Synthesis of Pyrimidine 2′-Deoxy Ribonucleosides Branched at the 2′-Position via Radical Atom-Transfer Cyclization Reaction with a Vinylsilyl Group as a Radical-Acceptor Tether[1]

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Recently, we developed a regio- and stereoselective method for introducing a vinyl group at the position β to a hydroxyl group in halohydrins or α-phenylselenoalkanols via a radical atom-transfer cyclization reaction with a vinylsilyl group as a temporary connecting radical-acceptor tether. The synthesis of 2′-deoxy-2′-*C*-vinyl- and 2′-deoxy-2′-*C*-hydroxymethyluridines (**7** and **8**, respectively) and the corresponding 2′-deoxycytidine congeners (**10** and **11**, respectively), which were designed as potential antitumor and/or antiviral agents, was achieved using this radical atom-transfer cyclization as the key step. When the 2′-deoxy-2′-iodo-5′-*O*-monomethoxytrityl (MMTr) uridine derivative **19a**, bearing a vinylsilyl group at the 3′-hydroxyl group, was heated with $(Me_3Sn)_2$ and AIBN in benzene, the corresponding radical atom-transfer product was generated, which in turn was successively treated with tetrabutylammonium fluoride and TBSCl/imidazole to give the desired 2′-deoxy-5′-*O*-MMTr-3′-*O*-TBS-2′-*C*-vinyluridine (**25**). Compound **25** was successfully converted into the target 2′-deoxy-2′-branched pyrimidine ribonucleosides **7**, **8**, **10**, and **11**.

Introduction

Much attention has been focused on branched-chain sugar nucleosides because of their biological importance. We have developed stereoselective synthetic methods for a variety of branched-chain sugar nucleosides[2−7] and have found that 1-(2-deoxy-2-methylene-β-D-*erythro*-pentofuranosyl)cytosine (DMDC, **1**),[5] 1-(2-*C*-cyano-2-deoxy-β-D-*arabino*-pentofuranosyl)cytosine (CNDAC, **2**),[6] and 1-(3-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)cytosine (ECyd, **3**)[7] are potent antitumor nucleosides which significantly inhibit the growth of various human solid tumor cells both in vitro and in vivo. We also identified 2′-deoxy-4′-*C*-ethynylcytidine (**4**)[3f] and 4′-*C* -vinylthymidine (**5**)[3d] as potent antiviral and/or antitumor agents.

A variety of procedures for preparing branched-chain sugar nucleosides have been extensively studied. However, examples of 2′-deoxy-2′-branched ribonucleosides reported[8] are limited, and their biological activities have not yet been investigated in a systematic manner, perhaps because of a lack of efficient synthetic methods of 2′-deoxy-2′-branched ribonucleosides.

On the other hand, we synthesized a series of nucleoside analogues having a hydroxyamino group at the sugar moiety[9] and found that 1-(2-deoxy-2-hydroxyamino-β-D-*ribo*-pentofuranosyl)cytosine (2′-DHAC, **6**), which has a hydroxyamino group at the 2′-position, had a significant

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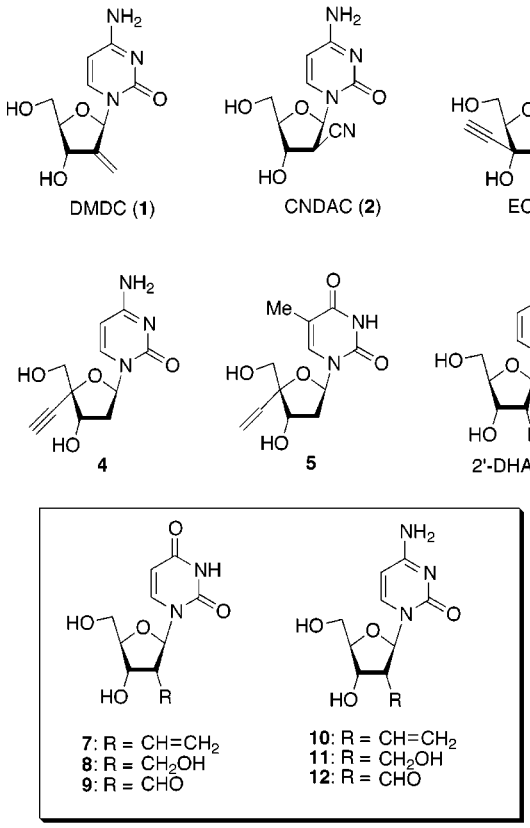

Figure 1.

antitumor effect both in vitro and in vivo,[9a,b] even though the compound was rather unstable.

