51 (3H, d, $J_{6,Me}$ = 1.2 Hz, 5-Me), 3.84 (3H, s, CO_2Me), 4.27 (2H, s, H-5′), 5.29 (1H, t, $J_{2',3'} = J_{1',2'}$ = 10.7 Hz, H-2′), 6.19 (1H, d, $J_{2',3'}$ = 10.7 Hz, H-3′), 6.64 (1H, d, $J_{1',2'}$ = 10.7 Hz, H-1′), 7.32 (1H, d, $J_{6,Me}$ = 1.2 Hz, H-6), 7.34−7.60 (1H, m, Ph), 7.44−7.57 (6H, m, Ph), 7.70−7.78 (6H, m, Ph), 8.12−8.14 (2H, m, Ph), 9.83 (1H, br, NH); ^{13}C NMR(CD_2Cl_2) δ 12.6 (5-Me), 20.1 (Si*C*Me$_3$), 27.8 (Si*CMe*$_3$), 28.1 (C-2′), 54.1 (CO_2*Me*), 60.3 (C-1′), 62.0 (C-4′), 65.8 (C-5′), 81.5 (C-3′), 96.9 (C-5), 128.8, 128.9, 129.4, 130.9, 131.0, 131.1, 134.6, 136.1 and 136.3 (Ph-tertiary), 129.4, 132.7 and 133.6 (Ph-quaternary), 135.0 (C-6), 151.5 (C-2), 164.1 (C-4), 165.9 (*C*OPh), 170.7 (*C*O_2Me); FAB-MS (*m/z*) 785 (M^+ + H). Anal. Calcd for $C_{35}H_{37}IN_2O_7SSi$: C, 53.57; H, 4.75; N, 3.57. Found: C, 53.44; H, 4.64; N, 3.53.

Physical data for **17**α: mp 221−223 °C; UV (MeOH) λ_{max} 265 nm (ϵ 12 500), λ_{min} 249 nm (ϵ 8000); ^{1}H NMR (CD_2Cl_2) δ 0.93 (9H, s, SiBu-*t*), 1.93 (3H, d, $J_{6,Me}$ = 1.2 Hz, 5-Me), 3.70 (3H, s, CO_2Me), 4.03 and 4.10 (2H, each as d, J_{gem} = 10.0 Hz, H-5′), 5.03 (1H, dd, $J_{1',2'}$ = 11.2 Hz and $J_{2',3'}$ = 2.9 Hz, H-2′), 6.53 (1H, d, $J_{2',3'}$ =2.9 Hz, H-3′), 6.57 (1H, d, $J_{1',2'}$ = 11.2 Hz, H-1′), 6.53−6.58 (2H, m, Ph), 7.09 (1H, d, $J_{6,Me}$ = 1.2 Hz, H-6), 7.22−7.35 (5H, m, Ph), 7.39−7.44 (1H, m, Ph), 7.50−7.56 (4H, m, Ph), 7.68−7.72 (1H, m, Ph), 7.72−8.10 (2H, m, Ph), 8.70 (1H, br, NH); ^{13}C NMR (CD_2Cl_2) δ 13.1 (5-Me), 19.3 (Si*C*Me$_3$), 26.9 (Si*CMe*$_3$), 28.6 (C-2′), 53.8 (CO_2*Me*), 64.5 (C-4′), 65.3 (C-5′), 66.2 (C-1′), 76.1 (C-3′), 113.7 (C-5), 128.0, 128.2, 129.4, 130.2, 130.5, 130.6, 134.4, 135.9 and 136.3 (Ph-tertiary), 129.6, 132.7 and 132.8 (Ph-quaternary), 134.9 (C-6), 151.0 (C-2), 163.4 (C-4), 164.4 (*C*OPh), 173.0 (*C*O_2Me); FAB-MS (*m/z*) 785 (M^+ + H). Anal. Calcd for $C_{35}H_{37}IN_2O_7SSi'1/3H_2O$: C, 53.16; H, 4.80; N, 3.54. Found: C, 53.17; H, 4.72; N, 3.45.

