C(17)-H), 3.98 (s, 3 H, OCH_3), 3.85 (dt, J = 9.6, 3.1 Hz, 1 H, C(5)-H), 3.52 (d, J = 6.8 Hz, 1 H, C(3)-H), 3.18 (dd, J = 8.2, 4.0 Hz, 1 H, C(20)-H), 2.96 (d, J = 8.2 Hz, 1 H, C(20)-H), 2.42 (m, 2 H, C(6)-H and C(16)-H), 2.36-2.10 (m, 2 H, C(14)-H and C-(15)-H), 1.81-1.69 (m, 3 H, C(6)-H, C(14)-H, and N*H*); ^{13}C NMR ($CDCl_3$) δ 176.52, 140.09, 129.42, 128.98, 127.95, 122.57, 106.92, 74.48, 63.52, 62.51, 57.48, 54.20, 39.46, 35.31, 31.30, 29.98; MS, m/e (rel intensity) 301 (M^+ + 1, 1.3), 300 (M^+, 6.8), 271 (1.2), 270 (7.7), 185 (2.2), 158 (3.6), 149 (10.9), 124 (100.0), 111 (10.9), 85 (20.0); high-resolution mass spectrum for $C_{17}H_{20}N_2O_3$ requires 300.1473, measured 300.1450.

(±)-4-(1,1'-Biphenyl-4-ylcarbonyl)-7-epi-20-desethylgelsedine (24). To a solution of **23** (0.008 g, 0.0266 mmol) in methylene chloride (3 mL) cooled to -70 °C was added *p*-phenylbenzoyl chloride (0.0144 g, 0.0665 mmol), and the solution was stirred at -78 °C for 10 min. Triethylamine (0.02 mL) was added and the reaction was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was poured into water (3 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 3 mL). The combined organic solution was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (ethyl acetate-ether, 9:1) to give 0.009 g (70%) of **24** as a mixture of conformers: mp 248-249 °C dec; IR ($CHCl_3$) 3020, 1735, 1620, 1420, 1220 cm^{-1}; MS, m/e (rel intensity) 481 (M^+ + 1, 12.5), 480 (M^+, 38.5), 450 (28.2), 449 (30.0), 305 (55.5), 181 (100.0), 152 (53.0), 124 (16.1).

Acknowledgment. Partial support of this research by grant CA-18846, awarded by the National Cancer Institute, is gratefully acknowledged.

Registry No. **5**, 65816-14-0; **7**, 124155-67-5; **7** (hydroxy ester), 10080-68-9; **8**, 5602-94-8; **9**, 124155-68-6; (±)-**10**, 124155-69-7; (±)-(*E*)-**11**, 124155-66-4; (±)-(*Z*)-**11**, 124223-45-6; (±)-**12**, 124155-70-0; (±)-**13**, 124155-71-1; (±)-**14**, 124155-72-2; (±)-**16**, 124155-73-3; (±)-(*E*)-**18**, 124155-65-3; (±)-(*Z*)-**18**, 124223-46-7; (±)-**19** (isomer 1), 124223-47-8; (±)-**19** (isomer 2), 124155-74-4; (±)-**20** (isomer 1), 124155-75-5; (±)-**20** (isomer 2), 124223-50-3; (±)-**20** (isomer 3), 124223-51-4; (±)-**20** (isomer 4), 124223-52-5; (±)-**22b**, 124223-48-9; (±)-**23**, 124223-49-0; (±)-**24**, 124242-39-3; $Ph_3P{=}CHCO_2Bu$-*t*, 35000-38-5; $H_2NCH_2CO_2Et{\cdot}HCl$, 623-33-6; *p*-PhBzCl, 14002-51-8.

Supplementary Material Available: Crystal data parameters, fractional coordinates, bond distances, bond angles, torsional angles, nearest intermolecular contacts, and anisotropic temperature factors for compound **24** (16 pages); observed and calculated structural factor amplitudes for the X-ray crystallographic determination of compound **24** (10 pages). Ordering information can be found on any current masthead page.

Facile Synthesis of 3'-*O*-Methylthymidine and 3'-Deoxythymidine and Related Deoxygenated Thymidine Derivative: A New Method for Selective Deoxygenation of Secondary Hydroxy Groups

Mitsuo Sekine* and Takeshi Nakanishi

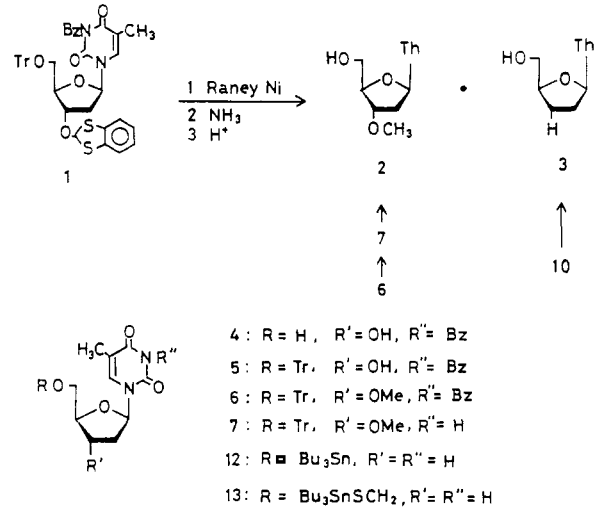
Department of Environmental Chemistry and Engineering, Tokyo Institute of Technology, Midoriku, Yokohama 227, Japan

Received April 3, 1989

This paper deals with convenient syntheses of 3'-*O*-methylthymidine (**2**) and 3'-deoxythymidine (**3**), which involve Ag_2O-promoted methylation and Barton-Robins reductive deoxygenation, respectively. New methods for the regioselective 3'- and 5'-deoxygenation of thymidine have also been developed. Namely, compound **3** was synthesized by the 3',5'-O-diacylation of thymidine with phenyl chlorothionoformate (PTCF) followed by the selective 3'-reduction with tributyltin hydride and successive alkaline hydrolysis. 5'-Deoxythymidine (**18**) was obtained by the 5'-selective acylation of thymidine with PTCF followed by reduction with tributyltin hydride.