These findings prompted us to synthesize the 2′-deoxy pyrimidine ribonucleosides branched at the 2′-position, **7**−**12**, the structures of which are shown in Figure 1, and to investigate their biological properties. Since most of the presently known branched-chain sugar nucleosides having an antitumor and/or antiviral effect bear a relatively small unsaturated carbon chain at the sugar moiety (Figure 1), we sought to synthesize the 2′-deoxy-2′-*C*-vinyluridine (**7**) and -cytidine (**10**). The 2′-deoxy-2′-*C*-hydroxymethyluridine (**8**) and -cytidine (**11**), which correspond to the carbon-analogue of 2′-DHAC, were also our synthetic targets.

Nucleoside analogues bearing an electron-withdrawing substituent at the 2′-position may cause a DNA strand break after their incorporation into DNA for the following reasons. The 2′-proton is rather acidic due to the electron-withdrawing substituent so that β-elimination of the 3′-phosphate may occur resulting in a DNA strand break. In fact, we previously showed that CNDAC (**2**), bearing an electron-withdrawing cyano group at the 2′-position, functioned as such a DNA strand-breaking agent in cells.[6e,f] Thus, we designed the 2′-deoxy-2′-*C*-formyluridine (**9**) and -cytidine (**12**) expecting them to be DNA strand-breaking antitumor agents.

Results and Discussion

Synthetic Plan. We planned to synthesize the target branched-chain sugar nucleosides using, as the key step, a radical cyclization reaction, which is a highly versatile method for forming C−C bonds. Since silicon-containing tethers are very useful for the regio- and stereoselective introduction of a carbon substituent based on a temporary silicon connection, there has been a growing interest in their use in intramolecular radical cyclization reactions.[10] Recently, we developed a regio- and stereoselective method for introducing 1-hydroxyethyl, 2-hydroxyethyl, and vinyl groups at the position β to a hydroxyl group in halohydrins or α-phenylselenoalkanols using an intramolecular radical cyclization reaction with a dimethyl- or diphenylvinylsilyl group as a temporary connecting radical-acceptor tether (Scheme 1).[3a−e,g,11] Thus, the selective introduction of both the 1-hydroxyethyl and the 2-hydroxyethyl groups can be achieved, depending on the concentration of Bu_3SnH in the reaction system, via a 5-*exo*-cyclization intermediate **E** or a 6-*endo*-cyclization intermediate **F**, respectively, after oxidative ring-cleavage by treatment of the cyclization products under Tamao oxidation conditions,[12] as shown in Scheme 1.[11c] A vinyl group can also be introduced by photoreaction of the vinylsilyl ether **A** in the presence of $(Bu_3Sn)_2$, followed by treatment of the resulting atom-transfer 5-*exo*-cyclization product **I** with fluoride ion.[3e] We next investigated the radical cyclization mechanism.[3a,b,11b,c] The results showed that the kinetically favored 5-*exo*-cyclized radical **C**, formed from radical **B**, was trapped when the concentration of Bu_3SnH was high enough to give **E**. At lower concentrations of Bu_3SnH and higher reaction temperatures, radical **C** rearranged into the more stable ring-enlarged 4-oxa-3-silacyclohexyl radical **D**, which was then trapped with Bu_3SnH to give **F**. This ring-enlarging rearrangement was proved to occur via a pentavalent-like silicon-bridging transition state **X**.[11c] This radical reaction with a vinylsilyl tether has been successfully applied to the synthesis of biologically important 4′-branched-chain sugar nucleosides[3a−e,g] and *C*-glycosides.[11a]

On the other hand, Chattopadhyaya and co-workers reported a facile method for introducing a hydroxypropyl group at the 2′-positon of thymine nucleosides via radical

