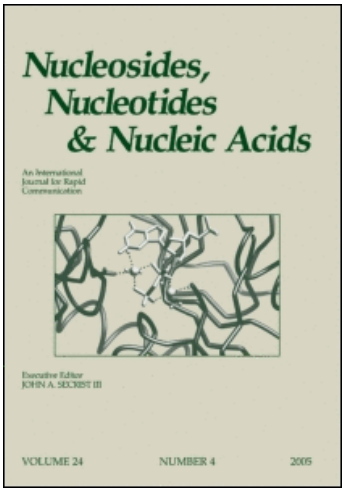

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NEW 3′-DEOXYTHYMIDINES BEARING A NUCLEOPHILIC 3′-SUBSTITUENT

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ABSTRACT

New potential cancer-driven as well as HIV-driven nucleoside hetero-analogs, such as 3′-thio- and 3′- as well as 5′-selenosubstituted thymidines, have been synthesized. We also report an effective method for the preparation of novel nucleoside derivatives, bis(deoxynucleoside) diselenides, in nearly quantitative yields. The North conformation is significantly populated in the conformational equilibrium for 3′-α-alkylthiothymidines.

Many 3′-modified deoxynuleosides are antiretroviral and anticancer agents of varying potency (1). For instance, 3′-azido-3′-deoxythymidine (AZT) is still one of the most widely used drugs in the AIDS treatment. After being triphosphorylated in vivo, these agents essentially suppress virus reproduction or cell proliferation via termination of the cDNA chain elongation, a polymerization reaction, which is provided by the viral reverse transcriptase (RT) or cellular DNA-polymerases (DNApol), respectively [see Schinazi and DeClercq (1)]. The mechanism of this termination involves inhibition of the RT-mediated transcription of viral RNA or DNApol-assisted replication of genomic DNA via attachment of a 3′-modified nucleoside analog to the growing 3′-terminus of the cDNA strain [see Schinazi, DeClercq, and Arnold and Arnold (1)].

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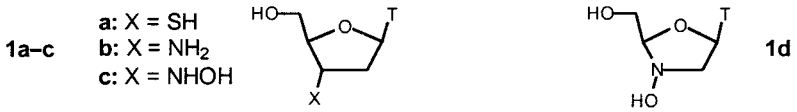

Figure 1. Highly active nucleosides with nucleophilic 3′-substituent.

Among the relatively small number of known 3′-deoxynucleoside analogs bearing a nucleophilic 3′-substituent [see Schinazi, DeClercq, Arnold and Arnold, and DeClercq (1) as well as (2)], a significant proportion of these compounds possesses remarkable termination activity. For instance, 3′-mercapto derivative **1a** (see Fig. 1) demonstrates the same termination activity as AZT (3). Also, the 3′-amino analog **1b** effectively blocks the biosynthesis of cDNA, being attached to the 3′-terminus by RT [see Kedar et al. (1)] or DNApol [see Chidgeavadze et al. (2)]. Other nucleoside inhibitors of the virus and cell reproductive cycle are hydroxylamines **1c** and **1d** [see Ng and Orgel (1); Schreiber and Ikemoto (4)].

Normal cDNA biosynthesis involves nucleophilic attack of the 3′-OH group in the cDNA 3′-terminus on the 5′-triphosphate fragment of nucleotide substrates. Thymidines **1a** and **1b** are incorporated by RT or DNApol into the nascent DNA chain; however, this cDNA chain with the 3′-SH or 3′-NH_2 function in the 3′-terminus is not elongated further by the enzymes [see Kedar et al. (1); Chidgeavadze et al. (2); Yuzhakov et al. (3)]. We consider it likely that the inhibition by thymidine derivatives with *nucleophilic* 3′-substituents (SH or NH_2) may be caused by binding of bivalent metal cations [see Domenico et al. and Johannsen et al. (5)], necessary components of the RT as well as DNApol polymerization domains [see Kati et al. and Wohrl et al. (5)], by these electron donating 3′-substituents as complexation ligands.

