A Short and Efficient Synthesis of L-Thioarabinose Derivative: A Versatile Synthon for the Synthesis of L-2′-Deoxy-2′,2′-disubstituted-4′-thionucleosides

Lak Shin Jeong,*,† Hyung Ryong Moon,† Yeon Ju Choi,‡ Moon Woo Chun,‡ and Hea Ok Kim§

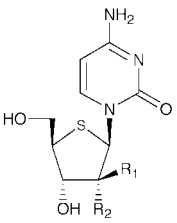
Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea, College of Pharmacy, Seoul National University, Seoul 151-742, Korea, and Department of Industrial Safety and Hygiene, Kyungin Women's College, Incheon 407-050, Korea

Received February 4, 1998

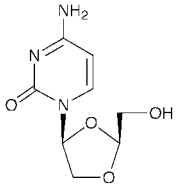
Introduction

4′-Thionucleosides, which are bioisosteric to clinically useful 4′-oxonucleosides, show interesting activities such as antibiotic,[1] antiviral,[2] and antineoplastic.[3] Despite these encouraging results and other inherent advantages, such as having a more stable glycosyl bond and increased metabolic stability,[4] difficulties in accessing the requisite 4-thiosugars,[5] which normally involves numerous and low-yielding steps, have prevented their development as clinical agents. Although several groups published improved syntheses of D-2′-deoxy-4′-thio-,[6] D-4′-thioribo-,[7] and D-2′,3′-dideoxy-4′-thionucleosides[8] in the early 1990s, the synthesis of 4-thiosugars continues to be a challenge for the synthesis of 4′-thionucleosides.

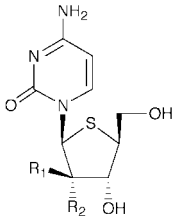
Current interest in the L-nucleosides as biologically active compounds has also spilled over to the 4′-thio series. Indeed, both D- and L-2′-deoxy-4′-thiopyrimidine nucleosides have been shown to have antitumor activities.[9] More recently, Yoshimura and co-workers have reported the elegant synthesis of D-2′-deoxy-2′,2′-disubstituted-4′-thiocytidines **1** and **2** via an anhydrothiosugar prepared from D-glucose. The 2′,2′-difluoro analogue (**1**) exhibited weak antineoplastic activity, while 2′-*C*-methylene derivative (**2**) showed very potent antileukemic activity.[10]



1 : $R_1 = R_2 = F$
2 : $R_1 = R_2 = CH_2$



3 : L(-)OddC



4 : $R_1 = R_2 = F$
5 : $R_1 = R_2 = CH_2$

Another type of nucleoside belonging to the L-series, such as (−)-L-*β*-1,3-dioxolanylcytosine [**3**, L(−)OddC],[11] has been shown to be highly active against solid tumors and is currently under development. Its mechanism of action appears to be chain termination of the DNA polymer after incorporation.[12] This finding prompted us to investigate the corresponding L-2′-deoxy-2′,2′-disubstituted-4′-thiocytidine analogues (**4** and **5**), which were expected to combine the properties of 4′-thio and L-nucleoside series. In keeping with Yoshimura's methodology, L-glucose appeared to be the logical starting material of choice. However, L-glucose is too expensive, and D-xylose was chosen instead. In this paper, we wish to report a short and efficient synthesis of L-4-thioarabitol derivative **12** starting from 1,2-isopropyidene-D-xylose. Compound **12** represents a versatile synthon for the synthesis of L-2′-deoxy-2′,2′-disubstituted-4′-thionucleosides **4** and **5**.

Results and Discussion

The synthesis of our key L-4-thioarabitol intermediate **12** is illustrated in Scheme 1. Commercially available 1,2-isopropylidene-D-xylose (**6**) was benzylated as the dibenzyl ether **7**, which was obtained in quantitative yield. Removal of the isopropylidene group under acidic conditions (*p*-TsOH, MeOH) followed by esterification of the 2-hydroxyl function provided compound **8** in excellent yield (86%). Next, we attempted to perform an acid-catalyzed ring opening reaction with benzyl mercaptan (BnSH). Although several groups have tried this reaction on similar substrates, they involved the use of perbenzylated sugars, which required a rather lengthy process to later functionalize selectively 2-position. The advantage of compound **8** is that 2-position is protected as a benzoyl ester that can be easily and selectively removed for proper functionalization.

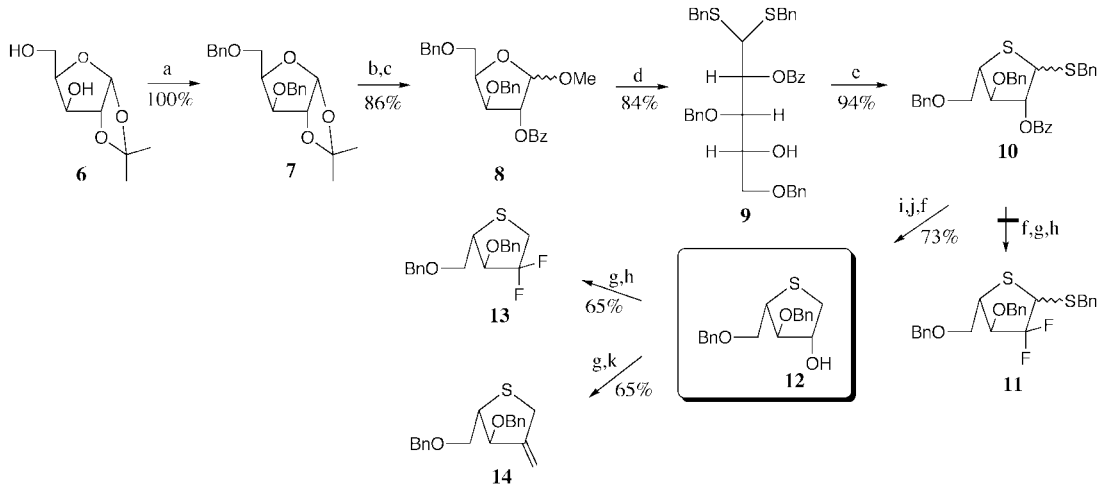
We first tried a conventional approach involving the reaction of **8** with BnSH in conc HCl,[13] but the reaction produced many byproducts and the yield of **9** was very

* To whom correspondence should be addressed. Tel.: 82-2-360-3466. Fax: 82-2-360-2851. E-mail: lakjeong@mm.ewha.ac.kr.
† Ewha Womans University.
‡ Seoul National University.
§ Kyungin Women's College.