A wide variety of nucleoside derivatives have been synthesized to find biologically active species such as antivirus, antitumor, and antimicrobial agents.[1-5] Among them, deoxyribonucleotide derivatives with 3'-blocked structures are of great importance as inhibitors specific for various enzyme reactions that catalyze nucleic acid metabolism[6-11] and are useful particularly for molecular biology as shown in M13 DNA sequencing[12] which utilizes dideoxyribonucleotide triphosphates as chain termina-

Scheme I



(1) Suhadolnik, R. J. *Nucleic Acids Res. Mol. Biol.* **1979**, *22*, 193.
(2) Walker, R. T., De Clercq, E., Eckstein, F., Eds. *Nucleoside Analogues, Chemistry, Biology and Medical Applications*; Plenum Press: New York, 1979.
(3) Scheit, K. H. *Nucleotide Analogs, Synthesis and Biological Functions*; John Wiley: New York, 1980.
(4) De Clercq, E. *Chem. Scr.* **1986**, *26*, 41.
(5) Ueda, T. *Synthesis and Reaction of Pyrimidine Nucleosides*; Plenum Press: London, in press.
(6) Baker, B. R.; Schwan, T. J.; Santi, D. V. *J. Med. Chem.* **1966**, *9*, 66.
(7) Chidgeavadze, Z. G.; Beabealashvilli, R. S.; Atrazhev, A. M.; Kukhanova, M. K.; Azhayev, A. V.; Krayevsky, A. *Nucleic Acids Res.* **1984**, *12*, 1671.
(8) Krayevsky, A. A.; Kukhanova, M.; Alexandrova, A.; Belyakova, N.; Krutyakov, V. *Biochim. Biophys. Acta* **1984**, *783*, 216.
(9) Kukhanova, M. Krayevsky, A. A.; Terentyeva, N.; Rasskazov, V. *Biochim. Biophys. Acta* **1984**, *783*, 221.
(10) Chidgeavadze, Z. G.; Scamrov, A. V.; Beabealashvilli, R. S.; Kvasyuk, E. I.; Zaitseva, G. V.; Mikhailopulo, I. A.; Kowollik, G.; Langen, P. *FEBS Lett.* **1985**, *183*, 275.
(11) Krayevsky, A. A.; Kukhanova, M. K.; Atrazhev, A. M.; Chidgeavadze, Z. G.; Beabealashvilli, R. S. *Mol. Biol. (Russian)* **1987**, *20*, 33.
(12) Sanger, F.; Nicklen, S.; Coulson, A. R. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5463.

0022-3263/90/1955-0924$02.50/0

tors.[13] A number of 5′-deoxygenated deoxyribonucleoside derivatives have also been examined for inhibitory experiments of a wide variety of enzymes such as thymidine kinase.[6,14-18]

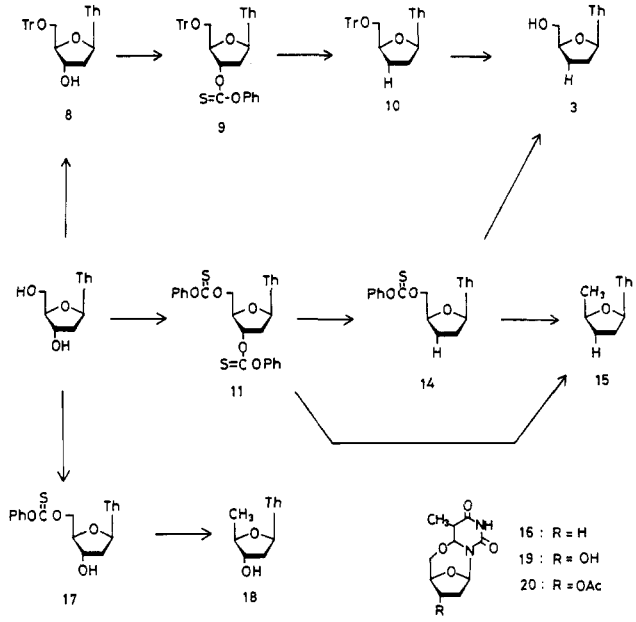
In this paper, we report a convenient method for the synthesis of 3′-*O*-methylthymidine (**2**) as a synthetic precursor of such chain terminators and new synthetic approaches to 3′-deoxythymidine (**3**) and 5′-deoxythymidine (**18**), which involve regioselective deoxygenation processes.

In our continuing study of the synthesis of O-methylated nucleoside derivatives,[19] we have recently found that reduction of 3′-*O*-(1,3-benzodithiol-2-yl)-5′-*O*-trityl-N^3-benzoylthymidine (**1**) with Raney Ni followed by deprotection gave a ca. 1:1 mixture of **2** and **3** (Scheme I). Although compound **2** has a simple structure, our extensive literature survey unexpectedly disclosed no reference concerning the synthesis of **2**.[20,21] As one of related compounds, only 3′-*O*-methylthymidine 5′-triphosphate has been reported for the assay of its inhibitory effects on several enzyme reactions.[11] Since it was expected that **2** would be utilized as a new class of fascinating substrates for various biological studies as well as a synthetic precursor of a chain terminator as suggested by numerous examples of biological studies using **3**,[12,13,22,23] we have searched for a more effective method for the synthesis of **2** and also shorter synthetic routes to **3**.