Thus, a more nucleophilic 3′-substituent (such as SeH) is desirable for inhibition of RT/DNApol-directed polymerization from the viewpoint of the complexation hypothesis. However, deoxynucleoside selenols themselves are so far unknown and are not an attractive synthetic goal because of the extreme susceptibility of an SeH function to oxidation. We therefore considered a prodrug approach* and report herein the synthesis of new nucleosides with a nucleophilic 3′-substituent, which include novel seleno deoxynucleosides, namely bis(deoxynucleoside) diselenides. The latter were chosen as potential in vivo precursors of the corresponding deoxynucleoside selenols. Indeed, similarly to the well-known enzymatic transformation of the S−S function to SH groups, Se−Se compounds are also reduced in vivo to selenols (7). Among nucleoside diselenides, only thymidine diselenide **6b** has been reported as a by-product of the hydrolysis of the corresponding 3′,5′-dithymidine selenophosphate (8).

We developed a synthesis of the bis(deoxynucleoside) diselenides, using deoxynucleoside selenocyanates and easily handled borohydride reagents. A

*Recently we proposed deoxynucleoside selenocyanates as masked selenol deoxynucleosides.

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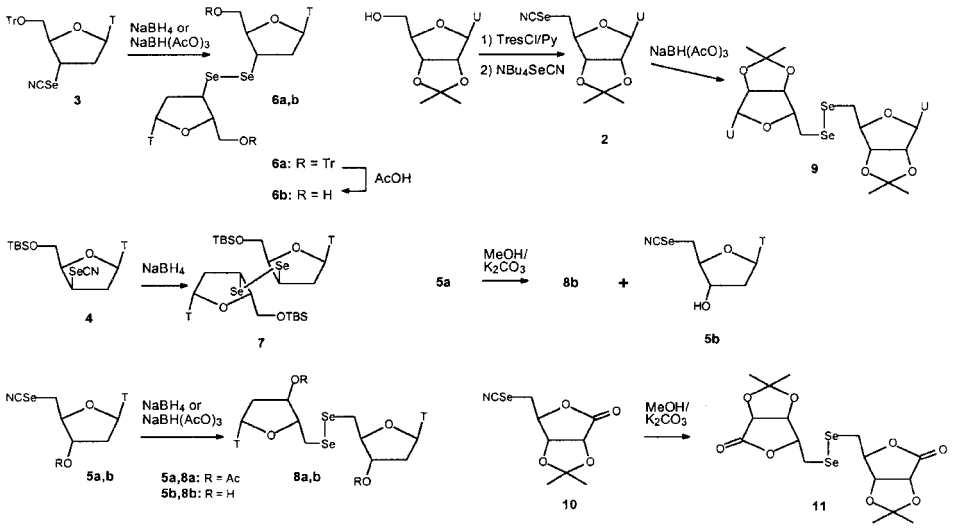


Scheme 1. Preparation of bis(nucleoside) diselenides.

convenient method for preparation of thymidine selenocyanates has been described recently (6). Uridine selenocyanate **2** was obtained in 56% yield in the same manner from the corresponding 5′-tresylate and NBu_4SeCN (see Scheme 1). Hydride reduction of simple alkylselenocyanates to corresponding diselenides have been reported [see Salama and Charles, Witczak and Czernecki, and Krief et al. (9)]. However, conditions for minimal side-product formation [see Krief et al. (9)] (0.25 eq. of $NaBH_4$, EtOH, 0°C, Ar atmosphere) led to conversion of nucleoside selenocyanates **3–5a** into diselenides **6a–8a** only in 25–50% yields. Deprotection of trityl derivative **6a** (80% AcOH, reflux) led to the desired deoxythymidine **6b**.

