dark-purple solution was then poured into a separatory funnel containing $CHCl_3$ (20 mL) and 5% NH_4OH (20 mL). After partitioning, the aqueous layer was concentrated to ca. 10 mL, and the solution was applied onto a Dowex 50W-X2 column (2 × 25 cm, H^+ form) which was eluted first with a large volume of H_2O and then with 3% NH_4OH. Collected fractions were freeze-dried to a solid which was purified further on a DEAE-cellulose column (1.5 × 25 cm, HCO_3^- form) with 0.2 M NH_4HCO_3 as the eluent. HPLC-pure fractions were pooled and *promptly* freeze-dried to obtain **5** as a light-yellow solid (92 mg, 61%); dec >300 °C; HPLC 10% MeCN in 0.1 M NH_4OAc, pH 7.0, retention time 5.7 min; IR (KBr) ν 3450, 2990 sh, 1710 sh, 1645, 1620, 1570, 1525, 1465, 1395, 1370 sh, 1315, 1270 cm^{-1}; NMR (d_6-DMSO) δ 1.8–2.4 (m, CH_2CH_2), 3.20 (s, N^{10}-Me), 4.90 (s, CH_2N, overlapping another s, H_2O), 6.78 (d, J = 9 Hz, 3′- and 5′-H), 7.65 (d, J = 9 Hz, 2′- and 6′-H), 7.8–8.2 (broad m, NH_2), 8.47 (s, 2-H), 8.88 (s, 7-H); UV λ_{max} (pH 7.4) 219 nm (ϵ 19700), 246 (19400), 303 (24000), 345 infl (6900), λ_{max} (0.1 N HCl) 223 nm (ϵ 21200), 305 (23600), 343 infl (9000). Anal. ($C_{20}H_{21}N_7O_5 \cdot 0.5NH_3 \cdot 1.5H_2O$) C, H, N.

***N*-[4-[[(4-Amino-2-methylpteridin-6-yl)methyl]methylamino]benzoyl]-L-glutamic Acid (6) ("2-Desamino-2-methylMTX").** Diester **17** (195 mg, 0.345 mmol) was hydrolyzed exactly as in the preceding experiment to obtain **6** as a light-yellow solid (109 mg, 65%); dec >300 °C; HPLC 10% MeCN in 0.1 M NH_4OAc, pH 7.0, retention time, 8.6 min; IR (KBr) ν 3420, 3220 sh, 2950 sh, 2600 br, 1910 br, 1700 br, 1635, 1610, 1570, 1560, 1520, 1455 sh, 1420 sh, 1395, 1345, 1305, 1255 cm^{-1}; NMR (d_6-DMSO) δ 1.8–2.4 (m, CH_2CH_2), 2.45 (s, 2-Me), 3.22 (s, N^{10}-Me), 4.90 (s, CH_2N, overlapping another s, H_2O), 6.80 (d, J = 8 Hz, 3′- and 5′-H), 7.68 (d, J = 8 Hz, 2′- and 6′-H), 7.7–8.1 (broad m, NH_2), 8.87 (s, 7-H); UV λ_{max} (pH 7.4) 218 nm (ϵ 20300), 247 (21300), 303 (24200), 345 infl (7100) λ_{max} (0.1 N HCl) 222 nm (ϵ 21300), 305 (23400), 345 infl (8900). Anal. ($C_{21}H_{23}N_7O_5 \cdot 0.5NH_3 \cdot 2H_2O$) C, H, N.

Hydrolysis with Carboxypeptidase G_1. Small samples (1 mg) of compounds **3** and **4** were treated at room temperature in 1 M NaOAc (10 mL) containing $ZnCl_2$ (10 mg) with freshly thawed enzyme solution (0.3 μL, 4500 units/mL). In less than 15 min, glutamate hydrolysis was nearly complete according to HPLC analysis (20% MeCN in 0.1 M NH_4OAc, pH 7.5), which showed the disappearance of >95% of the starting material (**3**, 2.5 min; **4**, 2.89 min) and the appearance of new peaks (3.0 and 3.3 min) assumed to be the 2-desamino and 2-desamino-2-methyl derivatives of 4-amino-4-deoxypteroic acid, respectively. Under identical conditions, clinical grade MTX (mainly the L form, 3.0 min) was cleaved to 4-amino-4-deoxy-N^{10}-methylpteroic acid (4.0 min), whereas D-MTX (3.0 min, preformed from clinical grade MTX by carboxypeptidase G_1 treatment)[27] was resistant to further treatment with the enzyme.

Acknowledgment. This work was supported in part by Grants CA25394 (A.R.), CA39867 (A.R., R.G.M.) and CA41461 (J.H.F.) from the National Cancer Institute (DHHS).

Registry No. **3**, 118869-51-5; **4**, 118869-52-6; **5**, 129780-79-6; **6**, 129780-80-9; **7**, 40127-91-1; **8**, 118869-53-7; **9**, 118869-54-8; **10**, 118869-55-9; **11**, 118869-56-0; **12**, 118869-57-1; **13**, 43111-44-0; **14**, 129780-81-0; **15**, 129780-83-2; **16**, 129780-82-1; **17**, 129780-84-3; DHFR, 9002-03-3; 4-H_2NC_6HyCO-Glu(ONu-*t*)-OBu-*t*, 76282-66-1; 4-H_2NC_6HyCO-Hlu(OMe)-OMe, 52407-60-0; 4-H_2NC_6HyCO-Glu-OH, 4271-30-1; HN=$CHNH_2$·AcOH, 3473-63-0; HN=$CMeNH_2$·AcOH, 36896-17-0; 4-(MeNH)$C_6HyCOOH$, 10541-83-0; H-Glu(OBu-*t*)-OBu-*t*·HCl, 32677-01-3.

Nucleosides and Nucleotides. 94. Radical Deoxygenation of *tert*-Alcohols in 1-(2-*C*-Alkylpentofuranosyl)pyrimidines: Synthesis of (2′*S*)-2′-Deoxy-2′-*C*-methylcytidine, an Antileukemic Nucleoside[1]

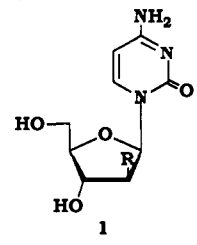
Akira Matsuda,*,† Kenji Takenuki,† Takuma Sasaki,‡ and Tohru Ueda†

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan, and Cancer Research Institute, Kanazawa University, Takara-machi, Kanazawa 920, Japan. *Received April 24, 1990*

(2′*S* and 2′*R*)-2′-Deoxy-2′-*C*-methylcytidine (**1i** and **15**) and (2′*S*)-2′-deoxy-2′-*C*-ethylcytidine (**1j**) have been synthesized from the corresponding 2′-*C*-alkylarabinofuranosyl- or -ribofuranosylpyrimidine derivatives **3** and **4** by radical deoxygenation of the methyl oxalyl esters of the 2′-*tert*-alcohol, followed by sequential deblocking and amination at the 4-position. (2′*S*)-2′-Deoxy-2′-*C*-methyl-5-methyluridine (**8**) has also been synthesized in a similar manner. Among them, compound **1i** exhibits the most potent cytotoxicity to L1210 cells with potency comparable to that of 1-β-D-arabinofuranosylcytosine (**1a**). The size of the 2′-substituents and the configuration at the 2′-position are the most important for the cytotoxicity. Cytotoxicity in vitro of **1i** against various human cancer cell lines was also examined and compared with that of **1a** and 5-fluorouracil.