For the synthesis of **2**, we have chosen N^3-benzoylthymidine (**4**) as the starting material to avoid the competitive N^3-methylation at the stage of the 3′-O-methylation. This compound could be prepared on a large scale from thymidine without chromatographic separation via crystalline 3′,5′-*O*-bis(trimethylsilyl)-N^3-benzoylthymidine.[24] Tritylation of **4** with trityl chloride in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine[25] (DMAP) gave compound **5** in 94% yield. Treatment of **5** with methyl iodide in the presence of silver oxide[26,27] gave the 3′-*O*-methylated product **6** in 82% yield. Subsequent debenzoylation gave 3′-*O*-methyl-5′-*O*-tritylthymidine (**7**) in 72% yield. Detritylation of **7** with 80% acetic acid gave **2** as fine needles in 84% yield.

Several methods for the synthesis of **3** have been reported,[28-32] since **3** has proved to be useful as inhibitors for DNA biosynthesis[22] and as antiviral agents.[23] In our hand, compound **3** was synthesized by a series of reactions as follows. Treatment of 5′-*O*-tritylthymidine (**8**)[33] with 1.1 equiv of phenyl chlorothionoformate (PCTF)[34,35] in pyridine gave the thiocarbonate derivative **9** in 84% yield. Reductive C–O bond cleavage of **9** with tributyltin hydride (TBTH)[34,38] in the presence of AIBN gave the deoxygenated product **10** in 85% yield. Subsequent detritylation gave **3** in 93% yield (Scheme II).

Scheme II



We have also searched for an alternative route to **3** by using TBTH. TBTH has been used extensively for deoxygenation of secondary alcoholic functions (R^1R^2CHOH)[39-41] via thiocarbonate ester derivatives represented by $R^1R^2CHOC(S)X$ (X = imidazolyl,[36,42-45] phenyl,[36,46,47] SMe,[30,36,38,46,48] OMe,[31] and OPh[34,35,49,50]). This is based on Barton's early observation[36] that, upon treatment with TBTH under the usual conditions, the corresponding thioester derivatives ($RCH_2OC(S)X$) of primary alcohols (RCH_2OH) did not give deoxygenated products but different products such as RCH_2OSnBu_3,

(13) Atkinson, M. R.; Deutscher, M. P.; Kornberg, A.; Russell, A. F.; Moffat, J. G. *Biochemistry* **1969**, *8*, 4897.
(14) Baker, E. R.; Neenan, J. P. *J. Med. Chem.* **1972**, *15*, 940.
(15) Neenan, J. P.; Rohde, W. *J. Med. Chem.* **1973**, *16*, 580.
(16) Doskocil, J. Holy, A. *Nucleic Acids Res.* **1974**, *1*, 491.
(17) Leung, K. K.; Visser, D. W. *Biochem. Med.* **1976**, *16*, 127.
(18) Edstrom, R. D.; Prody, C. A.; Hogenkamp, H. P. C. *Biochem. Biophys. Res., Commun.* **1977**, *77*, 1522.
(19) Sekine, M.; Peshakova, L. S.; Hata, T. *J. Org. Chem.* **1987**, *52*, 5060.
(20) A. Matsuda, private communication: Ueda, T. et al. have recently synthesized **2** in a different way involving metalation of 5′-*O*-tritylthymidine with NaH followed by the 3′-*O*-methylation. This reaction required longer periods of time.
(21) In connection with this study, Hampton reported the synthesis of 3′-*O*-ethylthymidine by reaction of 5′-*O*-tritylthymidine with ethyl iodide in the presence of potassium hydroxide followed by acidic treatment: Hampton, A.; Chawla, R. R.; Kappler, F. *J. Med. Chem.* **1982**, *25*, 644.
(22) Mitsuya, H.; Broder, S.; *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.
(23) For a comprehensive review, see: De Clercq, E. *J. Med. Chem.* **1986**, *29*, 1561.
(24) Sekine, M.; Fujii, M.; Nagai, H.; Hata, T. *Synthesis* **1987**, 1119.
(25) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 95.
(26) Furukawa, Y.; Kobayashi, K.; Kanai, Y.; Honjo, M. *Chem. Pharm. Bull.* **1965**, *13*, 1273.
(27) Kamimura, T.; Masegi, T.; Hata, T. *Chem. Lett.* **1982**, 965.
(28) Michelson, A. M.; Todd, A. R. *J. Chem. Soc.* **1955**, 816.
(29) Pfitzner, K. E.; Moffat, J. G. *J. Org. Chem.* **1964**, *29*, 1508.
(30) Samukov, V. V.; Ofitserov, V. I. *Bioorg. Khim.* **1983**, *9*, 52.
(31) Prisbe, E. J.; Martin, J. C. *Synth. Commun.* **1985**, *15*, 401.
(32) Nagato, Y.; Nishino, S.; Ishido, Y. *Abstract of the 8th Symposium of the Society of Synthetic Organic Chemistry (Japan) in Niigata*, 1987, 21.
(33) Gilham, P. T.; Khorana, H. G. *J. Am. Chem. Soc.* **1958**, *80*, 6212.
(34) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
(35) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.
(36) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans 1* **1975**, 1574.
(37) Barton, D. H. R.; Subramanian, R. J. *J. Chem. Soc., Perkin Trans 1* **1977**, 1718.
(38) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.
(39) Kuivila, H. G. *Synthesis* **1970**, 499.
(40) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
(41) Neumann, W. P. *Synthesis* **1987**, 665.
(42) Rassmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843.
(43) Fukukawa, K.; Ueda, T.; Hirano, T. *Chem. Pharm. Bull.* **1981**, *29*, 597.
(44) Pankiewicz, K.; Matsuda, A.; Watanabe, K. A. *J. Org. Chem.* **1982**, *47*, 485.
(45) Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; Usman, N. *Tetrahedron Lett.* **1983**, *24*, 865.
(46) Acton, E. M.; Goerner, R. N.; Uh, H. S.; Ryan, K. J.; Henry, D. W.; Cass, C. E.; LePage, G. A. *J. Med. Chem.* **1979**, *22*, 518.
(47) Lessor, R. A.; Leonard, N. J. *J. Org. Chem.* **1981**, *46*, 4300.
(48) Fuller, T. S.; Stick, R. V. *Aust. J. Chem.* **1980**, *33*, 2509.
(49) Seela, F.; Muth, H.-P. *Liebigs Ann. Chem.* **1988**, 215.
(50) Seela, F.; Muth, H.-P.; Bindig, U. *Synthesis* **1988**, 670.