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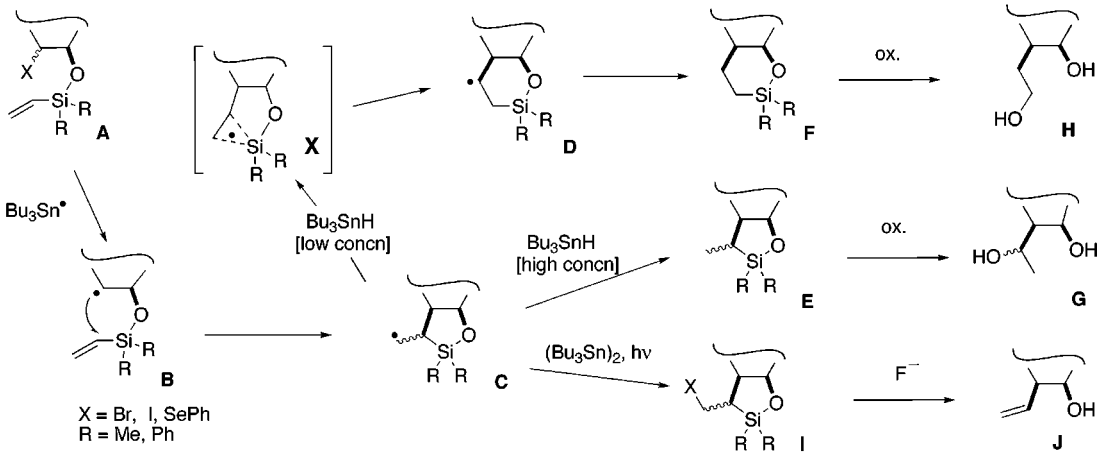
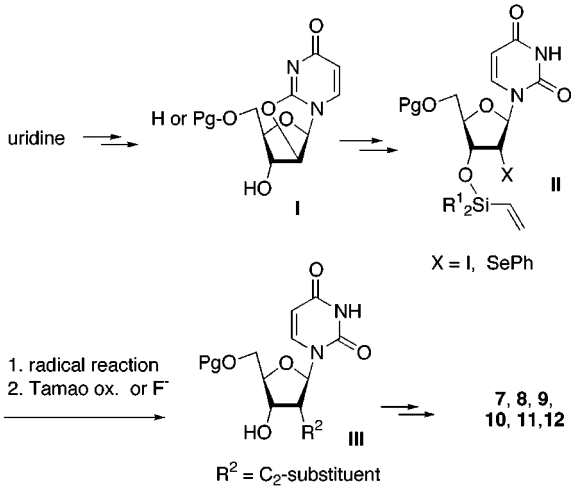
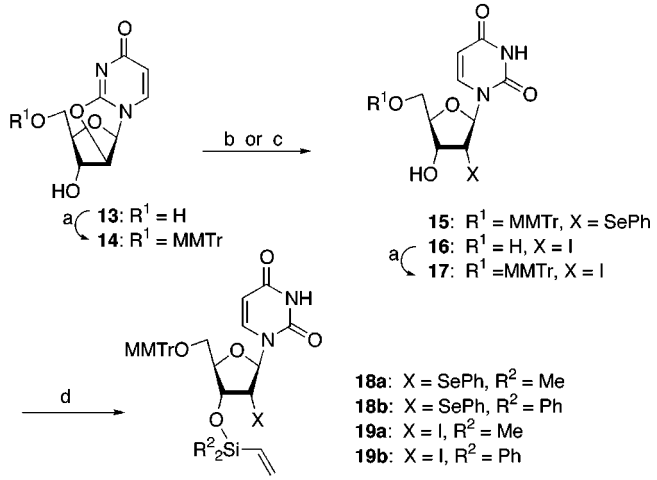
Scheme 1



Scheme 2



Scheme 3[a]



[a] Conditions: (a) MMTrCl, py, 82% (**14**), 65% (**17**); (b) $(PhSe)_2$, $NaBH_4$, EtOH/THF, reflux, 90% (**15**); (c) NaI, TsOH, acetone, 50 °C, 98% (**16**); 21.(d) $R^2_2(CH_2{=}CH)SiCl$, DMAP, Et_3N, toluene, rt, 83% (**18a**), 98% (**18b**), 84% (**19a**), 88% (**19b**).

cyclization reaction of 2′-phenylseleno-3′-*O*-allyldimethylsilylated substrate.[8a]