1-β-D-Arabinofuranosylcytosine (*ara*-C, **1a**, Chart I) is one of the most effective drugs for the treatment of human acute myeloblastic leukemia.[2-4] Its usefulness is, however, limited by several drawbacks: a short half-life time in plasma due in part to the deamination to inactive 1-β-D-arabinofuranosyluracil by the action of cytidine deaminase, development of drug resistance, and ineffectiveness to solid tumors.[5-7] Consequently, with the objective of overcoming these problems, efforts have been made to develop a large number of prodrugs[8] of *ara*-C or introduce certain other substituents into the 2′-*arabino* position in place of the hydrogen atom of 2′-deoxycytidine. As a latter approach, 2′-azido- and 2′-amino-2′-deoxy-β-D-arabinofuranosylcytosines (**1b,c**) were found to be resistant to cytidine deaminase and also potent inhibitors of mouse leukemic cells L1210 in vitro as well as in vivo.[9,10] Among a series of 2′-deoxy-2′-halo-β-D-arabinofuranosylcytosines (**1d-**

Chart I



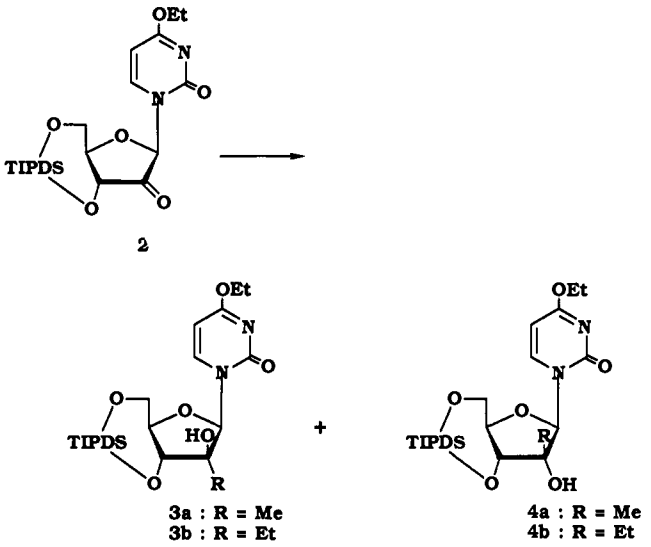
1

	R
a	OH
b	N_3
c	NH_2
d	F
e	Cl
f	Br
g	I
h	SCH_3
i	CH_3
j	CH_2CH_3

* Author to whom correspondence should be addressed.
† Hokkaido University.
‡ Kanazawa University.

0022-2623/91/1834-0234$02.50/0

Scheme I



g),[11,12] 2'-fluoro derivative **1d** showed a potent cell-growth inhibition of mouse leukemic cells L5178Y in vitro, although it was found to be susceptible to the deaminase.[13] On the other hand, 2'-deoxy-2'-(methylthio)-β-D-arabinofuranosylcytosine (**1h**) did not show cytotoxicity against L5178Y cells in vitro.[14] When such a nucleoside exhibits biological activity, it must be phosphorylated at the 5'-position by deoxycytidine kinase. Therefore, the nature of the substitutents being introduced at the 2'-*arabino* position of 2'-deoxycytidine, such as bulkiness, electronegativity, or hydrogen-bond-forming ability, seems to be critical for the enzyme recognition. In addition, these substituents would affect the overall shape of the nucleoside including sugar conformation, which should influence to the spatial position of the 5'-hydroxyl group as well as that of the 3'-hydroxyl group. Although the significance of the susceptibility of a substrate to cytidine deaminase is not fully understood in terms of antileukemic activity, this would cause a change in their half-life times and reflect the anabolic and/or catabolic process.

In order to investigate the most important factor of the substituents at the 2'-*arabino* position of 2'-deoxycytidine for exhibiting antileukemic activity, we have now synthesized 2'-*C*-alkyl derivatives of 2'-deoxycytidine, namely (2'*S*)-2'-deoxy-2'-*C*-methylcytidine (**1i**) and (2'*S*)-2'-deoxy-2'-*C*-ethylcytidine (**1j**).

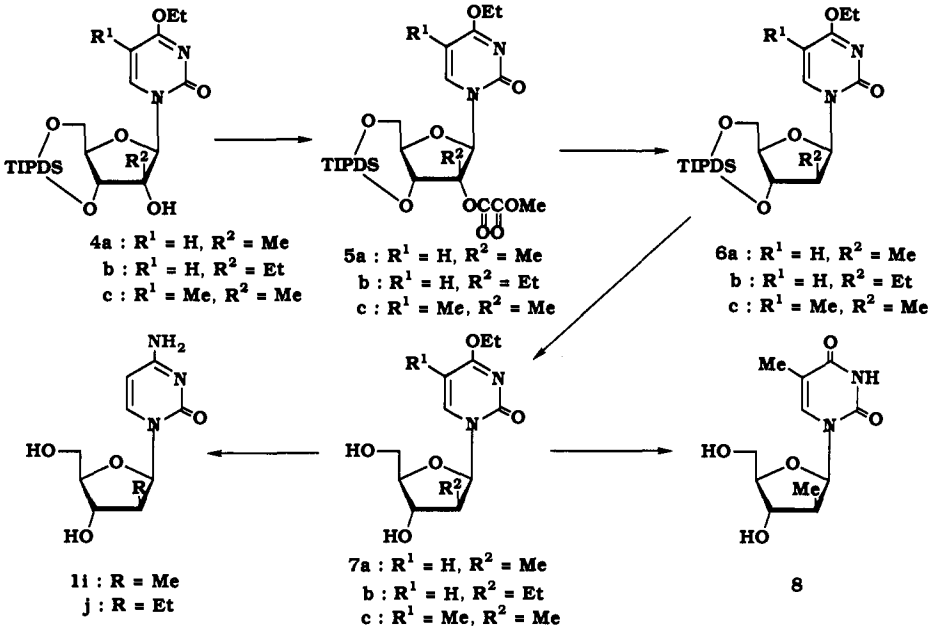
Recently, we have reported the alkyl addition reaction of various organometallics to 4-ethoxy-1-[3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-*erythro*-2-pentulofuranosyl]-2(1*H*)-pyrimidinone (**2**) producing 2'-branched-chain sugar nucleosides **3** and **4** in good yields (Scheme I).[15-17] We describe herein a radical deoxygenation of the *tert*-alcohol in 2'-branched-chain sugar pyrimidine nucleosides **3** and **4** to lead 2'-*C*-alkyl-2'-deoxy pyrimidine nucleosides. Their ability to inhibit tumor cell growth and comparison of the cytotoxicity of **1i** against various human tumor cells with *ara*-C and 5-fluorouracil (5-FU) are also described.