$RCH_2OCH_2SSnBu_3$, and RCH_2OH, when X was imidazolyl, phenyl, and SMe, respectively. Later, however, he also found that primary alcohols could be deoxygenated via $RCH_2OC(S)X$ (X = imidazolyl, phenyl, and SMe) at rather high temperatures of 130–150 °C that were corresponding to refluxing xylene and *p*-cymene.[38]

In consideration of these facts, we expected that, if a thymidine derivative (**11**) bearing two phenoxythiocarbonyl (PTC) groups at both the 3′ and 5′ positions was treated with TBTH, the 3′-deoxygenation would occur along with competitive 5′-modifications. It was further expected that, even if the side reactions above mentioned occurred simultaneously at the 5′-thiocarbonate site of **11** to give a stannyl ether (**12**), a hemithioacetal (**13**), and compound **3**, subsequent hydrolysis of the Sn–O bond of **12** and the Sn–S bond of **13** under certain conditions would lead ultimately to conversion to **3**. If the selective deoxygenation took place at the 3′-position, the product of 3′-deoxy-5′-*O*-(phenoxythiocarbonyl)thymidine (**14**) could also be converted to **3** by alkaline treatment.

First, to ascertain this expectation, **11** was synthesized as crystals in 94% yield by treatment of thymidine with 2.2 equiv of PCTF. Reduction of **11** with 3 equiv of TBTH in refluxing benzene in the presence of AIBN resulted in 3′- and 5′-deoxygenation and 6,5′-cyclization, but side reactions giving rise to **12** and **13** did not occur. Compound **14** was obtained in 15% yield. A ca. 1:1 mixture of 3′,5′-dideoxythymidine (**15**)[51] and 6,5′-cyclo-5′-deoxy-5,6-dihydrothymidine (**16**) was also obtained in 75% yield. The latter was formed as a pair of stereoisomers in a ratio of 1:1. These side products could not be separated by chromatography. Structural analysis of these compounds was based on 270-MHz NMR. Ueda[52] has recently reported that 5′-halogenothymidine derivatives were converted upon treatment with TBTH into 6,5′-cyclo-5,6-dihydrothymidine derivatives via 5′-carbon radical intermediates. The formation of **16** was rationalized in terms of a similar 5′-carbon radical intermediate.[52]

A smaller amount (1.2 equiv) of TBTH was used in the deoxygenation of **11** to see if the reaction rate of 3′-deoxygenation is different from that of 5′-deoxygenation. Consequently, this reaction gave **14** in 62% yield, along with recovery of 10% of **11**. A mixture of **15** and **16** was obtained in 6% yield. This result clearly suggested that the 3′-position was predominantly deoxygenated and the 5′-PTC group remained rather intact when a nearly stoichiometric amount of TBTH was used. It was confirmed that the 5′ PTC group could be easily removed from **14** by dilute NaOH to give the desired product **3** in 88% yield. For a practical reason, the TBTH reduction and subsequent alkaline hydrolysis were performed in situ. In this case, 1.3 equiv of TBTH was used for disappearance of **11**. Consequently, 3′-deoxythymidine (**3**) could be synthesized in 72% overall yield from **11** by a two-step procedure. It should be emphasized that this method is the shortest approach to the synthesis of **3** from thymidine. In the previous methods for the synthesis of **3**, it was necessary to protect selectively the 5′-hydroxyl group of thymidine with MMTr, $tBuMe_2Si$, Ac, Bz, etc., and then remove the 3′-hydroxyl group via 3′-halogeno derivatives[28,29] or 3′-thiocarbonate ester derivatives.[30–32] The present process eliminated this bothersome stepwise protection. In this sense, the 5′-PTC group served as "protecting group" for introduction of the 3′-PTC group more successible to the TBTH reduction.

On the other hand, reaction of thymidine with 1.2 equiv of PCTF in pyridine gave selectively the 5′-acylated product (**17**) in 82% yield. This compound was readily crystallized after extractive workup. Expectedly, reaction of **17** with TBTH afforded a mixture of 5′-deoxythymidine (**18**)[28,51,53] and 6,5′-cyclo-5′-deoxy-5,6-dihydrothymidine (**19**), which appeared at almost the same position on TLC. Crystallization from methanol gave selectively **18** as crystals in 35% yield. Acetylation of the uncrystallized mixture followed by crystallization from ethanol gave a 2:1 pair of stereoisomers **20**, one of which was identified with the 5*R*,6*R* isomer reported previously[52] by 500-MHz 2D-NMR analysis.

Conclusion

It is noteworthy that the two regioisomers **3** and **18** could be obtained in a regioselective manner by use of the inherent selectivities of the deoxygenation with TBTH toward secondary thiocarbonate esters and of the acylation with PCTF toward primary hydroxyl groups, respectively. We observed that primary thiocarbonate esters were deoxygenated at a considerably lower temperature (80 °C) than those (130–150 °C) reported by Barton.[38] This implies that, if there are no neighboring-group participations such as the 5′,6-cyclization associated with the uracil 5,6 double bond, primary alcohols should be converted in better yields, although we did not examine this possibility.