Since the low-yield problems could arise due to the presence of four active hydrogen atoms inthe borohydride anion [see Krief et al., *Tetrahedron* (9)], we chose $NaBH(AcO)_3$ as a simple and successful alternative for the nucleoside selenocyanate–diselenide transformation. Using this reagent, compounds **2**, **3**, **5a**, and **5b** were reduced (EtOH, 25°C, 1 h, Ar atmosphere) to diselenides **9**, **6a**, **8a**, and **8b**, respectively, in 85–100% yields. Our attempts to find a mild solvolytic route to diselenides were less successful: treatment of selenocyanates **10** and **5a** in a MeOH solution with catalytic amount of K_2CO_3 led to formation of diselenides **11** and **8b**, respectively, only in 15–20% yields [see Krief et al., *Angew. Chem., Int. Ed.* (9) for related reactions]. Alcohol **5b** was a major product in the case of acetate **5a**. The yield of **5b** was lowered when a 10-fold larger amount of the base was employed; however, no proportional increase of the yield of **8b** was observed.

In principle, reduced **6b** (i.e., the 3′-SeH compound) may possess DNA elongation activity despite the supposed complexation ability, if incorporated into the cDNA chain. Therefore we turned to the synthesis of 3′-deoxythymidines possessing a remote nucleophilic group at the 3′-position. These model bidentate S,X-containing (X = OH, SH, NH_2) nucleoside ligands (compounds of type **15** or **17**)

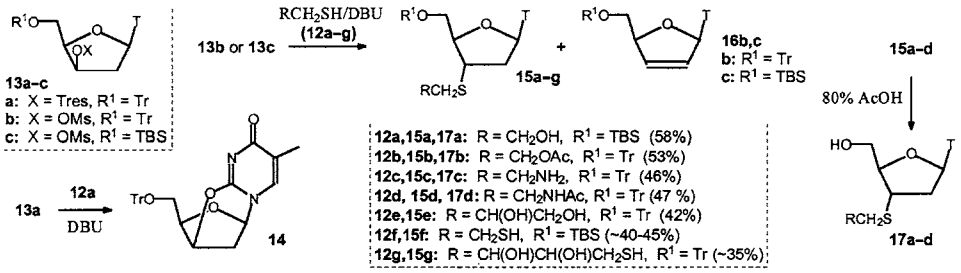


Figure 2. Preparation of 3′-S-alkyl-3′-deoxythymidines.

could be capable of metal cation chelation [see Domenico et al. and Johannsen et al. (5)], but should possess no activity in the DNApol or RT-mediated chain elongation due to the absence of the 3′-OH group.

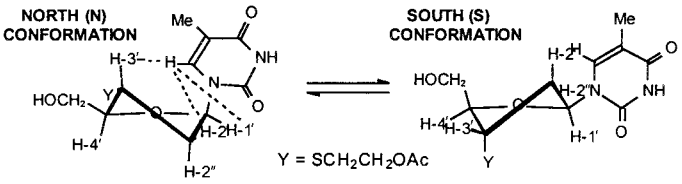
This involved mesylate-based activation of the 3′-β-OH group, in spite of complications due to concurrent mesylate elimination expected to occur when mercaptan nucleophiles are employed [see Bera et al. (10)]. Thus, interaction of three-fold excess of mercaptans **12a–f** with mesylate **13b** or **13c** in the presence of 3 eq. of DBU (DMF, 70°C, 5–20 h) led to the corresponding nucleosides **15a–f** and accompanying elimination products **16b** or **16c**, respectively (see Fig. 2). Deprotection of the 5′-hydroxy group of **15a–d** (reflux in 80% AcOH) led to desired substrate analogs **17a–d**.

The more reactive tresylate **13a** was converted only into the intramolecular cyclization product **14** in the reaction with **12a** and DBU (DMF, 25°C, 4 h). Relatively high yields of 3′-α-deoxythymidine sulfides have been reported for the interaction of the corresponding 2,3′-anhydro compounds with nonfunctionalized thiolates (*iso*-PrSNa [see Joshi and Reese (10)] as well as PhSH in the presence of Pr_3N [see Joshi et al. (10)]) at 100–120°C. However, compound **14** did not react with thiol **12a**: a weak electrophile **14** decomposed slowly even under milder conditions (DBU, MeCN, 70°C) and only traces of **15a** were formed.