Chemistry

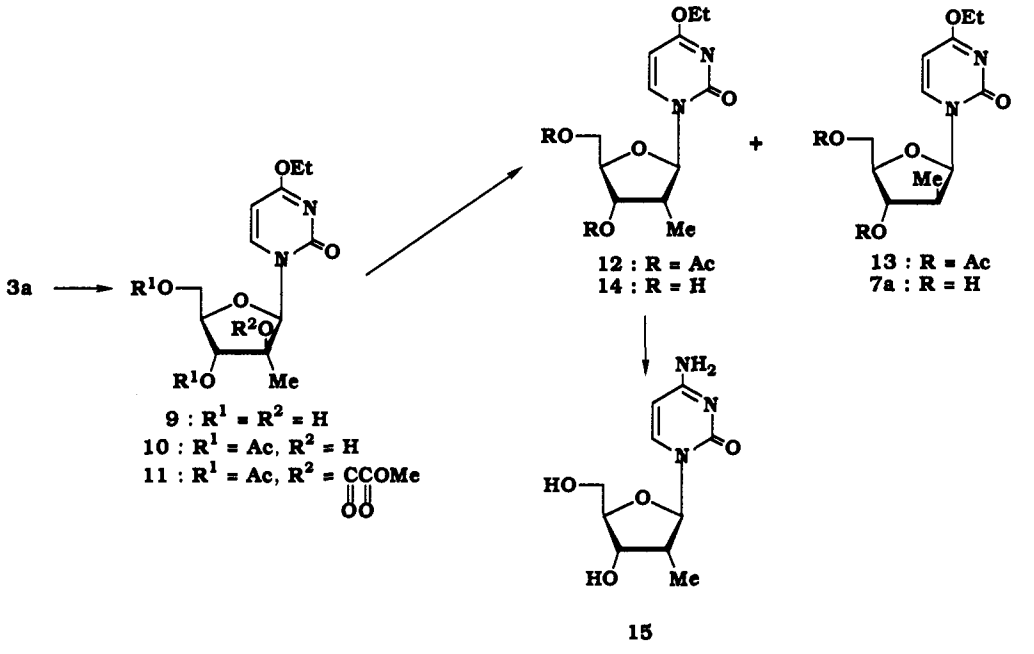
Deoxygenation of the sugar hydroxyl groups of nucleosides is generally performed by the Barton method, radical deoxygenation of the imidazoylthiocarbonyl esters or phenoxythiocarbonyl esters using tributyltin hydride (Bu_3SnH) in the presence of radical initiators.[18-21] However, application of this methodology to *tert*-alcohols would often result in the Chugaev type elimination. Recently, Dolan and MacMillan reported a new method for deoxygenation of *tert*-alcohols via a methyl oxalyl ester with Bu_3SnH in the presence of 2,2'-azobis(isobutyronitrile) (AIBN) as a radical initiator.[22] We applied this method to our system (Scheme II). When 4-ethoxy-1-[2-*C*-methyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-*ribo*-pentofuranosyl]-2(1*H*)-pyrimidinone (**4a**)[15,16] was treated with methoxalyl chloride in the presence of 2 equiv of 4-(dimethylamino)pyridine (DMAP) in dry acetonitrile, the desired methyl oxalyl ester **5a** was obtained in almost quantitative yield based on a thin-layer chromatography (TLC). However, this material (**5a**) is unstable and a considerable amount of **4a** was recovered along with **5a** during purification by silica gel column chromatography. Therefore, the crude **5a** was submitted to radical deoxygenation with Bu_3SnH in the presence of AIBN in toluene at 100 °C. Purification of the reaction mixture with silica gel column chromatography afforded a nucleosidic product (**6a**) whose mass spectral data showed a molecular ion peak at m/z 512. The ^1H NMR spectrum of this compound exhibited the 1'-proton at 6.38 ppm as a doublet while the 1'-proton of **5a** appeared at 6.36 ppm as a singlet. This result showed that the deoxygenation occurred exclusively to produce a 2'-deoxy-2'-*C*-methyl derivative. The configuration of this nucleoside at the 2'-position could not be determined at this stage because the 2'-*C*-methyl proton signals were overlapped with those of isopropyl protons of the protecting group. Deblocking of the nucleoside **6a** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) gave a crystalline 4-ethoxy-1-(2-deoxy-2-*C*-methyl-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone (**7a**). The 1'-proton signal of **7a** appeared at 6.15 ppm

(1) Part 93: Takenuki, K.; Itoh, H.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1990**, *38*, 2947.
(2) Carey, R. W.; Ribas-Mundo, M.; Ellison, R. R. *Cancer* **1976**, *36*, 1516.
(3) Clarkson, B.; Dowling, M. D.; Gee, T. S.; Cunningham, I. B.; Burchenal, J. H. *Cancer* **1976**, *36*, 775.
(4) Bodey, G. P.; Rodriguez, V. *Semin. Hematol.* **1978**, *15*, 221.
(5) Chabner, B.; Hande, K. R.; Drake, J. C. *Bull. Cancer* **1979**, *66*, 89.
(6) Prince, H. N.; Grumberg, E.; Buck, M.; Cleeland, R. *Proc. Soc. Exp. Biol. Med.* **1969**, *130*, 1080.
(7) Ho, W. D. H. *Cancer Res.* **1973**, *33*, 2816.
(8) For a review on prodrugs, see: Hadfield, A. F.; Sartorelli, A. C. *Adv. Pharmacol. Chemother.* **1984**, *20*, 21.
(9) Bobek, M.; Cheng, Y. C.; Bloch, A. *J. Med. Chem.* **1978**, *21*, 660.
(10) Bobek, M.; Cheng, Y. C.; Mihich, E.; Bloch, A. *Recent Results Cancer Res.* **1980**, *74*, 78.
(11) Watanabe, K. A.; Reichiman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1978**, *21*, 597.
(12) Su, T.-L.; Watanabe, K. A.; Shinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21 and references cited therein.
(13) Kreis, W.; Watanabe, K. A.; Fox, J. J. *Helv. Chim. Acta* **1978**, *61*, 1011.
(14) Shibuya, S.; Ueda, T. J. *Carbohydr. Nucleosides Nucleotides* **1980**, *7*, 49.
(15) Matsuda, A.; Itoh, H.; Takenuki, K.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 945.
(16) Matsuda, A.; Takenuki, K.; Itoh, H.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1987**, *35*, 3967.
(17) Ueda, T.; Matsuda, A.; Yoshimura, Y.; Takenuki, K. *Nucleosides Nucleotides* **1989**, *8*, 743.
(18) Barton, D. H. R.; Hay Motherwell, R. S.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1.* **1981**, 2363.
(19) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
(20) Pankiewicz, K.; Matsuda, A.; Watanabe, K. A. *J. Org. Chem.* **1982**, *47*, 485.
(21) Fukukawa, K.; Ueda, T.; Hirano, T. *Chem. Pharm. Bull.* **1983**, *31*, 1842.
(22) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588.