The present method would provide a new method for the selective deoxygenation of primary or secondary hydroxyl groups, especially, the latter, when both primary and secondary hydroxyl groups were present in the same molecule.

Experimental Section

Melting points were obtained on a Mitamura Melt-temp apparatus and are uncorrected. ^1H NMR spectra were recorded at 60 MHz on a Hitachi 24B spectrometer (unless otherwise noted), at 270 MHz on a JEOL-GX 270 spectrometer, and at 500 MHz on a JEOL-GX 500 spectrometer with Me_4Si as the internal standard. TLC was performed on precoated TLC plates of silica gel 60 F-254 (Merck). Column chromatography was performed with silica gel C-200 purchased from Waco Co. Ltd., and a minipump for a goldfish bowl was conveniently used to attain sufficient pressure for rapid chromatographic separation. Raney Ni was prepared freshly by the literature procedure.[54] PCTF was purchased from Aldrich Co. Ltd. TBTH was purchased from Kanto Kagaku Co. Ltd.

3′-*O*-(1,3-Benzodithiol-2-yl)-5′-*O*-trityl-*N*^{3}-benzoylthymidine (1). To a solution of **5** (294 mg, 0.5 mmol) and 1,3-benzodithiolium tetrafluoroborate (180 mg, 0.75 mmol) in dry CH_2Cl_2 (2 mL) was added dry pyridine (0.1 mL). After being stirred at room temperature for 24 h, the mixture was treated with triethylamine (0.1 mL, 0.75 mmol) to decompose the reagent and partitioned between CH_2Cl_2 and water. The organic phase was collected and the aqueous phase was extracted twice with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the residue on a column of silica gel (20 g) with hexane–CH_2Cl_2 gave **1** (375 mg, 96%): ^1H NMR ($CDCl_3$) δ 1.46 (s, 3 H, 5-CH_3), 2.33 (m, 2 H, 2′-H), 3.31 (m, 2 H, 5′-H), 4.02 (m, 1 H, 4′-H), 4.40 (m, 1 H, 3′-H), 6.17 (t, 1 H, J = 6.5 Hz, 1′-H), 6.51 (s, 1 H, SCHS), 7.17 (m, 23 H, Ar H and 6-H), 7.79 (2 H, Ar H). Anal. Calcd for $C_{43}H_{36}O_6N_2S_2 \cdot {}^1/_2H_2O$: C, 68.87; H, 4.97; N, 3.74; S, 8.55. Found: C, 68.87; H, 4.71; N, 3.52; S, 8.96.

Raney Ni Reduction of 1. To a suspension of Raney Ni (W-2) (2.5 g, 4.25 mL) in dioxane (10 mL) was added **1** (371 mg, 0.5

(51) Wang, Y.; Hogenkamp, H. P. C.; Long, R. A.; Revankar, G. R.; Robins, R. K. *Carbohydr. Res.* **1977**, *59*, 449.
(52) Suzuki, Y.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1987**, *35*, 1085. See also: Suzuki, Y.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1987**, *35*, 1808.
(53) Holy, A. *Tetrahedron Lett.* **1972**, 585.
(54) Billica, H. R.; Adkins, H. *Org. Synth.* **1955**, *3*, 176.

mmol). The mixture was vigorously stirred at room temperature for 3 h. Then the Raney Ni was removed by filtration on Celite and washed with hot ethanol (250 mL). The filtrate and washing were combined and evaporated under reduced pressure. The residue was dissolved in pyridine (50 mL) and concentrated ammonia (25 mL) was added. The mixture was kept at room temperature for 1 h and then evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (5 g) to give a mixture (198 mg) of 3′-*O*-methyl-5′-*O*-tritylthymidine and 3′-deoxy-5′-*O*-tritylthymidine. The mixture was dissolved in 80% acetic acid (20 mL) and the solution was heated at 95 °C for 1 h. The solvent was removed under reduced pressure. The residue was chromatographed on a preparative TLC plate with CH_2Cl_2–MeOH (10:1, v/v) and gave a mixture (57 mg) of **2** and **3** in a ca. 1:1 ratio, which was estimated by ^1H NMR.

***N*³-Benzoyl-5′-*O*-tritylthymidine (5).** To a solution of **4**[24] (3.46 g, 10 mmol) in dry CH_2Cl_2 (100 mL) were successively added triethylamine (2.5 mL, 18 mmol), 4-(*N*,*N*-dimethylamino)pyridine (96 mg, 0.5 mmol), and trityl chloride (3.06 g, 11 mmol). The mixture was stirred for 13 h, at which time the reaction was incomplete. Trityl chloride (557 mg, 2 mmol) was added and stirring was continued for an additional 5 h. Then extraction with CH_2Cl_2 followed by silica gel column chromatography with CH_2Cl_2–MeOH gave **5** (5.56 g, 94%) as a foam: ^1H NMR ($CDCl_3$) δ 1.51 (s, 3 H, CH_3), 2.27 (m, 2 H, 2′-H), 3.42 (m, 2 H, 5′-H), 3.96 (m, 1 H, 4′-H), 4.47 (m, 1 H, 3′-H), 6.27 (t, 1 H, *J* = 6.5 Hz, 1′-H), 7.02–8.07 (m, 21 H, Ar H and 6-H). Anal. Calcd for $C_{36}H_{32}O_6N_2$: C, 73.45; H, 5.78; N, 4.76. Found: C, 73.45; H, 5.39; N, 4.35.