(1) Bobek, M.; Whistler, R. L. *J. Med. Chem.* **1972**, *15*, 168−171.
(2) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Chem. Soc., Chem. Commun.* **1991**, 741−742.
(3) (a) Ototani, N.; Whistler, R. L. *J. Med. Chem.* **1974**, *17*, 535−537. (b) Secrest, J. A., III; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361−2366.
(4) Parks, R. E., Jr.; Stoeckler, J. D.; Cambor, C.; Savarese, T. M.; Crabtree, G. W.; Chu, S.-H. Purine Nucleoside Phosphorylase and 5′-Methylthioadenosine Phosphorylase: Targets of Chemotherapy. In *Molecular Actions and Targets for Cancer Chemotherapeutic Agents*; Sartorelli, A. C., Lazo, J. S., Bertino, J. R., Eds.; Academic Press: New York, 1981; pp 229−252.
(5) Fu, Y.-L.; Bobek, M. *J. Org. Chem.* **1976**, *41*, 3831−3834.
(6) (a) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782−2786. (b) Uenishi, J.; Mototama, M.; Nishiyama, Y.; Wakabayashi, S. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1421−1422. (c) Dyson, M. R.; Coe, P. L.; Walker, R. T. *Carbohydr. Res.* **1991**, *216*, 237−248. (d) Uenishi, J.; Takahashi, K.; Motoyama, M.; Akashi, H.; Sasaki, T. *Nucleosides Nucleotides* **1994**, *13*, 1347−1361.
(7) (a) Bellon, L.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *13*, 1467−1479. (b) Leydier, C.; Bellon, L.; Barascut, J.-L.; Deydier, J.; Maury, G.; Pelicano, H.; El Alaoui, M. A.; Imbach, J.-L. *Nucleosides Nucleotides* **1994**, *13*, 2035−2050.
(8) Secrest, J. A., III; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med. Chem.* **1992**, *35*, 533−538.
(9) Uenishi, J.; Takahashi, K.; Motoyama, M.; Akashi, H.; Sasaki, T. *Nucleosides Nucleotides* **1994**, *13*, 1347−1361.
(10) (a) Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822−823. (b) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140−3152.
(11) (a) Kim, H. O.; Shanmuganathan, K.; Alves, A. J.; Jeong, L. S.; Beach, J. W.; Schinazi, R. F.; Chang, C.-N.; Cheng, Y.-C.; Chu, C. K. *Tetrahedron Lett.* **1992**, *57*, 2217−2219. (b) Kim, H. O.; Schinazi, R. F.; Shanmuganathan, K.; Jeong, L. S.; Beach, J. W.; Nampalli, S.; Cannon, D. L.; Chu, C. K. *J. Med. Chem.* **1993**, *36*, 519−528.

S0022-3263(98)00196-0 CCC: $15.00
Published on Web 06/12/1998

Scheme 1[a]



[a] Reagents: (a) NaH, *n*-Bu_4NI, BnBr, THF; (b) *p*-TsOH, MeOH, rt; (c) BzCl, pyridine, rt; (d) BnSH, $BF_3{\cdot}Et_2O$, 40 °C; (e) MsCl, pyridine, rt, then *n*-Bu_4NI, $BaCO_3$, reflux; (f) NaOMe, MeOH, CH_2Cl_2, rt; (g) DMSO, Ac_2O, rt; (h) DAST, CH_2Cl_2, rt; (i) $Hg(OAc)_2$, AcOH, rt; (j) Et_3SiH, TMSOTf, rt; (k) Ph_3PCH_3Br, NaH, *tert*-amyl alcohol, rt.

low. Among the several combinations of Lewis acid catalysts[14] (i.e., $TiCl_4$, TMSOTf, $SnCl_4$, and $BF_3{\cdot}Et_2O$) and solvents (i.e., THF, CH_2Cl_2, and $ClCH_2CH_2Cl$) only $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 40 °C gave a clean reaction with an excellent yield of **9** (84%).[15] A longer reaction time (>2 h) resulted in increased decomposition of the product **9**. Compound **9** was recyclized to the corresponding thiosugar **10** in 94% yield via the corresponding methanesulfonate ester in the presence of *n*-Bu_4NI and $BaCO_3$.[7] Initially, we wanted to synthesize the difluoro anlogue **11** in three steps involving hydrolysis of **10**, oxidation of the resulting alcohol to the ketone, and DAST fluorination. However, during the oxidation, extensive decomposition was observed without formation of the desired ketone. Since it was felt that the benzylthio aglycon was associated with the failure of the oxidation reaction, it was decided to remove this functionality prior to modifying the 2-position. Thus, compound **10** was converted to the acetate after treatment with $Hg(OAc)_2$/AcOH, and the removal of the acetate was subsequently performed with Et_3SiH and TMSOTf to give the L-arabitol derivative.[16] To the best of our knowledge, this is the first example describing the removal of an anomeric acetate group from a thiofuranose with Et_3SiH/TMSOTf. Hydrolysis of the benzoate ester produced the desired key intermediate **12**, which was obtained in 50% overall yield from 1,2-isopropylidene-D-xylose (**6**). Oxidation of **12** with DMSO/Ac_2O afforded the corresponding ketone, which was smoothly converted either to the difluoro derivative **13** after DAST treatment or into the methylidene **14** by Wittig reaction.[10]

Synthesis of the target nucleosides **4** and **5** is shown in Scheme 2. The difluoro derivative **13** was oxidized to the sulfoxide with *m*-CPBA, and this was condensed with persilylated *N*-benzoylcytosine and TMSOTf as Lewis acid catalyst to give **16**α (22%) and **16**β (18%) after silica gel column chromatography.[10,17] When benzyl ether groups in **13** were changed to benzoates, to simplify the final deblocking step, condensation with persilylated *N*-benzoylcytosine under the same conditions resulted in an inseparable anomeric mixture of products with an increased α/β ratio of products (6.5/1). In the case of the methylidene derivative, however, benzoate protection improved the α/β ratio of products (2/1) and resulted in a better separation, by TLC, than that achieved with benzyl ether protection. Treatment of **14** with BBr_3 in CH_2Cl_2 gave the corresponding diol, which was benzoylated to give dibenzoate **15**. Under the same conditions used in the preparation of **16**α,β, the condensation reaction with **15** produced **17**α (27%) and **17**β (14%). Treatment of **16**α and **16**β with BBr_3/CH_2Cl_2 followed by hydrolysis with NaOMe afforded target compounds **4**α (65%) and **4**β (85%), respectively. All benzoyl groups were removed from **17**α and **17**β using NaOMe/MeOH to give **5**α (99%) and **5**β (99%), respectively. The spectroscopic data of the final products (**4** and **5**) were identical to those of their enantiomers (**1** and **2**).[10]

The nucleosides **4**α, **4**β, **5**α, and **5**β were evaluated for antitumor activity against a panel of cancer cell lines including SKMEL-2 (melanoma), A 549 (lung cancer), SKOV3 (ovarian cancer), SNU-1 (stomach cancer), and K562 (leukemia). In contrast to D-4′-thio compounds **1** and **2**, none of our compounds were effective against these tumor cell lines at concentrations >100 μg/mL.