Scheme II



Scheme III



as a doublet ($J_{1',2'}$ = 7.6 Hz) and the 2′-*C*-methyl proton signals were observed at 0.74 ppm as a doublet in its ^{1}H NMR spectrum. A nuclear Overhauser effect (NOE) between 2′-*C*-methyl protons and the 6-H proton at the base moiety was observed (5.4%). Therefore the configuration at the 2′-position was determined as *S*. Thus, the radical deoxygenation of **5a** proceeded in a stereospecific manner from α-side of the sugar ring.

4-Ethoxy-1-[2-*C*-ethyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-*ribo*-pentofuranosyl]-2(1*H*)-pyrimidinone (**4b**) and 4-ethoxy-5-methyl-1-[2-*C*-methyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-*ribo*-pentofuranosyl]-2-(1*H*)-pyrimidinone (**4c**)[1] were likewise converted to the corresponding 2′-*O*-methyl oxalyl esters **5b**,**c** and deoxygenated in a similar manner. The desired (2′*S*)-2′-deoxy-2′-*C*-ethyl derivative **6b** and (2′*S*)-2′-deoxy-2′-*C*-methyl derivative **6c** were obtained stereospecifically in 75% and 67% yields, respectively. These nucleosides were converted into the corresponding free nucleosides **7b**,**c**, in good yields.

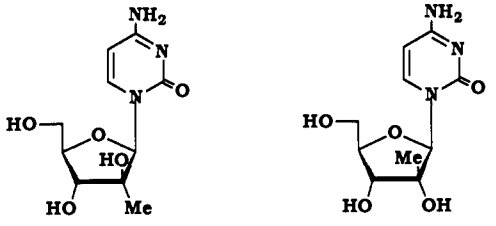
By contrast, esterification of the 2′-hydroxy group of 4-ethoxy-1-[2-*C*-methyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-*arabino*-pentofuranosyl]-2(1*H*)-pyrimidinone (**3a**) with methoxalyl chloride under similar conditions described above or even under forced conditions proceeded in low yield, perhaps due to steric hindrance around the hydroxyl group. The TIPDS group of **3a** was then removed by TBAF in THF, giving **9**, and the 3′- and 5′-hydroxyl groups of **9** were subsequently acetylated to afford **10** (Scheme III). Treatment of **10** with methoxalyl chloride in the presence of DMAP gave the desired 2′-*O*-methyl oxalate **11**. The crude ester **11** was directly reacted with Bu_3SnH in the presence of AIBN in toluene. The reaction mixture was purified by a silica gel column chromatography, giving nucleosidic products. The ^{1}H NMR spectrum of the products showed a set of 3′-protons

Table I. IC_{50} Values of 2'-Branched-Chain Sugar Pyrimidine Nucleosides on L1210 Cell Growth in Vitro[a]

compd	IC_{50},[b] μg/mL	compd	IC_{50},[b] μg/mL
1i	0.26	8	32
1j	>100	16	>100
15	40	17	12

[a,b] See Table II.

Chart II



16 17

at 5.20 ppm (as double doublet) and 4.90 ppm (as triplet) in a ratio of 1/3. At this stage, these nucleosides could not be separated. After removal of the acetyl groups of the mixture by treatment with sodium ethoxide in ethanol, the products showed two spots with very close R_f values in TLC (chloroform/ethanol 10/1). The mixture was finally separated by high-performance liquid chromatography using a C_{18} reverse-phase column. Retention times of these nucleosides were 3.6 and 5.2 min (in a ratio of 3/1), respectively, with 30% ethanol in H_2O as an eluting solvent at a flow rate of 3 mL/min. The compound having a 3.6 min retention time (t_R) was obtained in 55% yield and its spectral data were identical with those of **7a** described above. From the latter fractions, compound **14** was obtained in 18% yield. The mass spectrum of **14** showed a molecular ion peak at m/z 270 and its ^1H NMR spectrum showed a doublet at 1.14 ppm for the 2'-*C*-methyl protons and a doublet at 5.78 ppm for the 1'-proton ($J_{1'2'}$ = 6.8 Hz). As expected, when the 2'-*C*-methyl protons were irradiated, an NOE was observed at the 1'-proton (11.2%) but not at the 6-proton. From these results, the configuration of **14** at the 2'-position was assigned as *R*. It follows, therefore, that the 2'-*tert*-radical initially generated from **11** was not easily hydrogenated from the β-side by Bu_3SnH to give **12** because of the steric hindrance by the base moiety and, hence, the hydrogenation occurred predominantly from the α-side to give **13**. This result is consistent with that observed in the stereochemistry of reduction of (2'*R* or 2'*S*)-2'-chloro-2'-deoxyadenosines by Bu_3SnH.[23,24]

Treatment of these 4-ethoxy derivatives **7a**, **7b**, and **14** with methanolic ammonia in a sealed steel tube furnished the corresponding cytosine derivatives **1i**, **1j**, and **15** in good yields, respectively. Compound **7c** was converted into (2'*S*)-2'-deoxy-2'-*C*-methylthymidine (**8**) by mild acid treatment.