3′-*O*-Methyl-5′-*O*-tritylthymidine (7). To a solution of **5** (1.77 g, 3 mmol), which was rendered anhydrous by coevaporation two times with dry toluene, in methyl iodide (28.8 mL) was added silver oxide (3.78 g, 16.3 mmol). The resulting mixture was refluxed for 3 h and silver salts were removed by filtration. Washing of the salts was done with ether. The filtrate and washing were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (40 g) with CH_2Cl_2–MeOH to give 1.49 g of **6** as crude material containing a small amount of impurity that appeared a little earlier than **6**. This crude material was dissolved in a mixture of pyridine (9 mL) and ethanol (14 mL). To the solution was added 2 M sodium hydroxide (4 mL) at 0 °C. The mixture was kept at 0 °C for 40 min and 2 M sodium hydroxide (2 mL) was added. After being kept at the same temperature for an additional 1.5 h, the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with saturated sodium bicarbonate solution and dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (30 g) with CH_2Cl_2–MeOH to give **7** (886 mg, 72%) as a foam: ^1H NMR ($CDCl_3$) δ 1.50 (s, 3 H, CH_3), 2.27 (m, 2 H, 2′-H), 3.27 (s, 3 H, OCH_3), 3.40 (m, 2 H, 5′-H), 4.07 (m, 2 H, 3′,4′-H), 6.24 (t, 1 H, *J* = 6.5 Hz, 1′-H), 7.27 (m, 16 H, Ar H and 6-H), 9.03 (br, 1 H, NH). Anal. Calcd for $C_{30}H_{30}O_5N_2$: C, 72.27; H, 6.07; N, 5.62. Found: C, 72.36; H, 5.95; N, 5.53.

3′-*O*-Methylthymidine (2). Compound **7** (798 mg, 1.6 mmol) was dissolved in 80% acetic acid (60 mL). The solution was heated on a water bath at 95 °C for 55 min and then cooled to room temperature. After being evaporated under reduced pressure, the mixture was partitioned between ether and water. The aqueous phase was collected and the ethereal layer was further extracted several times with water. The combined extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the residue on a column of silica gel (9 g) with CH_2Cl_2–MeOH gave **2** (346 mg, 84%), which was crystallized from methanol: mp 130–133 °C; ^1H NMR ($CDCl_3$) δ 1.89 (s, 3 H, CH_3), 2.31 (m, 2 H, 2′-H), 3.33 (s, 3 H, OCH_3), 3.47 (m, 2 H, 5′-H), 3.83 (m, 1 H, 4′-H), 4.03 (m, 1 H, 3′-H), 6.04 (t, 1 H, *J* = 7.0 Hz, 1′-H), 7.37 (s, 1 H, 6-H), 10.21 (br, 1 H, NH). Anal. $C_{11}H_{16}O_5N_2 \cdot {}^1/_4H_2O$: C, 50.67; H, 6.38; N, 10.74. Found: C, 50.53; H, 6.35; N, 10.48.

3′-*O*-(Phenoxythiocarbonyl)-5′-*O*-tritylthymidine (9). To a solution of **8**[33] (benzene adduct, 562 mg, 1 mmol) in dry CH_2Cl_2 (10 mL) were added pyridine (0.3 mL, 3.7 mmol) and PTCF (0.2 mL, 1.1 mmol). After being stirred at room temperature for 16 h, the mixture was extracted with CH_2Cl_2–$NaHCO_3$. The CH_2Cl_2 extract was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the residue on a column of silica gel (20 g) with CH_2Cl_2–MeOH followed by reprecipitation from CH_2Cl_2 into hexane gave **9** (520 mg, 84%): ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 2.67 (m, 2 H, 2′-H), 3.57 (m, 2 H, 5′-H), 4.37 (m, 1 H, 4′-H), 5.96 (d, 1 H, *J* = 5.0 Hz, 3′-H), 6.49 (dd, 1 H, *J* = 5.4 Hz, *J* = 8.3 Hz, 1′-H), 6.92–7.60 (m, 20 H, Ar H), 7.63 (s, 3 H, 5-CH_3), 8.62 (br, 1 H, NH). Anal. Calcd for $C_{36}H_{32}O_6N_2S$: C, 69.66; H, 5.20; N, 4.51; S, 5.17. Found: C, 69.53; H, 5.59; N, 4.29; S, 5.00.

5′-*O*-Trityl-3′-deoxythymidine (10). A solution of **9** (310 mg, 0.5 mmol), TBTH (0.20 mL, 0.75 mmol), and AIBN (16 mg, 0.1 mmol) in dry toluene (6 mL) was heated at 80 °C for 6 h. Then the mixture was subjected to a column of silica gel (10 g) and elution with CH_2Cl_2–MeOH gave **10** (220 mg, 94%) as a foam: ^1H NMR ($CDCl_3$) δ 1.55 (s, 3 H, CH_3), 2.09 (m, 4 H, 2′,3′-H), 3.35 (m, 2 H, 5′-H), 4.15 (m, 1 H, 4′-H), 6.06 (m, 1 H, 1′-H), 7.30 (s, 1 H, 6-H). Anal. Calcd for $C_{29}H_{28}O_4N_2$: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.11; H, 6.13; N, 6.07.