(12) Cheng, Y.-C.; Chu, C. K.; Grove, K. L.; Guo, X. XII International Roundtable, Sep 15−19, 1996, La Jolla, CA, pp 40 (OP26).

(13) (a) Beauchamp, L.; Sterling, B. L.; Kelsey, J. E.; Biron, K. K.; Collins, P.; Selway, J.; Lin, J. J.; Schaeffer, H. J. *J. Med. Chem.* **1988**, *31*, 144−149. (b) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172−4177.

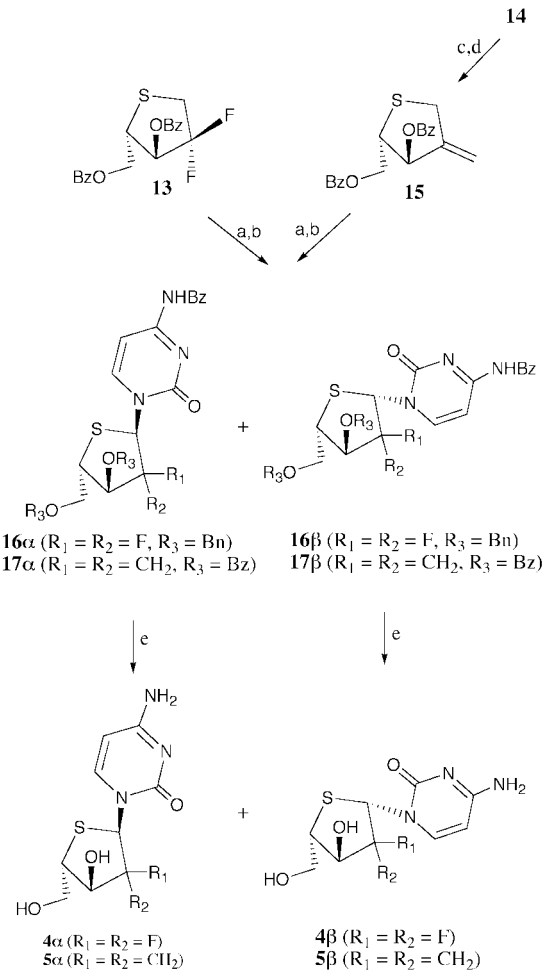
(14) Branalt, J.; Kvarnstrom, I.; Niklasson, G.; Svensson, S. C. T. *J. Org. Chem.* **1994**, *59*, 1783−1788.

(15) The ring-opening reaction of **8** with $BF_3{\cdot}Et_2O$ proceeded via an intermediate 2-benzoyl-3,5-dibenzyl-1-(benzylthio)-D-xylofuranose, which was detectable by TLC. This intermediate, which could be isolated by column chromatography, was easily converted to the desired product **9** after further reaction with benzyl mercaptan and $BF_3{\cdot}Et_2O$. This two-step process is recommended over a direct conversion approach that leads to the formation of a major side product on longer reaction time. This side product was almost overlapped with the intermediate when detected on TLC.

(16) (a) Nair, V.; Jeffery, A. *Tetrahedron Lett.* **1995**, *36*, 3627−3630. (b) The anomeric thiobenzyl group in **10** could not be removed directly unless it was converted to the acetate. The successful removal of the acetate depended upon the amounts of Et_3SiH and TMSOTf used. Optimal conditions were achieved with 3 equiv of Et_3SiH and 2 equiv of TMSOTf.

(17) (a) Kita, Y.; Tamura, O.; Yasuda, H.; Itoh, F.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4235−4241. (b) O'Neil, I. A.; Hamilton, K. M. *Synlett* **1992**, 791−792.

Scheme 2[a]



[a] Reagents: (a) *m*-CPBA, CH_2Cl_2, −40 °C; (b) silylated *N*-benzoylcytosine, TMSOTf, $ClCH_2CH_2Cl$, 0 °C to rt; (c) BBr_3, CH_2Cl_2, −40 °C; (d) BzCl, pyridine, 50 °C; (e) BBr_3, CH_2Cl_2, −40 °C, then NaOMe, MeOH for **16**, NaOMe, MeOH for **17**.

In summary, we have completed a short and efficient synthesis of L-4-thioarabinose derivative, the versatile synthon **12** from an inexpensive source, such as D-xylose. This compound serves as a convenient synthon for the synthesis of 2′-deoxy-2′,2′-disubstituted-4′-thionucleosides. None of the target compounds showed antitumor activity against a panel of five different tumor cell lines.

Experimental Section

General Methods. Melting points are uncorrected. NMR data were recorded on a 250 and 300 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are reported in ppm (δ). Coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Elemental analyses were performed by Ewha Womans University, general instrument laboratory, Seoul, Korea. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to use.