(±)-5′-*O*-(*tert*-Butyldiphenylsilyl)-4′-carbomethoxy-2′,3′-didehydro-3′-deoxy-4′-thiothymidine (18). A mixture of **17**β (2.27 g, 2.89 mmol) in THF (11.6 mL), AcOH (8.3 mL), and activated Zn, prepared from Zn powder (537 mg, 8.24 mmol) according to the published procedure,[18] was stirred at rt for 1 h. The reaction mixture was quenched by adding saturated aqueous $NaHCO_3$, and filtered through a Celite pad. The filtrate was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 3/1) of the organic layer gave **18** (1.55 g, 99%) as a solid. Crystallization from CH_2Cl_2−hexane gave an analytical sample: mp 184−185 °C; UV (MeOH) λ_{max} 271 nm (ϵ 10 000), λ_{min} 240 nm (ϵ 2900); ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s, SiBu-*t*), 1.68 (3H, d, $J_{6,Me}$ = 1.2 Hz, 5-Me), 3.79 and 4.26 (2H, each as d, J_{gem} = 9.7 Hz, H-5′), 3.80 (3H, s, CO_2Me), 5.83 (1H, dd, $J_{2',3'}$ = 6.3 Hz and $J_{1',2'}$ =2.4 Hz, H-2′), 6.55 (1H, dd, $J_{2',3'}$ = 6.3 Hz and $J_{1',3'}$ = 1.9 Hz, H-3′), 6.78 (1H, d, $J_{6,Me}$ = 1.2 Hz, H-6), 7.08 (1H, dd, $J_{1',2'}$ = 2.4 Hz and $J_{1',3'}$ = 1.9 Hz, H-1′), 7.38−7.46 (6H, m, Ph), 7.64−7.67 (4H, m, Ph), 8.91 (1H, br, NH); ^{13}C NMR($CDCl_3$) δ 12.5 (5-Me), 19.3 (Si*C*Me$_3$), 26.6 (Si*CMe*$_3$), 53.1 (CO_2*Me*), 67.5 (C-1′), 69.8 (C-4′), 70.2 (C-5′), 112.2 (C-5), 129.3 (C-2′), 135.1 (C-6), 127.9, 130.1, 135.4 and 135.5 (Ph-tertiary), 132.2 and 132.7 (Ph-quaternary), 136.9 (C-3′), 150.3 (C-2), 163.2 (C-4), 171.3 (*C*O_2Me); FAB-MS (*m/z*) 537 (M^+ + H). Anal. Calcd for $C_{28}H_{32}N_2O_5SSi\cdot1/3H_2O$: C, 61.97; H, 6.07; N, 5.16. Found: C, 61.99; H, 6.00; N, 5.05.