Considering these findings, we sought to apply our radical cyclization reaction with a vinylsilyl as a tether to the synthesis of the target 2′-deoxy-2′-branched ribonucleosides in the present study. Our synthetic plan is shown in Scheme 2. The 5′-*O*-protected 2′-phenylseleno- and 2′-iodo-2′-deoxyuridines are prepared by nucleophilic ring-opening reaction at the 2′-position of 2,2′-anhydrouridine **I**, which is readily derived from uridine. After introduction of the dimethyl- or diphenylvinylsilyl group at the 3′-hydroxyl providing **II**, the radical reaction of **II** and subsequent Tamao oxidation or fluoride ion treatment would afford the corresponding 2′-branched-chain sugar nucleoside **III**. The target nucleosides can be synthesized by the functional group transformations of **III**.

Synthesis of the 3′-*O*-Vinylsilyl-Tethered Substrates. After protection of the 5′-hydroxyl of 2,2′-anhydrouridine (**13**)[13] by a monomethoxyltrityl (MMTr) group, the resulting **14** was heated with $(PhSe)_2/NaBH_4$ in EtOH−THF[14] to give the 2′-phenylseleno product **15** in a high yield. On the other hand, heating **13** with NaI/TsOH in acetone gave quantitatively 2′-deoxy-2′-iodouridine (**16**), which was treated with MMTrCl in pyridine to give **17**. A vinylsilyl group was introduced at the 3′-hydroxyl by treating **15** and **17** with dimethyl- or diphenylvinylchlorosilane, DMAP, and Et_3N in toluene to give **18a**, **18b**, **19a**, and **19b**, substrates for the radical reaction, as shown in Scheme 3.

Radical Reactions of the 3′-*O*-Vinylsilyl Ether Substrates under Reductive Conditions. The radical reactions of the 2′-*C*-phenylselenouridine derivatives **18a** and **18b**, bearing a dimethyl- or diphenylvinylsilyl group at the 3′-position, respectively, were performed under reductive conditions with Bu_3SnH (1.2 equiv) and AIBN (0.6 equiv) in refluxing benzene, and the products were purified after the Tamao oxidation.[12] The results are summarized in Table 1.

Heating **18a** in the presence of 1.2 equiv of Bu_3SnH and 0.6 equiv of AIBN in refluxing benzene (method A, kinetic conditions) gave the expected mixture of the 2′-deoxy-2′-*C*-[(*R*)-1-hydroxyethyl]uridine derivative **20R** and the corresponding *S*-diastereomer **20S** (Scheme 4), which were derived from the corresponding 5-*exo*-cyclized products, along with the directly reduced product **22** (entry 1, yield 77%). The ratio of the 2′-[(*R*)-1-hydroxyethyl]-product **20R** and the 2′-[(*S*)-1-hydroxyethyl]-product **20S** was about 1:2. After converting **20R** and **20S** into the corresponding acetonides **23R** and **23S**, the structures were confirmed by their H−H COSY and ^{13}C

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Table 1. Radical Reactions of 18a and 18b with Bu_3SnH/AIBN in Benzene

entry	substrate	method[a]	yield	products (ratio)[b]
1	**18a**	A	77	**20R**, **20S**, **22** (28:63:9)
2	**18a**	B	48	**20R**, **20S**, **21**, **22** (10:8:74:8)
3	**18b**	A	51	**20R**, **20S**, **21**, **22** (26:55:13:6)
4	**18b**	B	29[c]	**21**

[a] A: A mixture of the substrate, Bu_3SnH (1.2 equiv), and AIBN (0.6 equiv) in benzene was heated under reflux for 1 h. B: To a refluxing solution of the substrate in benzene was added a mixture of Bu_3SnH (1.2 equiv) and AIBN (0.6 equiv) in the same solvent slowly over 4 h. [b] After silica gel column chromatography, the products ratio was determined by the ^1H NMR spectrum. [c] Isolated as the silylated derivative **24**.