Attempts to reduce formation of elimination product **16** were unsuccessful. No reaction was observed without DBU. The use of weaker amino bases instead of DBU for the interaction of **13c** and mercaptan **12a** in DMF resulted in recovery of starting mesylate **13c** (48-h heating with pyridine) or in incomplete reaction (72-h heating with diisopropylamine led to a 1:1:2 mixture of the substitution product **15a**, the elimination product **16**, and the starting material).

Unfortunately, nucleosides **15f** and **15g** possessing a strong nucleophilic group were unstable, possibly because of ncleophilic attack of the SH group on the anomeric position of the ring; they were not isolated, since appreciable decomposition occurred even on an inert reverse phase HPLC column, and only their yield was estimated (by NMR).

Since one of the ribose ring conformations, namely the North (N) conformation, is considered important for RT and DNApol assisted catalysis [see



Scheme 2. Selected NOE interactions and conformational equilibrium for nucleoside **17b**.

Schinazi (1)], we also examined deoxynucleoside **17b** by NMR. NOESY experiments allowed us to estimate qualitatively a S↔N conformational equilibrium (11) for 3′-alkylthio-3′-deoxythmidines (see Scheme 2 for selected NOE interactions).

As in the case of 3′-selenocyanate deoxythymidines (6), NOE interactions between the olefinic proton of the pyrimidine ring and the H-3′-furanose proton are observed. Thus, the N-conformation of the deoxyribose ring and the *anti*-conformation of the nucleobase are appreciably populated for **17b**. Unfortunately, we were unable to study the S↔N equilibrium for diselenides **6a,b** because of overlapping ring proton signals.

3′-Substituted nucleoside **17a**, containing a remote nucleophilic group, showed no remarkable anticancer activity in cytotoxicity experiments in 60 human cancer cell lines (E. Sausville personal communication NCI's primary anticancer screen, Bethesda (12). In contrast, masked 3′-selenol **6b** demonstrated significant cytostatic activity in preliminary studies in colon and breast cancer cells *in similar concentrations as fluorouracil* (e.g., for colon cancer the cell cytotoxicity is 75 and 70% for a 45 μg/mL concentration of **6b** and fluorouracil, respectively) (12). Detailed anticancer studies for **6b** as well as other new nucleoside heteroanalogs will be reported separately.

EXPERIMENTAL

Materials and methods. All reaction have been carried out in anhydrous solvents under a dry argon atmosphere. The reactions were monitored by TLC. Flash column chromatography was performed using Merck 60 silica gel, washed with a 3:1 mixture of $CHCl_3$–EtOH followed by prolonged washing with eluent mixture. Analytical separations were performed in a gradient regime on a Waters 501 HPLC instrument equipped with a semipreparative Merck RP18 column. The purity of new compounds was determined by ^{1}H and ^{13}C NMR, HPLC as well as TLC (for diselenides) in 2–3 chromatographic systems. NMR spectra have been recorded on Brucker AM-300 as well as Brucker-600 spectrometers. Mass spectra (including high-resolution mass spectra) were obtained on a Fisons VG AutoSpec instrument, using chemical ionization (by *i*-BuH or CH_4) or fast atom bombardment (glycerol matrix) methods. Detected MH^+ values are given for ^{80}Se-containing ions. The analytical spectral data for related compounds (e.g., **15a–g**) are given for selected examples (e.g., for compound **15d**).