3,5-Dibenzyl-1,2-isopropylidene-α-D-xylofuranose (7). To a suspension of NaH (60% in oil, 21.5 g, 0.537 mol) and *n*-Bu_4NI (5.83 g, 0.0158 mol) in anhydrous THF (700 mL) was added **6** (30 g, 0.158 mol) in THF (50 mL) slowly at 0 °C, and the mixture was stirred for 20 min at the same temperature and then for 30 min at room temperature. The mixture was cooled to 0 °C, treated with BnBr (41 mL, 0.345 mol) in anhydrous THF (30 mL), and then stirred at room temperature for 19 h. The reaction mixture was quenched with water and extracted with ethyl acetate (500 mL). The organic layer was washed with brine (200 mL), dried ($MgSO_4$), filtered, and evaporated to give crude **7** (58 g) as an oil. The crude sample was purified by silica gel column chromatography (hexanes/ethyl acetate = 5:1) to give analytical sample **7**: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.48 (s, 3 H), 3.74 (dd, 1H, J = 6.0, 9.6 Hz), 3.78 (dd, 1 H, J = 6.0, 9.6 Hz), 3.97 (d, 1 H, J = 3.3 Hz), 4.40 (dt, 1 H, J = 3.3, 9.6 Hz), 4.51 (d, 1 H, J = 12.0 Hz), 4.52 (d, 1 H, J = 12.0 Hz), 4.60 (d, 1 H, J = 3.9 Hz), 4.61 (d, 1 H, J = 12.0 Hz), 4.66 (d, 1 H, J = 12.0 Hz), 5.93 (d, 1 H, J = 3.9 Hz), 7.24−7.36 (m, 10 H).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.55; H, 6.97.

Methyl 2-Benzoyl-3,5-dibenzyl-α,β-D-xylofuranoside (8). To a solution of crude **7** (58 g) in methanol (210 mL) was added *p*-TsOH (5.98 g, 31 mmol), and the mixture was stirred at room temperature overnight. The mixture was neutralized with triethylamine and evaporated to give the residue. The residue was dissolved in ethyl acetate (300 mL), washed with brine (150 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 2:1) to give methyl glycoside (50.1 g, 92% from **6**) as an oil.

α-Isomer: ^{1}H NMR ($CDCl_3$) δ 1.86 (d, 1 H, J = 1.8 Hz), 3.41 (s, 3 H), 3.70 (dd, 1 H, J = 7.3, 10.3 Hz), 3.77 (dd, 1H, J = 4.9, 10.3 Hz), 3.96 (dd, 1 H, J = 2.9, 6.1 Hz), 4.22 (m, 1 H), 4.48 (m, 1 H), 4.55 (d, 1 H, J = 12.2 Hz), 4.56 (d, 1 H, J = 12.2 Hz), 4.62 (d, 1 H, J = 12.2 Hz), 4.65 (d, 1 H, J = 12.2 Hz), 4.81 (d, 1 H, J = 1.7 Hz), 7.28−7.35 (m, 10 H).

***β*-Isomer**: ^{1}H NMR ($CDCl_3$) δ 2.72 (d, 1 H, J = 7.3 Hz), 3.53 (s, 3 H), 3.65 (dd, 1 H, J = 6.5, 10.5 Hz), 3.72 (dd, 1H, J = 4.1, 10.5 Hz), 3.99 (dd, 1 H, J = 4.1, 5.9 Hz), 4.26 (dt, 1 H, J = 4.1, 7.3 Hz), 4.39 (dt, 1 H, J = 4.1, 6.5 Hz), 4.52 (d, 1 H, J = 12.0 Hz), 4.54 (d, 1 H, J = 12.0 Hz), 4.63 (d, 1 H, J = 12.0 Hz), 4.73 (d, 1 H, J = 12.0 Hz), 4.99 (d, 1 H, J = 4.7 Hz), 7.24−7.35 (m, 10 H).

To a solution of methyl glycoside (50.1 g, 0.146 mol), (*N*,*N*-dimethylamino)pyridine (1.78 g, 0.0146 mol), and pyridine (35 mL, 0.433 mol) in anhydrous methylene chloride (500 mL) was added benzoyl chloride (18 mL, 0.155 mol) at 0 °C, and the mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (400 mL), washed with diluted HCl and saturated sodium bicarbonate solution, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 7:1) to give **8** (60.9 g, 93%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 3 H), 3.46 (s, 3 H), 3.71 (dd, 1H, J = 5.9, 10.5 Hz), 3.77−3.82 (m, 3 H), 4.07 (d, 1 H, J = 5.3 Hz), 4.43−4.70 (m, 10 H), 4.85 (d, 1 H, J = 12.0 Hz), 5.08 (s, 1 H), 5.22 (t, 1 H, J = 4.5 Hz), 5.29 (d, 1 H, J = 4.5 Hz), 5.41 (s, 1 H), 7.25−7.35 (m, 10 H), 7.42−8.05 (m, 5 H).

Anal. Calcd for $C_{27}H_{28}O_6$: C, 73.30; H, 6.29. Found: C, 72.99; H, 6.57.

2-Benzoyl-3,5-dibenzyl-D-xylose Dibenzyl Dithioacetal (9). To a solution of **8** (47.7 g, 0.106 mol) and benzyl mercaptan (50 mL, 0.426 mol) in methylene chloride (210 mL) was added boron trifluoride etherate (6.5 mL, 0.053 mol), and the mixture was stirred at 40 °C for 2 h. The mixture was diluted with saturated $NaHCO_3$ solution and extracted with methylene chloride (500 mL). The organic layer was dissolved in ethyl acetate (300 mL), washed with brine (150 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 4:1) to give **9** as a syrup and the intermediate, 2-benzoyl-3,5-dibenzyl-1-benzylthio-D-xylofuranose, which was repeated under the same conditions except reaction time (1 h) to give total 59.3 g (84%) of **9** as a colorless syrup.

2-Benzoyl-3,5-dibenzyl-1-benzylthio-D-xylofuranose. *β*-Isomer: ^{1}H NMR ($CDCl_3$) δ 3.82 (d, 1 H, J = 5.3 Hz), 3.96 (d, 1 H, J = 5.3 Hz), 3.90 (d, 1 H, J = 13.5 Hz), 3.99 (d, 1H, J = 13.5 Hz), 4.05 (d, 1 H, J = 4.5 Hz), 4.38 (pseudo q, 1 H, J = 4.5, 5.3 Hz), 4.53 (d, 1 H, J = 12.0 Hz), 4.60 (d, 1 H, J = 12.3 Hz), 4.61 (d, 1 H, J = 12.0 Hz), 4.88 (d, 1 H, J = 12.3 Hz), 5.17 (d, 1 H, J = 1.8 Hz), 5.55 (d, 1 H, J = 1.8 Hz), 7.24−7.98 (m, 20 H).

Anal. Calcd for $C_{33}H_{32}O_5S$: C, 73.31; H, 5.97; S, 5.93. Found: C, 73.43; H, 6.01; S, 5.99.