(±)-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-didehydro-3′-deoxy-4′-hydroxymethyl-4′-thiothymidine (19). To a solution of **18** (1.0 g, 1.86 mmol) in MeOH (10 mL) was added $NaBH_4$ (2.8 g, 74.5 mmol) by portions at 0 °C. The reaction mixture was stirred at rt for 3 h, quenched by adding AcOH, and then extracted with CH_2Cl_2. Column chromatography (hexane/EtOAc = 1/1) of the extract gave **19** (933 mg, 98%) as a solid. Crystallization from CH_2Cl_2−hexane gave an analytical sample: mp 166−171 °C; UV (MeOH) λ_{max} 272 nm (ϵ 9700), λ_{min} 240 nm (ϵ 2800); ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s, SiBu-*t*), 1.70 (3H, d, $J_{6,Me}$ = 1.1 Hz, 5-Me), 2.36 (1H, dd, $J_{5',OH}$ = 8.0 and *J*= 5.2 Hz, OH), 3.85−3.95 (4H, m, H-5′ and CH_2OH), 5.75 (1H, dd, $J_{2',3'}$ = 6.3 Hz and $J_{1',2'}$ = 2.3 Hz, H-2′), 6.23 (1H, dd, $J_{2',3'}$ = 6.3 Hz and $J_{1',3'}$ = 1.7 Hz, H-3′), 6.88 (1H, d, $J_{6,Me}$ = 1.1 Hz, H-6), 7.09 (1H, dd, $J_{1',2'}$ =2.3 Hz and $J_{1',3'}$ =1.7 Hz, H-1′), 7.38−7.47 (6H, m, Ph), 7.66−7.69 (4H, m, Ph), 9.19 (1H, br, NH); ^{13}C NMR($CDCl_3$) δ 12.5 (5-Me), 19.3 (Si*C*Me$_3$), 26.8 (Si*CMe*$_3$), 66.5 (*C*H_2OH), 66.9 (C-1′), 68.5 (C-5′), 72.4 (C-4′), 112.1 (C-5), 129.2 (C-2′), 135.6 (C-6), 127.8, 127.9 and 135.5 (Ph-tertiary), 132.3 and 132.7 (Ph-quaternary), 138.4 (C-3′), 150.6 (C-2), 163.5 (C-4); FAB-MS (*m/z*) 509 (M^+ + H). Anal. Calcd for $C_{27}H_{32}N_2O_4SSi$: C, 63.75; H, 6.34; N, 5.51. Found: C, 63.67; H, 6.21; N, 5.47.

(±)-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-didehydro-3′-deoxy-4′-formyl-4′-thiothymidine (20). A mixture of DMSO (0.46 mL, 3.67 mmol), $(CF_3CO)_2O$ (0.06 mL, 0.42 mmol), and CH_2Cl_2 (10.5 mL) was stirred at −80 °C for 15 min under positive pressure of dry Ar. To this was added a CH_2Cl_2 (7 mL) solution of **19** (933 mg, 1.83 mmol). The reaction mixture was stirred at at −80 °C for 1.5 h, quenched by adding Et_3N (0.65 mL), and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **20** (901 mg, 97%) as a solid. Crystallization from CH_2Cl_2−hexane gave an analytical sample: mp 147−152 °C; UV (MeOH) λ_{max} 271 nm (ϵ 10 000), λ_{min} 240 nm (ϵ 3000); ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s, SiBu-*t*), 1.66 (3H, d, $J_{6,Me}$ = 1.1 Hz, 5-Me), 4.12 and 4.16 (2H, each as d, J_{gem} = 10.9 Hz, H-5′), 6.02 (1H, dd, $J_{2',3'}$ = 6.3 Hz and $J_{1',2'}$ =2.3 Hz, H-2′), 6.18 (1H, dd, $J_{2',3'}$ = 6.3 Hz and $J_{1',3'}$ =1.7 Hz, H-3′), 6.95 (1H, d, $J_{6,Me}$ = 1.1 Hz, H-6), 7.22 (1H, dd, $J_{1',2'}$ = 2.3 Hz and $J_{1',3'}$ = 1.7 Hz, H-1′), 7.37−7.47 (6H, m, Ph), 7.66−7.71 (4H, m, Ph), 8.19 (1H, br, NH), 9.32 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ 12.4 (5-Me), 19.2 (Si*C*Me$_3$), 26.7 (Si*CMe*$_3$), 65.7 (C-5′), 67.5 (C-1′), 76.5 (C-4′), 112.6 (C-5), 127.9 130.0, 130.1, 135.5 and 135.6 (Ph-tertiary), 132.2 and 132.5 (Ph-quaternary), 133.2 (C-3′), 133.3 (C-2′), 135.1 (C-6), 150.5 (C-2), 163.5 (C-4), 192.0 (*C*HO); FAB-MS (*m/z*) 507 (M^+ + H). Anal. Calcd for $C_{27}H_{30}N_2O_4SSi$: C, 64.05; H, 5.97; N, 5.53. Found: C, 64.13; H, 6.03; N, 5.41.