Biological Activities

Cytotoxicities of the nucleosides **1i**, **1j**, **8**, and **15** toward mouse leukemic cells L1210 are summarized in Table I. For comparison, the results with compounds **16**[16] and **17**[16] (Chart II) were also included. Among the branched-chain sugar nucleosides, (2'*S*)-2'-deoxy-2'-*C*-methylcytidine (**1i**) exhibited the most potent cytotoxicity to L1210 cells. Its potency was 46 times greater than that of the corresponding ribonucleoside **17**. It is obvious that deletion of the 2'-*tert*-hydroxyl group is important for the cytotoxicity. However, (2'*R*)-2'-deoxy-2'-*C*-methyl derivative **15**, having a 2'-"down" methyl substituent, was 150 times less cytotoxic than **1i**. These results are consistent with the accumulated results that almost all 2'-modified nucleosides having a "down" substituent are less active than the corresponding nucleosides bearing an "up" substituent. Furthermore, the size of the substituent is a critical factor for determining the cytotoxicity since the 2'-ethyl derivative **1j** did not show any cytotoxicity up to 100 μg/mL. Thymidine derivative **8** was much less cytotoxic than the 2'-deoxycytidine derivative **1i**. This might be correlated to the different requirements of substrate specificities of cellular nucleoside kinases, deoxycytidine kinase, and thymidine kinase, for phosphorylation of the 5'-hydroxyl group.

Table II. Inhibitory Effects of (2'*S*)-2'-Deoxy-2'-*C*-methylcytidine (**1i**), *ara*-C, and 5-FU on the Growth of Various Mammalian Tumor Cell Line in Vitro[a]

	IC_{50},[b] μg/mL		
cell lines	1i	*ara*-C	5-FU
leukemic			
L1210[c]	0.26	0.097	0.32
CCRF CEM[d]	0.15	0.065	40
MOLT4[e]	0.032	0.056	3.8
HL60[f]	0.65	>0.1	
K562[g]	2.2	3.2	38
U937[h]	0.38	0.31	3.5
solid			
PC10[i]	81.8	>100	>100
PC14[j]	>100	>100	10
KATO III[k]	>100	>100	3.7
SW480[l]	>100	>100	3.3
TE2[m]	>100	>100	3.9
T24[n]	1.1	>100	6.1

[a] Antineoplastic activity in vitro was performed according to the method of Carmichael et al.[26] Each tumor cell line (1 × 10^4/well) was incubated in the presence or absence of test compound for 72 h. Then, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide was added and OD(570 nm) was measured. Percent inhibition was determined as follows: % inhibition = [1-OD(570 nm) of sample well/OD(570 nm) of control well] × 100. [b] IC_{50} was given as the concentration in μg/mL required for 50% inhibition of cell growth. [c] Mouse leukemia. [d] Human T-cell acute lymphoblastoid leukemia. [e] Human T-cell acute lymphoblastic leukemia. [f] Human promyelocytic leukemia. [g] Human chronic myelogenous leukemia. [h] Human histiocytic lymphoma. [i] Human lung squamous cell carcinoma. [j] Human lung adenocarcinoma. [k] Human gastric carcinoma. [l] Human colon adenocarcinoma. [m] Human esophagus adenocarcinoma. [n] Human bladder transitional-cell carcinoma.

We next compared the inhibitory activity spectrum of **1i** with *ara*-C and 5-FU on the growth of various human tumor cell lines in vitro (Table II).[25] *ara*-C showed inhibitory activity toward mouse leukemic, human T-cell acute leukemic, and chronic leukemic cell lines, but not against human carcinoma and adenocarcinoma cell lines. 5-FU exhibited a broad spectrum of cytotoxicity to this range of cells. Compound **1i** showed a quite similar inhibitory activity spectrum to that of *ara*-C except for T24 human bladder transition cell line.

In summary, it can therefore be concluded, that the analogue of 2'-deoxycytidine having a 2'-"up" substituent can be a potent antileukemic agent, and the *size* of the substituent is the most important for the cytotoxicity, the smaller the better. In addition, it is now evident that the

(23) Robins, M. J.; MacCoss, M.; Wilson, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 4660.
(24) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.
(25) The antineoplastic assay for various cell lines was performed by Drs. A. Fujii and K. Yamagami of Yoshitomi Pharmaceutical Industry Ltd., Iruma, Japan, to whom our thanks are due.
(26) Carmichael, J.; DeGraff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936.

hydrogen-bond-forming ability of the 2'-"up" substituent has no direct relation to order of the cytotoxicity because the 2'-methyl and the azide groups could not serve as a hydrogen-bonding acceptor or donor while the 2'-hydroxyl group could act as a donor and the 2'-fluoro group as an acceptor. Among the compounds listed in Chart I, the nucleosides having the 2'-substituents such as hydroxyl, fluoro, azide, amino, and methyl are almost equally cytotoxic to L1210 cells, in which the electronegativity of the 2'-substituent does not correlate the cytotoxicity. These factors may reflect the anabolic or catabolic process of these nucleosides.

Experimental Section

Melting points were determined on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a JEOL FT100FT or FX-270FT spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were measured on a JEOL JMX-DX303 spectrometer. TLC was performed on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70–230 mesh). HPLC analyses were performed on a JASCO TRI ROTAR-V system.