3′,5′-Bis-*O*-(phenoxythiocarbonyl)thymidine (11). To a solution of thymidine (484 mg, 2 mmol), which was rendered anhydrous by repeated coevaporation with dry pyridine, in dry pyridine (20 mL) was added PTCF (0.61 mL, 4.4 mmol). The solution was kept at 60 °C for 2.5 h and then extracted with CH_2Cl_2–water. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (20 g) with CH_2Cl_2–MeOH to give crude **11**, which was crystallized from ether to give pure **11** (962 mg, 94%): mp 112–114 °C (ether); ^1H NMR ($CDCl_3$) δ 1.91 (s, 3 H, CH_3), 2.56 (m, 2 H, 2′-H), 4.60 (m, 1 H, 4′-H), 4.78 (m, 2 H, 5′-H), 5.77 (m, 1 H, 3′-H), 6.50 (m, 1 H, 1′-H), 7.19 (s, 11 H, Ar H and 6-H), 9.92 (br, 1 H, NH). Anal. Calcd for $C_{24}H_{22}O_7N_2S_2 \cdot {}^1/_2H_2O$: C, 55.06; H, 4.42; N, 5.35. Found: C, 55.04; H, 4.42; N, 5.24.

Reaction of 11 with TBTH. A mixture of **11** (257 mg, 0.5 mmol), TBTH (403 μL, 1.5 mmol), and AIBN (16.4 mg, 0.1 mmol) in dry benzene (10 mL) was refluxed for 25 min under an argon atmosphere. After being cooled, the mixture was directly applied to a column of silica gel (25 g). Elution was performed with CH_2Cl_2–MeOH to give **14** (27 mg, 15%) and a mixture of **15** and **16** (79 mg, 75%). **14**: ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H, 5-CH_3), 2.17 (m, 4 H, 2′,3′-H), 4.42 (m, 1 H, 4′-H), 4.73 (d, 2 H, *J* = 3.2 Hz, 5′-H), 6.14 (m, 1 H, 1′-H), 6.86–7.33 (m, 6 H, Ar H and 6-H), 9.44 (br, 1 H, NH). Anal. Calcd for $C_{17}H_{18}O_5N_2 \cdot {}^1/_3H_2O$: C, 55.43; H, 5.11; N, 7.60; S, 8.70. Found: C, 55.28; H, 5.22; N, 7.97; S, 8.49. **15** and **16**: ^1H NMR 270 MHz, $CDCl_3$–DMSO-d_6, 9:1, v/v) δ 1.20 and 1.30 (d, *J* = 7.0 Hz, 5-CH_3 of isomeric **16**), 1.43 (d, *J* = 6.1 Hz, 5′-CH_3 of **15**), 1.95 (s, 5-CH_3 of **15**), 2.02, 2.38, 3.52, 3.77, 4.20, and 4.37 (m, 2′,3′,4′,5′-H), 6.05 (m, 1′-H of **16**), 6.13 (m, 1′-H of **15**), 9.60 and 9.70 (br, NH). Anal. Calcd for $C_{10}H_{14}O_3N_2$: C, 57.13; H, 6.71; N, 13.33. Found: C, 56.77; H, 6.54; N, 12.98.

When this reaction was carried out for 25 min by using a smaller amount (161 μL, 0.6 mmol) of TBTH, **14** (111 mg, 62%) and a mixture of **15** and **16** (6 mg, 6%) were obtained.

Reaction of 11 with a Large Excess Amount of TBTH. A solution of **11** (515 mg, 1 mmol), TBTH (1.08 mL, 4 mmol), and AIBN (33 mg, 0.2 mmol) in dry benzene (20 mL) was refluxed under an argon atmosphere for 50 min. Then TBTH (0.54 mL, 2 mmol) was added and refluxing was continued for an additional 1 h. At this time, **14** remained to a degree of 20%. The mixture was further refluxed for 4 h and a solution of AIBN (33 mg, 0.2 mmol) in dry benzene (1 mL) was added three times at an interval of 2 h during refluxing. The same workup described above gave a ca. 1:1 mixture of **15** and **16** (195 mg, 93%).

3′-Deoxythymidine (3).[28–32] **From 10.** Compound **10** (281 mg, 0.6 mmol) was dissolved in 80% acetic acid (40 mL) and the solution was heated at 100 °C for 10 min. The mixture was cooled to room temperature and evaporated under reduced pressure and the last traces of acetic acid were removed by coevaporation with ethanol. The residue was dissolved in MeOH (20 mL) and silica gel (7 g) was added. After the solvent was carefully removed under reduced pressure by a rotary evaporator, the silica gel was subjected to a column of silica gel (7 g). Elution was performed with CH_2Cl_2–MeOH to give **3** (126 mg, 93%): mp 146–148 °C (MeOH) [lit. mp 145 °C,[28] 147–149 °C,[29] 152–153 °C,[30] 150–152 °C (MeOH)[31]]; ^1H NMR ($CDCl_3$–CD_3OD) δ 1.90 (s, 3 H, CH_3), 2.07 (m, 4 H, 2′,3′-H), 3.77 (m, 2 H, 5′-H), 4.10 (m, 1 H, 4′-H), 6.05 (m, 1 H, 1′-H), 7.76 (m, 1 H, 1′-H).

From 11. A solution of **11** (257 mg, 0.5 mmol), TBTH (0.175 mL, 0.65 mmol), and AIBN (16.4 mg, 0.1 mmol) in dry benzene (10 mL) was refluxed for 20 min under an argon atmosphere. After being cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was dissolved in pyridine (4 mL) and ethanol (7 mL). To the solution was added 2 M NaOH (4 mL). The mixture was stirred at room temperature for 20 min. Then the solution was neutralized by addition of Dowex 50W × 8 (pyridinium form, 10 mL). The resin was removed by filtration and washed with pyridine–ethanol (12 mL–21 mL). The filtrate and washing were combined and evaporated under reduced pressure, and the residue was coevaporated with toluene (5 mL × 2). The resulting solid material was chromatographed on a column of silica gel (25 g) with CH_2Cl_2–MeOH (6:1, v/v) to give **3** (82 mg, 72%).