2′-*O*,3′-*O*-Isopropylidene-5′-deoxyuridine-5′-selenocyanate (2). A solution of 140 mg (0.085 mL, 0.77 mmol) of tresyl chloride in 3 ml of $CHCl_3$ was added dropwise at −20°C to a mixture of 200 mg (0.70 mmol) of 2′-*O*,3′-*O*-isopropylideneuridine (Sigma) and 61 mg (0.06 mL, 0.77 mmol) of dry pyridine in 3 ml of $CHCl_3$. After 2 h the mixture was allowed to warm to 0°C, washed with ice-water, cold 1% HCl, 1% $NaHCO_3$, and water. The $CHCl_3$ solution was dried over $MgSO_4$ and filtered to a flask with 364 mg (1.05 mmol) of tetrabutylammonium selenocyanate (6). The mixture was stirred 48 h at room temperature, evaporated and chromatographed. Yield: 73 mg (28%). ^{1}H NMR ($CDCl_3$): 1.36 (s, 3H; Me), 1.58 (s, 3H; Me), 3.86 (AB-part of ABX system, 2H, 17.9 and 3.6 Hz; H-5′, H-5″), 4.30 (m, 1H; H-4′), 4.99 (m, 2H; H-2′, H-3′), 5.56 (d, 1H, 1.5 Hz; H-1′), 5.76 (dd, 1H, 9.2 and 1.5 Hz; 5-H), 7.37 (d, 1H, 9.2 Hz; 6-H). Mass spectrum (*m/z*): 373 (MH^+).

5′-Deoxythymidine-5′-selenocyanate (5b) and bis(5′-deoxythymidine)-5′,5′-diselenide (8b). A mixture of 100 mg (0.27 mmol) of acetate **5a** (6), 4 mg (0.03 mmol) of K_2CO_3, and 8 mL of MeOH was stirred 48 h at room temperature and evaporated with 2 g of silica. The silica was added carefully to the silica gel of chromatography column, and chromatography separation (gradient EtOAc – EtOAc/MeOH 7:1) afforded 40 mg of deacylation product **5b** (44% yield) and 15 mg of diselenide **8b** (20% yield). Compound **5b** – ^{1}H NMR (acetone-d_6): 1.85 (d, 3H, 0.7 Hz; 5-Me), 2.33 (ddd, 1H, 10.0, 6.0, and 3.5 Hz; H-2′), 2.45 (m, 1H; H-2″), 3.55 (AB part of ABX system, 2H, $J_{5',5''} = 12.8$ Hz, $J_{4',5'} = 7.3$ Hz, $J_{4',5''} = 5.2$ Hz; H-5′, H-5″), 4.20 (m, 1H; H-4′), 4.50 (m, 1H; H-3′), 6.35 (dd, 1H, 7.0 Hz; H-1′), 7.53 (q, 1H, 0.7 Hz; H-6). Mass spectrum (*m/z*): 331 (MH^+). Compound **8b** – ^{1}H NMR (CD_3OD): 1.89 (s, 6H, 5-Me), 2.28 (dd, 2H, 5.9 and 4.9 Hz; H-2′), 3.27 (m, 2H; H-2″), 3.62 (m, 4H; H-5′, H-5″), 4.09 (m, 2H; H-4′), 4.33 (m, 2H; H-3′), 6.25 (dd, 2H, 11.7 and 11.7 Hz; H-1′), 7.49 (s, 2H; 6-H). Mass spectrum (*m/z*): 611 (MH^+).