4-Ethoxy-1-(2-deoxy-2-*C*-methyl-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone (7a). Methoxalyl chloride (138 μL, 1.5 mmol) was added to a solution of **4a**[16] (550 mg, 1.05 mmol) and 4-(dimethylamino)pyridine (DMAP; 244 mg, 2 mmol) in dry CH_3CN (10 mL). The mixture was stirred for 5 min under an Ar atmosphere at room temperature then diluted with EtOAc (50 mL). The mixture was washed successively with a saturated aqueous $NaHCO_3$ solution (10 mL) and H_2O (10 mL), the separated organic phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was coevaporated twice with toluene to afford 4-ethoxy-1-[2-*C*-methyl-2-*O*-(methoxyoxalyl)-3,5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (**5a**). ^{1}H NMR ($CDCl_3$): 1.00–1.10 (m, 31 H, isopropyl and 2'-CH_3), 1.37 (t, 3 H, 4-OCH$_2$CH_3, J = 7.1 Hz), 3.89 (s, 3 H, COCO$_2$CH_3), 4.07–4.20 (m, 4 H, 3',4',5',5''-H), 4.44 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 5.88 (d, 1 H, 5-H, $J_{5,6}$ = 7.6 Hz), 6.36 (s, 1 H, 1'-H), 7.98 (d, 1 H, 6-H, $J_{5,6}$ Hz). This compound is unstable during purification by silica gel column chromatography. Without further purification, **5a** was used for the next step. A mixture of Bu_3SnH (0.42 mL, 1.58 mmol) and 2,2'-azobis(isobutyronitrile) (AIBN; 10 mg) in dry toluene (5 mL) was added to a solution of **5a** obtained above under an Ar atmosphere. The mixture was heated at 100 °C for 1 h and the solvent was removed by evaporation under reduced pressure. The residue was purified by a silica gel column (2.4 × 28 cm), eluted with 10% EtOAc-hexane to yield 4-ethoxy-1-[2-deoxy-2-*C*-methyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl]-2(1*H*)-pyrimidinone (**6a**, 292 mg, 56%) as a foam, which was subjected to further reaction without purification. MS m/z: 512 (M$^+$). ^{1}H NMR ($CDCl_3$): 0.95–1.10 (m, 31 H, isopropyl and 2'-CH_3), 1.36 (t, 3 H, 4-OCH$_2$CH_3, J = 7.1 Hz), 2.64 (m, 1 H, 2'-H), 3.80–4.25 (m, 4 H, 3',4',5',5''-H), 4.43 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 5.84 (d, 1 H, 5-H, $J_{5,6}$ = 7.6 Hz), 6.38 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.3 Hz), 8.02 (d, 1 H, 6-H, $J_{5,6}$ = 7.6 Hz). From the later fractions, the starting material (**4a**; 105 mg) was recovered. A THF solution of TBAF (1 M, 1.2 mL, 1.2 mmol) was added to a solution of **6a** (280 mg, 0.55 mmol) in dry THF (10 mL). The mixture was stirred for 10 min at room temperature and neutralized with AcOH. The residue obtained on evaporation of the solvent was purified by a silica gel column (2.4 × 13 cm) eluted with 5% EtOH/$CHCl_3$. The UV-absorbing fractions were combined and concentrated to dryness and the residue was crystallized from Et_2O to afford **7a** (130 mg, 88%). Mp: 148–149 °C. MS m/z: 270 (M$^+$). ^{1}H NMR (DMSO-d_6): 0.74 (d, 3 H, 2'-CH_3, J = 7.1 Hz), 1.28 (t, 3 H, 4-OCH$_2$CH_3, J = 7.1 Hz), 3.67 (m, 5 H, 2',3',4',5',5''-H), 4.29 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 5.17 (br t, 1 H, 5'-OH), 5.36 (d, 1 H, 3'-OH), 6.02 (d, 1 H, 5-H, $J_{5,6}$ = 7.6 Hz), 6.15 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.6 Hz), 8.30 (d, 1 H, 6-H, $J_{5,6}$ = 7.6 Hz). Anal. ($C_{12}H_{18}N_2O_5$) C, H, N.

(2'*S*)-2'-Deoxy-2'-*C*-methylcytidine Hydrochloride (1i). A solution of **7a** (100 mg, 0.37 mmol) in methanolic ammonia (saturated at 0 °C, 20 mL) was heated in a sealed tube for 2 days at 100 °C. The cooled tube was degassed and the solvent was removed under reduced pressure. The residue, dissolved in EtOH containing 0.25 mL of 2 *N* HCl, was evaporated and coevaporated several times with EtOH until crystalline materials appeared which was collected to give **1i** (78 mg, 76%). Mp: 167–169 °C. ^{1}H NMR (D_2O): 0.95 (d, 3 H, 2'-CH_3, J = 7.1 Hz), 2.74 (m, 1 H, 2'-H), 3.89–4.06 (m, 4 H, 3',4',5',5''-H) 6.24 (d, 1 H, 5-H, $J_{5,6}$ = 7.8 Hz), 6.29 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.6 Hz) 8.13 (d, 1 H, 6-H, $J_{5,6}$ = 7.8 Hz). Anal. ($C_{10}H_{15}N_3O_4$·HCl) C, H, N.

(2'*S*)-2'-Deoxy-2'-*C*-ethylcytidine Hydrochloride (1j). Methoxalyl chloride (70 μL, 0.6 mmol) was added to a solution of **4b**[16] (273 mg, 0.5 mmol), DMAP (73 mg, 0.6 mmol), and triethylamine (60 μL, 0.6 mmol) in dry CH_3CN (5 mL) under an Ar atmosphere at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then for 1 h at room temperature. The mixture was diluted with EtOAc (30 mL) and was washed twice with H_2O (10 mL). The separated organic phase was dried (Na_2SO_4) and the solvent was removed by evaporation to dryness and coevaporation twice with toluene to afford 4-ethoxy-1-[2-*C*-ethyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-2-*O*-(methoxyoxalyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (**5b**). A mixture of Bu_3SnH (0.2 mL, 0.75 mmol) and AIBN (5 mg) in dry toluene (5 mL) was added to a solution of the crude **5b** obtained above in dry toluene (5 mL) under an Ar atmosphere. The mixture was heated at 100 °C for 1 h and the solvent was concentrated to dryness in vacuo. The residue was purified by a silica gel column (2.4 × 16 cm) eluted with 20% EtOAc/hexane to yield 4-ethoxy-1-[2-*C*-ethyl-2-deoxy-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl]-2(1H)-pyrimidinone (**6b**, 197 mg, 75%) as a foam, which was subjected to further reaction without purification. MS m/z: 525 (M$^+$). ^{1}H NMR ($CDCl_3$): 0.92–1.62 (m, 36 H, isopropyl, 2'-CH$_2$CH_3, and 4-OCH$_2$CH_3), 2.35 (m, 1 H, 2'-H), 3.71 (dt, 1 H, 4'-H), 4.09–4.23 (m, 3 H, 3',5',5''-H), 4.43 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 5.84 (d, 1 H, 5-H, J = 7.6 Hz), 6.48 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.3 Hz), 7.92 (d, 1 H, 6-H, $J_{5,6}$ = 7.6 Hz). A THF solution of TBAF (1 M, 1 mL, 1 mmol) was added to a solution of **6b** (190 mg, 0.36 mmol) in dry THF (10 mL). The mixture was stirred for 10 min at room temperature and neutralized with AcOH. The residue obtained on evaporation of solvent was purified by a silica gel column (2.4 × 12 cm) eluted with 5% EtOH/$CHCl_3$ to yield 4-ethoxy-1-(2-*C*-ethyl-2-deoxy-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone (**7b**, 89 mg, 87%) as a foam. MS m/z: 284 (M$^+$). ^{1}H NMR (DMSO-d_6): 0.87–1.43 (m, 8 H, 2'-Et, 4-OCH$_2$CH_3), 2.35 (m, 1 H, 2'-H), 3.71–4.12 (m, 6 H, 3',4',5',5''-H, 3',5'-H), 4.39 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 6.04 (d, 1 H, 5-H, $J_{5,6}$ = 7.6 Hz), 6.19 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.3 Hz), 8.24 (d, 1 H, 6-H, $J_{5,6}$ = 7.6 Hz). A solution of **7b** (85 mg, 0.3 mmol) in methanolic ammonia (saturated at 0 °C, 20 mL) was heated in a sealed tube for 2 days at 100 °C. The cooled tube was degassed and the solvent was removed under reduced pressure. The residue, dissolved in EtOH containing 0.25 mL of 2 N HCl, was concentrated and coevaporated several times with EtOH until crystalline materials appeared, which was separated to give **1j** (62 mg, 71%); mp 167–169 °C. ^{1}H NMR (D_2O): 0.92 (d, 3 H, 2'-CH$_2$CH_3, J = 7.7 Hz), 1.27–1.35 (m, 2 H, 2'-CH_2CH$_3$), 2.54 (m, 1 H, 2'-H) 3.88–4.08 (m, 4 H, 3',4',5',5''-H), 6.22 (d, 1 H, 5-H, $J_{5,6}$ = 7.9 Hz) 6.35 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.5 Hz), 8.00 (d, 1 H, 6-H, $J_{5,6}$ = 7.9 Hz). Anal. ($C_{11}H_{17}N_3O_4$·HCl) C, H, N.