From 14. Compound **14** (80 mg, 0.22 mmol) was dissolved in pyridine–ethanol (1.0 mL–3.5 mL) and 2 M NaOH (2.0 mL) was added. The mixture was stirred at room temperature for 45 min. Then workup similar to that described in the above experiment followed by column chromatography gave **3** (44 mg, 88%).

5′-*O*-(Phenoxythiocarbonyl)thymidine (17). To a solution of thymidine (969 mg, 4 mmol), which was rendered anhydrous by repeated coevaporation with dry pyridine, in dry pyridine (50 mL) was added PTCF (0.664 mL, 4.8 mmol). The mixture was stirred at room temperature overnight and then quenched with methanol (2 mL). The resulting mixture was kept for 5 min and partitioned between CH_2Cl_2 and water. The organic phase was collected and the aqueous layer was further extracted twice with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was coevaporated three times with toluene and CH_2Cl_2 was added. After standing for a few minutes, the pecipitate appeared and was collected by filtration to give **17** (1.188 g, 82%): mp 157–158 °C; ^{1}H NMR ($CDCl_3$–DMSO)-d_6, 9:1, v/v) δ 1.86 (s, 3 H, 5-CH_3), 2.27 (m, 2 H, 2′-H), 4.19 (m, 1 H, 4′-H), 4.45 (m, 1 H, 3′-H), 4.77 (d, 2 H, J = 3.2 Hz, 5′-H), 6.32 (t, 1 H, J = 6.8 Hz, 1′-H), 7.06 (m, 2 H, Ar H), 7.35 (m, 4 H, Ar H and 6-H), 10.82 (br, 1 H, NH). Anal. Calcd for $C_{17}H_{18}O_6N_2S$: C, 52.71; H, 4.94; N, 7.23; S, 8.28. Found: C, 52.94; H, 4.83; N, 7.35; S, 8.46.

5′-Deoxythymidine (18).[28,51] A suspension of **17** (362 mg, 1 mmol), TBTH (0.807 mL, 3 mmol), and AIBN (32.8 mg, 0.2 mmol) in dry benzene (20 mL) was refluxed for 1.5 h under an argon atmosphere. The mixture was cooled to room temperature and evaporated under reduced pressure. Dry column chromatography with CH_2Cl_2–MeOH gave a ca. 5:2 mixture of **18** and **19** (162 mg, 71%), which was crystallized from MeOH to give **18** (80 mg, 35%): mp 181–183 °C (MeOH) [lit. mp 188 °C (EtOH),[28] 213 °C (H_2O)[51]]; ^{1}H NMR (270 MHz, $CDCl_3$–DMSO-d_6, 9:1, v/v) δ 1.36 (d, 3 H, J = 6.1 Hz, 5′-CH_3), 1.91 (s, 3 H, 5-CH_3), 2.11 (m, 1 H, 2′-Ha), 2.34 (m, 1 H, 2′-Hb), 4.03 (m, 2 H, 3′,4′-H), 4.30 (br, 1 H, OH), 6.24 (d, 1 H, J = 6.1 Hz, 1′-H), 7.17 (s, 1 H, 6-H), 10.12 (br, 1 H, NH). Anal. Calcd for $C_{10}H_{14}O_4N_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.85; H, 6.19; N, 12.37.

The filtrate obtained after crystallization of **18** was evaporated under reduced pressure and the residue was dissolved in dry pyridine (3 mL). Acetic anhydride (2 mL) was added and the solution was kept for 5 h. Then MeOH (1 mL) was added and the solution was kept for 30 min. The resulting mixture was evaporated under reduced pressure and coevaporated several times with toluene. The residue was crystallized from ethanol to give a stereoisomeric pair of **20** (28 mg). One of the isomers: ^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6, 9:1 v/v) δ 1.21 (d, 3 H, J = 6.8 Hz, 5-CH_3), 1.74 (m, 1 H, 5′-Ha), 2.03 (m, 5′-Hb), 2.08 (s, 3 H, Ac), 2.29 (m, 1 H, 2′-Ha), 2.38 (m, 2 H, 2′-Hb and H-5), 3.27 (m, 1 H, 6-H), 4.49 (d, J = 8.9 Hz, 4′-H), 5.15 (m, 1 H, 3′-H), 6.36 (m, 1 H, 1′-H), 9.61 (br, 1 H, NH). One of the isomers: ^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6, δ 1.17 (d, 3 H, J = 7.3 Hz, 5-CH_3), 2.10 (s, 3 H, Ac), 2.94 (1 H, 5-H), 3.45 and 3.55 (m, 2 H, 5′-H), 4.05 (m, 1 H, 4′-H), 4.30 (m, 1 H, 6-H), 5.21 (m, 1 H, 3′-H), 5.86 (m, 1 H, 1′-H), 9.40 (br, 1 H, NH).

Acknowledgment. We thank Prof. T. Hata, Tokyo Institute of Technology, for his encouragement throughout this study. We are also grateful to Prof. A. Matsuda, Hokkaido University, for his helpful discussion. This study was supported by a Grand-in-Aid for Scientific Research (63540421) from the Ministry of Education, Science and Culture.

Registry No. **1**, 123884-02-6; **2**, 108895-42-7; **3**, 3416-05-5; **4**, 94189-75-0; **5**, 123884-03-7; **6**, 123884-04-8; **7**, 123884-05-9; **8**, 7791-71-1; **9**, 123884-06-0; **10**, 107036-54-4; **11**, 123884-07-1; **14**, 123884-08-2; **15**, 29108-89-2; **16**, 123884-09-3; **17**, 123884-10-6; **18**, 3458-14-8; **19**, 123884-11-7; **20**, 123884-12-8; PTCF, 1005-56-7; 1,3-benzodithiolium tetrafluoroborate, 57842-27-0; thymidine, 50-89-5.