Bis(5′-*O*-*tert*-butyldimethylsilyl-3′-deoxythymidine)-3′-β-3′-β-diselenide (7). To a solution of 57 mg (0.1 mmol) of selenocyanate 4 (6) in 2 mL of EtOH, 1 mg (0.025 mmol) of $NaBH_4$ was added at 0°C. After 1 h the mixture was evaporated, water and $CHCl_3$ were added, and organic phase was dried over $MgSO_4$, filtered, and evaporated. Column chromatography afforded 12 mg of **7** (24% yield). ^{1}H NMR ($CDCl_3$): 0.15 (s, 12H; $SiMe_2$), 0.95 (s, 18H; Si*C*Me_3); 1.95 (d, 6H, 1.1 Hz; 5-Me), 2.24 (m, 2H; H-2′), 2.80 (ddd, 2H, 12.0, 7.0, and 5.1 Hz; H-2″), 3.92 (m, 6H; H-3′, H-5′, H-5″), 4.35 (m, 2H; H-4′), 6.04 (dd, 2H, 8.5 and 5.1 Hz; H-1′), 7.52 (q, 2H, 1.1 Hz; H-6). ^{13}C NMR ($CDCl_3$): −5.27 ($SiMe_2$), 12.53 (5-Me), 18.24 (Si*C*Me_3), 26.12 (Si*CMe*$_3$), 41.41 (C-2′), 45.29 (C-3′), 64.95 (C-5′), 81.20, 83.32 (C-1′ and C-4′), 111.06 (C-5), 134.97 (C-6), 150.77 (C-2), 168.74 (C-4). High-resolution mass spectrum (FAB$^+$) calcd. for $C_{32}H_{55}N_4O_8Se_2Si_2$ (MH^+): 839.190. Found: 839.167.

Bis(deoxynucleoside) diselenides by NaBH(AcO)$_3$-assisted reduction *(general procedure).* A mixture of 0.05 mmol of deoxynucleoside selenocyanate, 0.05 mmol of $NaBH(AcO)_3$, and 2 mL of EtOH was stirred 2 h at room temperature

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and evaporated. The residue was washed with water and *i*-PrOH and dried over P_2O_5.

Bis(3′-*O*-acetyl-5′-deoxythymidine)-5′,5′-diselenide (8a). It was obtained in 98% yield from bselenocyanate **5a** (6). ^{1}H NMR ($CDCl_3$): 1.95 (d, 6H, 0.9 Hz; 5-Me), 2.10 (s, 6H; MeCO), 2.40 (m, 4H; H-2′, H-2″), 3.45 (m, 4H; H-5′, H-5″), 4.25 (m, 2H; H-4′), 5.25 (m, 2H; H-3′), 6.20 (dd, 2H, 6.9 Hz; H-1′), 8.05 (q, 2H, 0.9 Hz; H-6). Mass spectrum (*m/z*): 695 (MH^+).

Bis(2′-*O*,3′-*O*-isopropylidene-5′-deoxyuridine)-5′,5′-diselenide (9). It was obtained in 86% yield from selenocyanate **2**. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H; Me), 1.58 (s, 6H; Me), 3.79 (m, 4H; H-5′, H-5″), 4.37 (m, 2H; H-4′), 4.94 (m, 4H; H-2′, H-3′), 5.69 (d, 2H, 2.7 Hz; H-1′), 5.75 (d, 2H, 7.4 Hz; H-5), 7.34 (d, 2H, 7.4 Hz; H-6).

Bis(3′-deoxythymidine)-3′-α-,3′-α-diselenide (6b). The residue, which was obtained according to the general procedure (see preceding) from selenocyanate **3** (6), was dissolved in 80% AcOH, refluxed 2 h, evaporated to a small volume, reevaporated with EtOH (5 × 50 mL), and chromatographed. Compound **6b** (74% yield) – ^{1}H NMR (acetone-d_6): 1.80 (s, 6H; Me), 2.55 (m, 4H; H-2′ and H-2″), 3.95 (m, 8H; H-3′, H-4′, H-5′, H-5″), 6.17 (dd, 2H; H-1′), 7.93 (s, 2H; H-6). ^{13}C NMR (acetone-d_6): 12.53 (5-Me), 30.07 (C-2′), 37.12 (C-3′), 61.47 (C-5′), 85.27, 88.10 (C-1′ and C-4′), 110.26 (C-5), 137.01 (C-6), 151.25 (C-2), 164.27 (C-4). High-resolution mass spectrum (FAB^+) calcd. for $C_{20}H_{27}N_4O_8Se_2$ (MH^+): 611.016. Found: 611.194.