4-Ethoxy-5-methyl-1-[2-deoxy-2-*C*-methyl-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl]-2(1*H*)-pyrimidinone (6c). Methoxalyl chloride (170 μL, 0.76 mmol) was added to a solution of **4c**[1] (340 mg, 0.63 mmol) and DMAP (100 mg, 0.81 mmol) under an Ar atmosphere. The mixture was stirred for 1 h at room temperature and was diluted with EtOAc (50 mL). The mixture was washed twice with H_2O (15 mL) and the separated organic phase was dried (Na_2SO_4) and concentrated to dryness, giving 4-ethoxy-5-methyl-1-[2-*C*-methyl-2-*O*-(methoxyoxalyl)-3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (**5c**); ^{1}H NMR ($CDCL_3$): 1.00–1.10 (m, 28 H, isopropyl), 1.38 (t, 3 H, 4-OCH$_2$CH_3, J = 7.1 Hz), 1.75 (s, 3 H, 2'-CH_3), 1.94 (d, 3 H, 5-CH_3, $J_{5\text{-Me},6}$ = 1 Hz), 3.89 (s, 3

H, 2'-OCOCO$_2$CH_3), 4.19 (m, 4 H, 3',4',5',5''-H), 4.46 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 6.33 (s, 1 H, 1'-H), 7.62 (d, 1 H, 6-H, $J_{5\text{-Me},6}$ = 1 Hz). The crude **5c** was used for the next step without further purifications. A mixture of Bu_3SnH (0.25 mL, 0.94 mmol) and AIBN (10 mg) in dry toluene (5 mL) was added to a solution of **5c** in dry toluene (15 mL) under an Ar atmosphere. The mixture was heated at 100 °C for 3 h. Bu_3SnH (84 μL, 0.3 mmol) was further added to the reaction mixture, the mixture was heated at 100 °C for 1 h further, and the solvent was removed under reduced pressure. The residue was purified by a silica gel column (2.5 × 16 cm) eluted with 20% EtOAc/hexane. The UV-absorbing fractions were combined and concentrated to leave an oil which was crystallized from EtOAc/hexane, giving **6c** (226 mg, 67%). Mp: 109–111 °C. MS m/z: 526 (M^+). ^{1}H NMR ($CDCl_3$): 0.99–1.10 (m, 31 H, 2'-Me and isopropyl), 1.36 (t, 3 H, 4-OCH_2CH_3, J = 7.1 Hz), 1.94 (d, 3 H, 5-CH_3, $J_{5\text{-Me},6}$ = 1.0 Hz), 2.54–2.78 (m, 1 H, 2'-H), 3.70 (m, 1 H, 4'-H), 3.94–4.26 (m, 3 H, 3',5'-H), 4.44 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 6.36 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.8 Hz), 7.67 (d, 1 H, 6-H, $J_{5\text{-Me},6}$ = 1.0 Hz). Anal. ($C_{25}H_{46}N_2O_6Si_2$) C, H, N.

4-Ethoxy-5-methyl-1-(2-deoxy-2-*C*-methyl-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone (7c). A THF solution of TBAF (1 M, 1 mL, 1 mmol) was added to a solution of **6c** (200 mg, 0.38 mmol) in dry THF (10 mL). The mixture was stirred for 20 min at room temperature and neutralized with AcOH. The residue obtained on evaporation of solvent was applied to a silica gel column (2.4 × 14 cm), which was eluted with 9% EtOH/$CHCl_3$. The UV-absorbing fractions were combined and concentrated to dryness. The residue was crystallized from EtOH/Et_2O to give **7c** (105 mg, 97%). Mp: 183–185 °C. MS m/z: 284 (M^+). ^{1}H NMR (DMSO-d_6): 0.73 (d, 3 H, 2'-CH_3, J = 7.0 Hz), 1.30 (t, 3 H, 4-OCH_2CH_3, J = 7.0 Hz), 1.87 (s, 3 H, 5-CH_3), 2.42–2.59 (m, 1 H, 2'-H), 3.62–3.80 (m, 4 H, 3',4',5',5''-H), 4.31 (q, 2 H, 4-OCH_2CH$_3$, J = 7.0 Hz), 5.22 (t, 1 H, 5'-OH), 5.32 (d, 1 H, 3'-OH), 6.13 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.3 Hz), 8.18 (s, 1 H, 6-H). Anal. ($C_{13}H_{20}N_2O_5$) C, H, N.

(2'*S*)-2'-Deoxy-2'-*C*-methylthymidine (8). Dowex 50 (H^+ form; 1 g) was added to a solution of **7c** (95 mg, 0.33 mmol) in a mixture of EtOH (1 mL) and H_2O (5 mL). The mixture was stirred for 4 h at room temperature. The resin was removed by filtration and the filtrate was concentrated to dryness. THe residue was crystallized from EtOH/hexane to afford **8** (63 mg, 74%). Mp: 179–180 °C. MS m/z: 256 (M^+). ^{1}H NMR (DMSO-d_6): 0.81 (d, 3 H, 2'-CH_3, J = 7.1 Hz), 1.75 (d, 3 H, 5-CH_3), 2.38–2.56 (m, 1 H, 2'-H), 3.57–3.80 (m, 4 H, 3',4',5',5''-H), 5.20 (t, 1 H, 5'-OH), 5.33 (d, 1 H, 3'-OH), 6.07 (d, 1 H, 1'-H, $J_{1',2'}$ = 7.7 Hz), 7.91 (d, 1 H, 6-H, $J_{5\text{-Me},6}$ = 1.1 Hz), 11.26 (br s, 1 H, NH). Anal. ($C_{11}H_{16}N_2O_5$) C, H, N.