α-Isomer: ^{1}H NMR ($CDCl_3$) δ 3.76 (dd, 1 H, J = 6.3, 10.0 Hz), 3.82 (dd, 1 H, J = 5.8, 10.0 Hz), 3.90 (s, 2 H), 4.15 (dd, 1H,

J = 1.5, 4.3 Hz), 4.52 (pseudo q, 1 H, J = 4.3, 5.3 Hz), 4.54 (d, 1 H, J = 12.0 Hz), 4.60 (d, 1 H, J = 13.0 Hz), 4.61 (d, 1 H, J = 12.0 Hz), 4.78 (d, 1 H, J = 13.0 Hz), 5.56 (dd, 1 H, J = 1.5, 5.3 Hz), 5.64 (d, 1 H, J = 5.3 Hz), 7.15−8.06 (m, 20 H).

Anal. Calcd for $C_{33}H_{32}O_5S$: C, 73.31; H, 5.97; S, 5.93. Found: C, 73.67; H, 6.32; S, 5.55.

Compound 9: ^{1}H NMR ($CDCl_3$) δ 2.13 (d, 1 H, J = 7.8 Hz), 3.13 (m, 1 H), 3.21 (dd, 1 H, J = 5.9, 9.3 Hz), 3.56 (dd, 1 H, J = 6.3, 9.3 Hz), 3.66 (d, 1 H, J = 13.4 Hz), 3.70 (d, 1H, J = 13.7 Hz), 3.71 (d, 1 H, J = 13.4 Hz), 3.76 (d, 1 H, J = 3.7 Hz), 3.84 (d, 1 H, J = 13.7 Hz), 3.97 (dd, 1 H, J = 2.4, 7.3 Hz), 4.34 (d, 1 H, J = 11.9 Hz), 4.40 (d, 1 H, J = 11.0 Hz), 4.42 (d, 1 H, J = 11.9 Hz), 4.49 (d, 1 H, J = 11.0 Hz), 5.87 (dd, 1 H, J = 3.7, 7.3 Hz), 6.89−7.35 (m, 20 H), 7.41−8.09 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 35.34, 35.91, 49.19, 69.01, 70.75, 73.15, 73.78, 75.15, 78.27, 127.05, 127.06, 127.65, 127.68, 127.70, 128.13, 128.16, 128.35, 128.39, 128.51, 128.61, 129.00, 129.28, 129.94, 129.97, 133.03, 137.58, 137.94, 138.09, 165.84.

Anal. Calcd for $C_{40}H_{40}O_5S_2$: C, 72.26; H, 6.06; S, 9.65. Found: C, 72.56; H, 6.46; S, 9.35.

Benzyl 2-Benzoyl-3,5-dibenzyl-1,4-dithio-α,*β*-L-arabinofuranoside (10). To a solution of dithioacetal **9** (56 g, 84.3 mmol) in anhydrous pyridine (720 mL) was added methanesulfonyl chloride (8.5 mL, 110.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 5 h. To the mixture were added barium carbonate (16.7 g, 84.6 mmol) and *n*-tetrabutylammonium iodide (31 g, 84.0 mmol), and the reaction mixture was heated under reflux for 3 h. The mixture was evaporated to give the residue. The residue was dissolved in methylene chloride (500 mL), washed with brine (150 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 7:1) to give **10** (44 g, 94%) as an oil. ^{1}H NMR indicated that the α-isomer was the major isomer.

α-Isomer: ^{1}H NMR ($CDCl_3$) δ 3.51−3.62 (m, 2 H), 3.75−3.76 (m, 1 H), 3.80 (s, 2H), 4.38 (dd, 1 H, J = 3.5, 5.3 Hz), 4.46 (d, 1 H, J = 12.0 Hz), 4.52 (d, 1 H, J = 12.0 Hz), 4.66 (s, 2 H), 4.69 (d, 1 H. J = 5.3 Hz), 5.89 (t, 1 H, J = 5.3 Hz), 7.21−8.04 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 31.12, 38.27, 49.90, 53.09, 73.86, 74.09, 74.56, 81.71, 85.81, 128.68, 129.08, 129.13, 129.21, 129.78, 129.82, 129.97, 130.01, 130.41, 130.85, 131.31, 134.81, 138.45, 139.07, 139.22, 166.90.

Anal. Calcd for $C_{33}H_{32}O_4S_2$: C, 71.19; H, 5.79; S, 11.52. Found: C, 71.19; H, 5.98; S, 11.23.

1,4-Anhydro-3,5-dibenzyl-4-thio-L-arabitol (12). To a solution of **10** (42.6 g, 76.6 mmol) in acetic acid (680 mL) was added mercuric acetate (48.8 g, 153.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 44 h. The mixture was evaporated to give the residue. The residue was dissolved in methylene chloride (700 mL), washed with saturated $NaHCO_3$ solution (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 5.5:1) to give acetyl 2-benzoyl-3,5-dibenzyl-L-thioarabinofuranoside (34.2 g, 91%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H, α), 2.11 (s, 3 H, *β*), 3.51−3.73 (m, 3 H, α; 2 H, *β*; 1 H), 3.93 (td, 1 H, J = 6.0, 6.6 Hz, *β*), 4.27 (t, 1 H, J = 4.2 Hz, *β*), 4.43 (dd, 1 H, J = 6.0, 9.0 Hz, α), 4.46 (d, 1H, J = 12.3 Hz, *β*), 4.51 (d, 1 H, J = 12.3 Hz, *β*), 4.56 (s, 2 H, α), 4.62 (d, 1 H, J = 12.0 Hz, *β*), 4.69 (d, 1 H, J = 12.0 Hz, α), 4.70 (d, 1 H, J = 12.0 Hz, *β*), 4.74 (d, 1 H, J = 12.0 Hz, α), 5.54 (dd, 1 H, J = 4.5, 9.0 Hz, α), 5.82 (dd, 1 H, J = 1.8, 4.2 Hz, *β*), 6.07 (d, 1 H, J = 1.8 Hz, *β*), 6.23 (d, 1 H, J = 4.5 Hz, α), 7.23−8.02 (m, 30 H, α; 15 H, *β*; 15 H).