(±)-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-didehydro-3′-deoxy-4′-ethynyl-4′-thiothymidine (21). To a solution of **20** (210 mg, 0.414 mmol) in MeOH (2.1 mL) were added dimethyl 1-diazo-(2-oxopropyl)phosphonate (142 mg, 0.75 mmol) and K_2CO_3 (115 mg, 0.83 mmol) under positive pressure of dry Ar. The reaction mixture was stirred at rt for 1.5 h. Quenching of the reaction mixture with saturated aqueous NH_4Cl was followed by extraction with CH_2Cl_2. Column chromatography (hexane/EtOAc = 3/1) of the extract gave **21** (176 mg, 85%) as a solid. Crystallization from CH_2Cl_2−hexane gave an analytical sample: mp 174−176 °C; UV (MeOH) λ_{max} 271 nm (ϵ 10 300), λ_{min} 240 nm (ϵ 3000); IR (neat) 3069 cm^{-1} (C≡CH); ^{1}H NMR ($CDCl_3$) δ 1.11 (9H, s, SiBu-*t*), 1.60 (3H, d, $J_{6,Me}$ = 1.1 Hz, 5-Me), 2.59 (1H, s, C≡CH), 3.90 and 3.95 (2H, each as d, J_{gem} = 9.7 Hz, H-5′), 5.80 (1H, dd, $J_{2',3'}$ = 6.0 Hz and $J_{1',2'}$ = 2.3 Hz, H-2′), 6.23 (1H, dd, $J_{2',3'}$ = 6.0 Hz and $J_{1',3'}$ = 1.7 Hz, H-3′), 6.93 (1H, d, $J_{6,Me}$ = 1.1 Hz, H-6), 7.23 (1H, dd, $J_{1',2'}$ = 2.3 Hz and $J_{1',3'}$ = 1.7 Hz, H-1′), 7.37−7.46 (6H, m, Ph), 7.68−7.72 (4H, m, Ph), 8.61 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.3 (5-Me), 19.5 (Si*C*Me$_3$), 26.8 (Si*CMe*$_3$), 61.0 (C-4′), 67.6 (C-1′), 71.4 (C-5′), 73.5 (C≡*C*H), 82.7 (*C*≡CH), 112.1 (C-5), 127.9, 130.0, 130.1 and 135.6 (Ph-tertiary), 128.9 (C-2′), 132.5 and 132.9 (Ph-quaternary), 135.4 (C-6), 137.8 (C-3′), 150.3 (C-2), 163.2 (C-4); FAB-MS (*m/z*) 503 (M^+ + H). Anal. Calcd for $C_{28}H_{30}N_2O_3SSi$: C, 66.90; H, 6.02; N, 5.57. Found: C, 66.96; H, 6.03; N, 5.57.

(±)-2′,3′-Didehydro-3′-deoxy-4′-ethynyl-4′-thiothymidine (29). To a THF (0.6 mL) solution of **21** (187 mg, 0.37 mmol) was added Bu_4NF (1 M in THF, 0.51 mL, 0.51 mmol). The reaction mixture was stirred at rt for 1.5 h. Addtion of CH_2Cl_2 and saturated aqueous $NaHCO_3$ to the reaction mixture gave **29** (54 mg, 55%) as a precipitate: mp 259−262 °C; UV (MeOH) λ_{max} 271 nm (ϵ 10 800), λ_{min} 239 nm (ϵ 3000); IR (neat) 3051 cm^{-1} (C≡CH); ^{1}H NMR (DMSO-d_6) δ 1.71 (3H, d, $J_{6,Me}$ = 1.2 Hz, 5-Me), 3.46 (1H, s, C≡CH), 3.58 and 3.79 (2H, each as dd, J_{gem} = 11.3 Hz and $J_{5',OH}$ = 6.1 Hz, H-5′), 5.75 (1H, t, $J_{5',OH}$ = 6.1 Hz, OH), 5.91 (1H, dd, $J_{2',3'}$ = 6.1 Hz and $J_{1',2'}$ = 2.7 Hz, H-2′), 6.08 (1H, dd, $J_{2',3'}$ = 6.1 Hz and $J_{1',3'}$ = 2.0 Hz, H-3′), 6.93 (1H, dd, $J_{1',2'}$ = 2.7 Hz and $J_{1',3'}$ = 2.0 Hz, H-1′), 7.69 (1H, d, $J_{6,Me}$ = 1.2 Hz, H-6), 11.33 (1H, br,