4-Ethoxy-1-(3,5-di-*O*-acetyl-2-*C*-methyl-β-D-arabinofuranosyl)-2(1H)-pyrimidinone (10). Acetic anhydride (90 μL, 0.95 mmol) was added to a suspension of **9**[16] (130 mg, 0.45 mmol), triethylamine (133 μL, 0.95 mmol), and DMAP (10 mg) in Ch_3CN (5 mL). The mixture was stirred for 20 min at room temperature. EtOH (0.5 mL) was added to the mixture and the solvent was removed under reduced pressure. The residue was purified by a silica gel column (2.4 × 13 cm) eluted with 50% EtOAc/hexane. The UV-absorbing fractions were combined and concentrated to dryness to give **10** (161 mg, 96%, hexane/EtOAc). Mp: 145–147 °C. MS m/z: 370 (M^+). ^{1}H NMR ($CDCl_3$): 1.33 (t, 3 H, 4-OCH_2CH_3, J = 7.1 Hz), 1.41 (s, 3 H, 2'-CH_3), 2.10 (s, 3 H, OAc), 2.13 (s, 3 H, OAc), 3.36 (br s, 1 H, 2'-OH), 4.08–4.59 (m, 5 H, 4',5',5''-H and 4-OCH_2CH$_3$), 4.94 (d, 1 H, 3'-H, $J_{2',3'}$ = 3.4 Hz), 5.87 (d, 1 H, 5-H, $J_{5,6}$ = 7.6 Hz), 6.12 (s, 1 H, 1'-H), 7.84 (d, 1 H, 6-H, $J_{5,6}$ = 7.6 Hz). Anal. ($C_{16}H_{22}N_2O_8$) C, H, N.

(2'*R*)-2'-Deoxy-2'-*C*-methylcytidine Hydrochloride (15). Methoxalyl chloride (146 μL, 0.5 mmol) was added to a solution of **10** (155 mg, 0.42 mmol) and DMAP (61 mg, 0.5 mmol) in dry CH_3CN (5 mL). The mixture was stirred for 10 min under an Ar atmosphere at room temperature and was diluted with EtOAc (30 mL). The mixture was washed with H_2O (10 mL × 2), dried (Na_2SO_4), and concentrated to dryness, and the residue was coevaporated with toluene (10 mL × 2) to leave an oily **11**. Bu_3SnH (184 μL, 0.63 mmol) and AIBN (10 mg) were added to the above mixture in toluene (5 mL) which was heated at 100 °C under an Ar atmosphere for 1 h. The solvent was removed under reduced pressure and the residue was purified by a silica gel column (2 × 12 cm) eluted with 20% EtOAc/hexane. The UV-absorbing fractions were combined and concentrated to dryness in vacuo to give 135 mg (89%) of a mixture of **12** and **13** [MS m/z: 354 (M^+), the ratio being 1/3 based on ^{1}H NMR signals at 4.90 and 5.20 ppm due to the corresponding 3'-protons]. NaOEt (1 M solution; 50 μL) was added to a solution of the mixture **12** and **13** (170 mg, 0.48 mmol) in absolute EtOH (10 mL). The mixture was stirred for 30 min at room temperature and then neutralized with AcOH. The solvent was removed under reduced pressure and the residue was purified by a silica gel column (3 × 16 cm) eluted with 6% EtOH/$CHCl_3$ to give a mixture of **14** and **7a** (118 mg, 91%). This mixture was separated by a preparative reverse-phase column (Gasukuro Kogyo, 4.6 × 250 mm) with 30% MeOH/H_2O at a flow rate of 3 mL/min; 70.8 mg of **7a** was obtained (55%; t_R = 3.6 min) whose spectral data were identical with those of **7a** previously described. Compound **14** (23.6 mg, 18%; t_R = 5.2 min) was assigned as 4-ethoxy-1-(2-deoxy-2-*C*-methyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone. MS m/z: 270 (M^+); ^{1}H NMR ($CDCl_3$): 1.14 (d, 3 H, 2'-CH_3, J = 7.1 Hz), 1.35 (t, 3 H, 4-OCH_2CH_3, J = 7.1 Hz), 2.49–2.70 (m, 1 H, 2'-H), 3.89 (br s, 2 H, 5',5''-H), 4.09 (dd, 1 H, 4'-H), 4.29–4.48 (m, 1 H, 3'-H), 4.43 (q, 2 H, 4-OCH_2CH$_3$, J = 7.1 Hz), 5.78 (d, 1 H, 1'-H, $J_{1',2'}$ = 6.8 Hz), 5.92 (d, 1 H, 5-H, $J_{5,6}$ = 7.3 Hz), 7.96 (d, 1 H, 6-H, $J_{5,6}$ = 7.3 Hz). A solution of **14** (30 mg, 0.11 mmol) in methanolic ammonia (saturated at 0 °C; 10 mL) was heated in a sealed tube for 2 days at 100 °C. The cooled tube was degassed and the solvent was removed under reduced pressure. The residue dissolved in EtOH containing 0.2 mL of 1 N HCl was evaporated and coevaporated several times with EtOH. The residue was crystallized from MeOH/acetone, giving **15** (27 mg, 88%). Mp: 182–185 °C dec. ^{1}H NMR (D_2O): 1.08 (d, 3 H, 2'-CH_3, J = 7.0 Hz), 2.47 (m, 1 H, 2'-H), 3.77 (dd, 1 H, 5'-H, $J_{4',5'}$ = 4.8 Hz, $J_{5',5''}$ = 12.5 Hz) 3.83 (dd, 1 H, 5''-H, $J_{4',5''}$ = 4.0 Hz, $J_{5',5''}$ = 12.5 Hz), 4.12 (m, 1 H, 4'-H), 4.28 (dd, 1 H, 3'-H, J = 2.6 Hz, J = 5.9 Hz), 5.94 (d, 1 H, 1'-H, $J_{1',2'}$ = 8.1 Hz), 6.25 (d, 1 H, 5-H, $J_{5,6}$ = 8.1 Hz), 8.08 (d, 1 H, 6-H, $J_{5,6}$ = 8.1 Hz). Anal. ($C_{10}H_{15}N_3O_4$·HCl) C, H, N.

Acknowledgment. This investigation was supported in part by Grants-in-Aid for Scientific Research, Cancer Research and Special Project Research on Cancer-Bioscience from the Ministry of Education, Science, and Culture of Japan.

Registry No. **1i**·HCl, 115494-63-8; **1j**·HCl, 119410-83-2; **4a**, 115494-61-6; **4b**, 116918-63-9; **4c**, 119410-88-7; **5a**, 115494-50-3; **5b**, 130407-90-8; **5c**, 130407-91-9; **6a**, 115494-51-4; **6b**, 130407-92-0; **6c**, 130407-93-1; **7a**, 115494-52-5; **7b**, 130407-94-2; **7c**, 119410-89-8; **8**, 130466-80-7; **9**, 115494-49-0; **10**, 115494-54-7; **11**, 115494-55-8; **12**, 115494-56-9; **13**, 115494-58-1; **14**, 115494-57-0; **15**·HCl, 115494-64-9.