To a solution of acetyl 2-benzoyl-3,5-dibenzyl-L-thioarabinofuranoside (34.2 g, 69.5 mmol) and triethylsilane (31 mL, 208 mmol) in anhydrous methylene chloride (400 mL) was slowly added trimethylsilyl trifluoromethanesulfonate (25 mL, 138 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into cold saturated $NaHCO_3$ solution and extracted with methylene chloride (500 mL). The organic layer was washed with brine (200 mL), dried ($MgSO_4$), filtered, and evaporated to give the residue. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 6:1) to give 1,4-anhydro-2-benzoyl-3,5-dibenzoyl-4-thio-L-arabitol (24.6 g, 82%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.01 (dd, 1 H, J = 3.3, 12.0 Hz), 3.42 (dd, 1 H, J = 5.1, 12.0 Hz), 3.53−3.59 (m, 1H), 3.65 (d, 1 H, J = 8.1 Hz), 3.70 (m, 1 H), 4.30 (t, 1 H, J = 1.8 Hz), 4.46 (d, 1 H, J = 12.0 Hz), 4.52 (d, 1 H. J = 12.0 Hz), 4.69 (s, 2 H), 5.64 (dt, 1 H, J = 3.3, 5.1 Hz), 7.21−7.95 (m, 15 H).

Anal. Calcd for $C_{26}H_{26}O_4S$: C, 71.86; H, 6.03; S, 7.38. Found: C, 71.67; H, 6.40; S, 7.05.

To a solution of 1,4-anhydro-2-benzoyl-3,5-dibenzoyl-4-thio-L-arabitol (24.6 g, 56.7 mmol) in methyl alcohol (350 mL) and methylene chloride (70 mL) was added sodium methoxide (5.7 mL, 5.7 mmol, 1 M methyl alcohol solution), and the mixture was stirred at room temperature for 2 h. The mixture was neutralized with acetic acid and evaporated to give the residue. The residue was dissolved in ethyl acetate (500 mL), washed with brine (100 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 3.5:1) to give L-thioarabitol **12** (18.4 g, 98%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.90 (dd, 1 H, J = 2.4, 11.4 Hz), 3.23 (dd, 1 H, J = 4.2, 11.4 Hz), 3.51−3.57 (m, 2H), 3.61−3.66 (m, 2 H), 3.94 (br. t, 1 H), 4.36−4.40 (m, 1 H), 4.53−4.64 (m, 4 H), 7.26−7.35 (m, 10 H).

Anal. Calcd for $C_{19}H_{22}O_3S$: C, 69.06; H, 6.71; S, 9.70. Found: C, 69.33; H, 6.70; S, 9.43.

1,4-Anhydro-2-deoxy-3,5-dibenzyl-2,2-difluoro-4-thio-L-*erythro*-pentitol (13). A mixture of **12** (0.978 g, 2.96 mmol), DMSO (15.8 mL, 0.223 mol), and acetic anhydride (7.9 mL, 83.3 mmol) was stirred at room temperature for 5 h. Diethyl ether and water were added to the mixture. The organic layer was washed with brine (50 mL) twice, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), filtered, and evaporated to give the residue. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 8:1) to give ketone (0.858 g, 88%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 3.35 (s, 2 H), 3.49−3.63 (m, 2 H), 3.72 (dd, 1 H, J = 4.2, 9.6 Hz), 4.02 (d, 1 H, J = 8.4 Hz), 4.48 (d, 1 H, J = 12.0 Hz), 4.54 (d, 1 H. J = 12.0 Hz), 4.60 (d, 1 H, J = 11.7 Hz), 4.92 (d, 1 H, J = 11.7 Hz), 7.26−7.37 (m, 10 H).

To a solution of ketone (0.308 g, 0.94 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DAST (0.56 mL, 4.2 mmol) solution in anhydrous CH_2Cl_2 (2 mL) dropwise over 10 min, and the mixture was stirred at room temperature for 20 h. Saturated $NaHCO_3$ solution (50 mL) was poured into the mixture and extracted with CH_2Cl_2. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to give the residue. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 15:1) to give **13** (0.241 g, 73%) as a syrup: $[\alpha]^{25}_D$ −63.0° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.13 (q, 1 H, J = 12.0 Hz), 3.27 (dt, 1 H, J = 12.0, 15.2 Hz), 3.46−3.52 (m, 1 H), 3.54−3.63 (m, 2 H), 4.00 (dt, 1 H, J = 5.2, 8.0 Hz), 4.49 (s, 2 H), 4.62 (d, 1 H, J = 12.0 Hz), 4.80 (d, 1 H, J = 12.0 Hz), 7.26−7.37 (m, 10 H).

Anal. Calcd for $C_{19}H_{20}F_2O_2S$: C, 65.12; H, 5.75; S, 9.15. Found: C, 65.52; H, 5.45; S, 9.06.

1,4-Anhydro-2-deoxy-3,5-dibenzyl-2-*C*-methylene-4-thio-L-*erythro*-pentitol (14). To a mixture of methyl triphenylphosphonium bromide (1.73 g, 4.84 mmol) and *tert*-amyl alcohol (0.58 mL, 5.3 mmol) in anhydrous THF (5 mL) was added NaH (60% in mineral oil, 0.213 g, 5.3 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to −10 °C, treated with a solution of the ketone intermediate (0.48 g, 1.46 mmol) in THF (2.5 mL) over 20 min, and stirred at room temperature overnight. The mixture was quenched with 1 M NH_4Cl (10 mL) and extracted with EtOAc. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to give the residue. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 20:1) to give **14** (0.404 g, 74%) as a syrup: $[\alpha]^{25}_D$ +2.67° (*c* 0.15, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.21−3.41 (m, 3 H), 3.52−3.58 (m, 1 H), 4.29 (d, 1 H, J = 1.2 Hz), 4.43 (d, 1 H, J = 12.0 Hz), 4.45 (d, 1 H, J = 12.0 Hz), 4.53 (d, 1 H, J = 12.0 Hz), 4.61 (d, 1 H, J = 12.0 Hz), 5.08 (d, 1 H, J = 1.2 Hz), 5.19 (s, 1 H), 7.26−7.34 (m, 10 H).

Anal. Calcd for $C_{20}H_{22}O_2S$: C, 73.58; H, 6.79; S, 9.82. Found: C, 73.24; H, 6.56; S, 9.74.