NH); ^{13}C NMR (DMSO-d_6) δ 12.2 (5-Me), 61.6 (C-4′), 67.4 (C-1′), 68.0 (C-5′), 75.9 (C≡*C*H), 82.8 (*C*≡CH), 109.6 (C-5), 129.1 (C-2′), 136.8 (C-6), 138.0 (C-3′), 150.5 (C-2), 163.6 (C-4); FAB-MS (*m/z*) 265 (M^++H). Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C,54.53; H, 4.58; N, 10.60. Found: C, 54.56; H, 4.39; N, 10.81.

Anti-HIV-1 Assay. MT-4 cells[27] were maintained in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 U/mL penicillin G, and 100 μg/mL streptomycin. The III_B strain of HIV-1 was used throughout the experiment. The virus was propagated and titrated in MT-4 cells. Virus stocks were stored −80 °C until use.

The anti-HIV-1 activity of the test compounds was determined by the inhibition of virus-induced cytopathogenicity in MT-4 cells.[28] Briefly, MT-4 cells (1×10^5 cells/mL) were infected with HIV-1 at a multiplicity of infection (MOI) of 0.02 and were cultured in the presence of various concentrations of the test compounds. After a 4-day incubation at 37 °C, the number of viable cells was monitored by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[29] The cytotoxicity of the compounds was evaluated in parallel with their antiviral activity, based on the viability of mock-infected cells as determined by the MTT method.

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Supporting Information Available: Synthetic procedures and characterization data for **11**, **12**, **14**, **15**β, **15**α, **16**β, **16**α, **22**−**26**, and **28**, procedures for optical resolution of **29**, and ORTEP drawing of **17**α. This material is available free of charge via the Intermet at http://pubs.acs.org.

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(14) During 3-*O*-acylation of **9**, formation of a small amount of epimer was observed. NMR data of the epimeric isomer of **13**: ^{1}H NMR ($CDCl_3$) δ 1.04 (9H, s, SiBu-*t*), 3.77 (3H, s, CO_2Me), 3.82 and 4.24 (2H, each as d, J_{gem} = 9.5 Hz, CH_2OSi), 6.14 (1H, dd, Hz, $J_{3,4}$ = 2.7 Hz and $J_{4,5}$ = 6.3 Hz, H-4), 6.65 (1H, d, $J_{4,5}$ = 6.3 Hz, H-5), 6.90 (1H, d, $J_{3,4}$ = 2.7 Hz, H-3), 7.32−7.45 (8H, m, ph), 7.53−7.57 (1H, m, Ph), 7.61−7.64 (4H, m, Ph), 7.90−7.92 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.3 (Si*C*Me$_3$), 26.6 (SiC*Me*$_3$), 52.8 (CO_2*Me*), 69.5 (C-2), 71.3 (*C*H_2OSi), 85.8 (C-3), 127.7, 128.4, 129.7, 129.8, 133.3 and 135.6 (Ph-tertiary), 129.4, 132.7 and 133.0 (Ph-quaternary), 129.2 (C-4), 137.5 (C-5), 165.9 (*C*OPh), 171.4 (*C*O_2Me).

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