3′-β-*O*-Mesyl-5′-*O*-*tert*-butyldimethylsilylthymidine (13c). The procedure was analogous to that for preparation of mesylate **13b** [see Bera et al. (10)]. Yield: 90%. ^{1}H NMR ($CDCl_3$): 0.10 (s, 6H; $SiMe_2$), 0.92 (s, 9H; $SiCMe_3$); 1.95 (d, 3H, 1.1 Hz; 5-Me), 2.43 (m, 1H, H-2′), 2.87 (m, 1H, H-2″), 3.05 (s, 3H; MeS), 3.9–4.1 (m, 3H; H-4′, H-5′, H-5″), 5.26 (m, 1H; H-3′), 6.32 (dd, 1H; H-1′), 7.42 (s, 1H; H-6).

Preparation of 3′-α-S-alkyl-3′-deoxythymidines *(general procedure).* A mixture of 6 mmol of mercaptan, 2.5 mmol of DBU, and 2 mL of DMF was heated at 60°C for 10 min. A solution of 1 mmol of mesylate **13b** [see Bera et al. (10)] or **13c** was added and the mixture was kept for 5–20 h at this temperature. EtOAc and water were added at 25°C, the organic phase was dried over $MgSO_4$ and chromatographed. The yields are shown in Figure 2.

5′-*O*-Trityl-3′-α-S-(N-acetyl-2-aminoethyl)-3′-deoxythymidine (15d). It was obtained from **13b** and **12b**. ^{1}H NMR ($CDCl_3$): 1.45 (d, 3H, 0.9 Hz; 5-Me), 1.95 (s, 3H, MeCO), 2.3–2.6 (m, 2H; H-2′, H-2″), 2.55 (t, 2H, 6.6 Hz; Ch_2S), 3.34 (m, 3H; H-5′, CH_2N), 3.67 (m, 2H; H-3′, H-5″), 3.95 (dt, 1H, 7.6 Hz, 3.0 Hz; H-4′), 6.21 (dd, 1H, 6.8 Hz, 4.0 Hz; H-1′), 7.2–7.4 (m, 15H; Ph), 7.75 (q, 1H, 0.9 Hz; 6-H). ^{13}C NMR ($CDCl_3$): 11.58 (5-Me), 22.56 (*Me*CO), 30.81 (C-2′), 38.59 (CH_2S), 40.02 (CH_2N), 40.43 (C-3′), 62.01 (C-5′), 84.33, 84.84 (C-1′, C-4′), 86.75 (Ph), 110.33 (C-5), 126.5–128.2 (Ph), 135.30 (C-6), 142.85 (Ph), 150.29 (C-2), 163.99 (C-4), 206.76 (CO). High-resolution mass spectrum (FAB^+) calcd. for $C_{33}H_{36}N_3O_5S$ (MH^+): 586.2376. Found: 586.2310.

Deprotection of 5′-*O*-protected 3′-α-S-alkyl-3′-deoxythymidines *(general procedure).* A mixture of 0.5 mmol of **15a–d** and 5 mL of 80% AOH was refluxed 1–2 h, evaporated, reevaporated several times with EtOH and once with toluene, and chromatographed.

3′-α-S-(N-acetyl-2-aminoethyl)-3′-deoxythymidine (17d). It was obtained from **15d** in 81% yield. ^{1}H NMR (CD_3OD): 1.85 (s, 3H; 5-Me), 1.96 (s, 3H; MeCO), 2.44 (m, 2H, H-2′, H-2″), 2.75 (t, 2H, 6.7 Hz; CH_2S), 3.37 (t, 2H; 6.7 Hz; CH_2N), 3.50 (m, 1H; H-5′), 3.87 (m, 3H; H-3′, H-4′, H-5″), 6.13 (dd, 1H, 7.0 and 4.2 Hz; H-1′), 7.9 (s, 1H; H-6). Mass spectrum (*m/z*): 344 (MH^+).

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