1,4-Anhydro-2-deoxy-3,5-dibenzoyl-2-*C*-methylene-4-thio-L-*erythro*-pentitol (15). To a solution of **14** (0.223 g, 0.68 mmol) in anhydrous CH_2Cl_2 (5 mL) was added BBr_3 (1 M in CH_2Cl_2, 2.7 mL, 2.7 mmol) at −40 °C, and the mixture was stirred at the same temperature for 20 min. The mixture was quenched

with pyridine (2.7 mL) and methanol (2.7 mL) and evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 13:1) to give the debenzylated compound (73 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 2.12 (br s, 1 H), 2.34 (br s, 1 H), 3.29 (q, 1 H, J = 5.7 Hz), 3.47−3.59 (m, 2 H), 3.70 (dd, 1 H, J = 6.0, 11.4 Hz), 3.75 (dd, 1 H, J = 5.4, 11.4 Hz), 4.50 (d, 1 H, J = 5.7 Hz), 5.10 (q, 1 H, J = 1.5 Hz), 5.24 (q, 1 H, J = 1.5 Hz).

The debenzylated compound (93 mg, 0.64 mmol) in anhydrous pyridine (2 mL) was treated with benzoyl chloride (0.19 mL, 1.64 mmol), and the mixture was stirred at 50 °C for 15 h. The mixture was poured into EtOAc, and the organic layer was washed with 1 M HCl (10 mL), saturated $NaHCO_3$ solution, and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to give the residue. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 8:1) to give **15** (0.194 g, 86%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 3.56 (dt, 1 H, J = 1.2, 13.2 Hz), 3.76 (dt, 1 H, J = 1.2, 13.2 Hz), 3.78−3.84 (m, 1 H), 4.27 (dd, 1 H, J = 9.0, 11.4 Hz), 4.40 (dd, 1 H, J = 5.7, 11.4 Hz), 5.29 (t, 1 H, J = 1.2 Hz), 5.41 (t, 1 H, J = 0.6 Hz), 5.92 (dd, 1 H, J = 0.6, 2.7 Hz), 7.38−8.07 (m, 10 H).

Anal. Calcd for $C_{20}H_{18}O_4S$: C, 67.78; H, 5.12; S, 9.05. Found: C, 67.77; H, 5.02; S, 9.00.

N*^{4}-Benzoyl-1-(2-deoxy-3,5-dibenzyl-2,2-difluoro-4-thio-α-L-*erythro*-pentofuranosyl)cytosine (16α) and *N*^{4}-Benzoyl-1-(2-deoxy-3,5-dibenzyl-2,2-difluoro-4-thio-*β*-L-*erythro*-pentofuranosyl)cytosine (16*β*).** To a solution of **13** (0.170 g, 0.49 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 70% *m*-CPBA (0.12 g, 0.49 mmol) at −78 °C, and the mixture was stirred at −40 °C for 30 min. The mixture was quenched with saturated $Na_2S_2O_3$ solution and $NaHCO_3$ solution. The mixture was poured into CH_2Cl_2, and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to give the sulfoxide. To a solution of silylated *N*-benzoylcytosine, prepared from refluxing *N*-benzoylcytosine (0.157 g, 0.73 mmol) and ammonium sulfate (catalytic amount) in HMDS (5 mL, 40.5 mmol), in anhydrous $ClCH_2CH_2Cl$ (3 mL) was added a solution of the sulfoxide in anhydrous $ClCH_2CH_2Cl$ (2 mL) followed by addition of TMSOTf (0.13 mL, 0.72 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h and then at room temperature for 30 min. The mixture was quenched with saturated $NaHCO_3$ solution, filtered through a Celite pad, and poured into CH_2Cl_2. The organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 1.8:1) to give **16**α (60 mg, 22%) and **16β* (49 mg, 18%).

16α: UV (MeOH) λ_{max} 301 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 3.51−3.55 (m, 1 H), 3.61−3.66 (m, 1 H), 3.72 (dd, 1 H, J = 3.3, 10.2 Hz), 4.18−4.23 (m, 1 H), 4.41 (d, 1 H, J = 10.8 Hz), 4.48 (d, 1 H, J = 10.8 Hz), 4.54 (d, 1 H, J = 11.7 Hz), 4.85 (d, 1 H, J = 11.7 Hz), 6.63 (dd, 1 H, J = 3.9, 9.9 Hz), 7.27−7.92 (m, 16 H), 8.53 (d, 1 H, J = 7.5 Hz).

Anal. Calcd for $C_{30}H_{27}F_2N_3O_4S$: C, 63.93; H, 4.83; N, 7.46; S, 5.69. Found: C, 63.86; H, 4.65; N, 7.67; S, 5.43.

16*β*: UV (MeOH) λ_{max} 302 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 3.46−3.52 (m, 1 H), 3.63−3.68 (m, 1 H), 3.81−3.85 (m, 1 H), 4.19 (dt, 1 H, J = 6.6, 9.0 Hz), 4.51 (s, 2 H), 4.61 (d, 1 H, J = 11.4 Hz), 4.78 (d, 1 H, J = 11.4 Hz), 6.77 (dd, 1 H, J = 7.8, 10.2 Hz), 7.27−7.92 (m, 16 H), 8.28 (d, 1 H, J = 7.8 Hz).

Anal. Calcd for $C_{30}H_{27}F_2N_3O_4S$: C, 63.93; H, 4.83; N, 7.46; S, 5.69. Found: C, 63.88; H, 4.31; N, 7.26; S, 5.60.

1-(2-Deoxy-2,2-difluoro-4-thio-α-L-*erythro*-pentofuranosyl)cytosine (4α). To a solution of **16**α (0.042 g, 0.08 mmol) in anhydrous CH_2Cl_2 (5 mL) was added BBr_3 (1 M in CH_2Cl_2, 0.3 mL, 0.3 mmol) at −40 °C, and the mixture was stirred at the same temperature for 20 min. The mixture was quenched with pyridine (0.3 mL) and methanol (0.3 mL) and evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 11:1) to give the debenzylated compound (21 mg, 73%): UV (MeOH) λ_{max} 270 nm (pH 7); ^{1}H NMR (DMSO-d_6) δ 3.47−3.58 (m, 1 H), 3.61−3.64 (m, 1 H), 3.77−3.84 (m, 1 H), 4.18−4.32 (m, 1 H), 5.23 (t, 1 H, J = 3.3 Hz), 6.45 (br s, 1 H), 6.61 (dd, 1 H, J = 9.9, 11.1 Hz), 7.38 (d, 1 H, J = 8.1 Hz), 7.48−8.01 (m, 5 H), 8.40 (d, 1 H, J = 8.1 Hz).

The debenzylated compound (21 mg, 0.055 mmol) was treated with NaOMe (1 M in methanol, 0.055 mL, 0.055 mmol) and MeOH (3 mL) and stirred at room temperature for 1.5 h. The mixture was neutralized with acetic acid and evaporated to give the residue, which was purified by silica gel column chromatography (methylene chloride/methanol = 3.5:1) to give **4**α (14 mg, 92%): mp 151 °C; UV (MeOH) λ_{max} 272 nm (pH 7). Anal. Calcd for $C_9H_{11}F_2N_3O_3S$: C, 38.71; H, 3.97; F, 13.61; N, 15.05; S, 11.48. Found: C, 38.77; H, 3.67; N, 15.23; S, 11.45.

1-(2-Deoxy-2,2-difluoro-4-thio-*β*-L-*erythro*-pentofuranosyl)cytosine (4*β*). **16***β* (37 mg, 0.07 mmol) was converted to **4***β* (16 mg, 85%) according to the similar procedure used for the preparation of **4**α.

Debenzylated compound: ^{1}H NMR (DMSO-d_6) δ 3.27−3.32 (m, 1 H), 3.72−3.85 (m, 2 H), 4.10−4.19 (m, 1 H), 5.45 (t, 1 H, J = 5.1 Hz), 6.35−6.39 (m, 2 H), 7.41 (d, 1 H, J = 7.5 Hz), 7.49−8.01 (m, 5 H), 8.66 (d, 1 H, J = 7.5 Hz), 11.38 (br s, 1 H).

4*β*: mp 153 °C; $[\alpha]^{25}_D$ −8.16° (*c* 0.1, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7). Anal. Calcd for $C_9H_{11}F_2N_3O_3S$: C, 38.71; H, 3.97; N, 15.05; S, 11.48. Found: C, 38.47; H, 4.08; N, 14.93; S, 11.08.

N*^{4}-Benzoyl-1-(2-deoxy-3,5-dibenzoyl-2-*C*-methylene-4-thio-α-L-*erythro*-pentofuranosyl)cytosine (17α) and *N*^{4}-Benzoyl-1-(2-deoxy-3,5-dibenzoyl-2-*C*-methylene-4-thio-*β*-L-*erythro*-pentofuranosyl)cytosine (17*β*).** Compound **15** (0.18 g, 0.51 mmol) was converted to **17**α (0.078 g, 27%) and **17β* (0.04 g, 14%) according to the similar procedure used for the preparation of **16**α and **16***β*.

17α: UV (MeOH) λ_{max} 300 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 4.08−4.13 (m, 1 H), 4.41 (dd, 1 H, J = 10.8, 11.7 Hz), 4.55 (dd, 1 H, J = 6.0, 11.7 Hz), 5.70 (s, 1 H), 5.77 (s, 1 H), 6.08 (d, 1 H, J = 3.6 Hz), 7.01 (s, 1 H), 7.40−8.06 (m, 16 H), 8.31 (d, 1 H, J = 7.2 Hz).

Anal. Calcd for $C_{31}H_{25}N_3O_6S$: C, 65.60; H, 4.44; N, 7.40; S, 5.65. Found: C, 65.85; H, 4.30; N, 7.66; S, 5.80.

17*β*: UV (MeOH) λ_{max} 301 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 3.91−3.97 (m, 1 H), 4.49 (dd, 1 H, J = 7.8, 11.7 Hz), 4.62 (dd, 1 H, J = 5.7, 11.7 Hz), 5.23 (s, 1 H), 5.68 (s, 1 H), 6.10 (d, 1 H, J = 1.8 Hz), 7.16 (s, 1 H), 7.45−8.09 (m, 17 H).

Anal. Calcd for $C_{31}H_{25}N_3O_6S$: C, 65.60; H, 4.44; N, 7.40; S, 5.65. Found: C, 66.01; H, 4.58; N, 7.80; S, 5.35.

1-(2-Deoxy-2-*C*-methylene-4-thio-α-L-*erythro*-pentofuranosyl)cytosine (5α). Compound **17**α (73 mg, 0.13 mmol) was treated with NaOMe (1 M in methanol, 0.13 mL, 0.13 mmol) in a solution of MeOH (4 mL) and CH_2Cl_2 (3 mL) and stirred at room temperature for 1 h. The mixture was neutralized with acetic acid and evaporated to give the residue, which was purified by silica gel column chromatography (methylene chloride/methanol = 3.5:1) to give **5**α (34 mg, 100%): mp 92 °C; UV (MeOH) λ_{max} 270 nm (pH 7). Anal. Calcd for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.13; N, 16.46; S, 12.56. Found: C, 47.45; H, 5.04; N, 16.75; S, 12.17.

1-(2-Deoxy-2-*C*-methylene-4-thio-*β*-L-*erythro*-pentofuranosyl)cytosine (5*β*). Compound **17***β* (0.03 g, 0.05 mmol) was converted to **5***β* (14 mg, 100%), according to the similar procedure used for the preparation of **5**α: mp 95 °C; $[\alpha]^{25}_D$ +72.2° (*c* 0.12, MeOH); UV (MeOH) λ_{max} 270 nm (pH 7). Anal. Calcd for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.13; N, 16.46; S, 12.56. Found: C, 47.24; H, 5.12; N, 16.46; S, 12.67.

In Vitro Antitumor Assay. Cells (5000, 10 000, and 20 000 cells/well) were exposed to drugs in a 96-well plate for 24−96 h, and cytotoxicities were determined by SRB assay[18] (SKMEL-2, A 549, and SKOV3) or MTT assay[19] (SNU-1) or dye exclusion method[20] (K562).

Acknowledgment. This research was supported by grants from the Korea Science and Engineering Foundation (KOSEF 96-0403-01-01-3) and Good Health R & D Project, Ministry of Health & Welfare (1996−1997). Dr. H. R. Moon thanks KOSEF for the postdoctoral fellowship award. The authors also wish to thank Dr. Eun-Ran Woo (Korea Advanced Institute of Science and Technology) for the antitumor activity testing.

JO980196+

(18) Monks, A.; Scudieero, D.; Skehan, P.; Boyd, M. R. *Proc. Am. Assoc. Cancer Res.* **1989**, *30*, 607.

(19) Park, J.-G.; Kramer, B. S.; Lai, S.-L.; Goldstein, L. J.; Gazdar, A. F. *J. Natl. Cancer Inst.* **1990**, *82*, 193.

(20) Mossman, T. J. *Immunol. Methods* **1983**, *65*, 55−63.