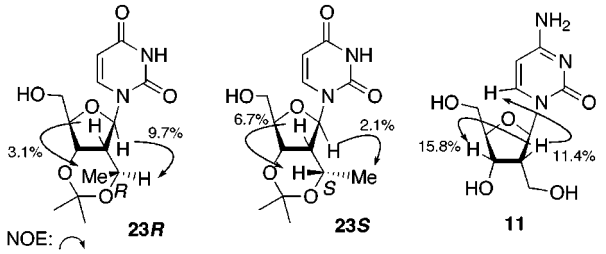
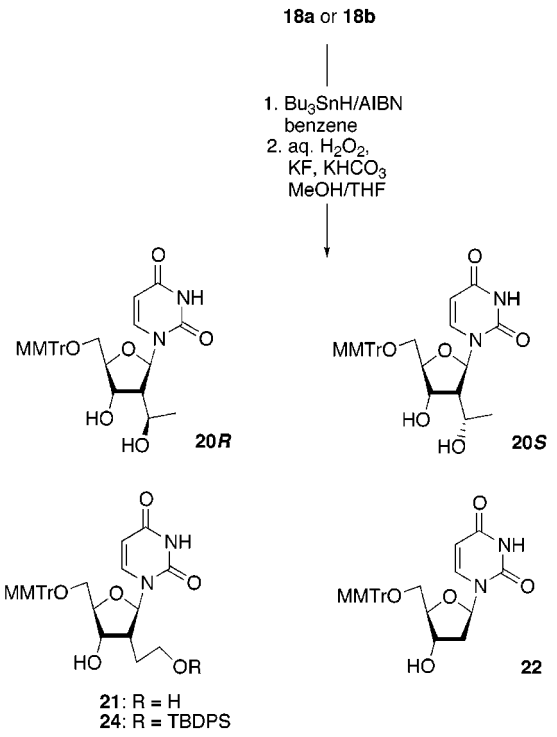


Figure 2.

Scheme 4



NMR spectra, and HRMS, and the stereochemistries were determined by NOE experiments, as shown in Figure 2. When the radical reaction of **18a** was carried out under thermodynamic conditions (method B), i.e., a mixture of Bu_3SnH and AIBN in benzene was added slowly over 4 h to a solution of **18a** in benzene under reflux, the desired 2′-deoxy-2′-*C*-(2-hydroxyethyl)uridine derivative **21**, formed from the corresponding 6-*endo*-cyclized product, was obtained as the major product, although the yield was unsatisfactory (entry 2, yield 48%, **20R**:**20S**:**21**:**22** = 10:8:74:8). The structure of compound **21** was confirmed after it was converted into the silylated derivative **24**. The reductive radical cyclization reactions

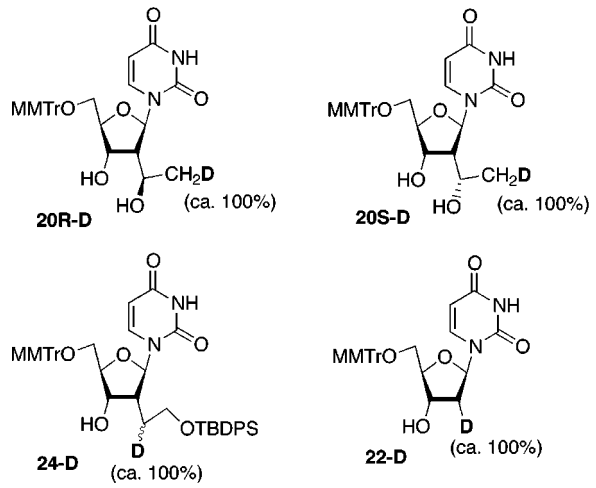


Figure 3.

Table 2. Synthesis of 2′α-*C*-vinyluridine Derivative 25 by the Radical Atom-Transfer Reaction[a]

entry	substrate	reagents (equiv)	solvent	temp, °C	yield, %[b]
1	**19a**	$(Bu_3Sn)_2$ (0.5), AIBN (0.6)	benzene	80	29
2	**19a**	$(Me_3Sn)_2$ (0.5), AIBN (0.6)	benzene	80	62
3	**19a**	$(Me_3Sn)_2$ (0.7), AIBN (0.6)	benzene	80	64
4	**19a**	$(Me_3Sn)_2$ (1.0), AIBN (0.6)	benzene	80	66
5	**19a**	$(Me_3Sn)_2$ (0.2), AIBN (0.6)	benzene	80	29
6	**19a**	$(Me_3Sn)_2$ (0.7), AIBN (0.6)	toluene	110	30
7	**19b**	$(Me_3Sn)_2$ (0.5), AIBN (0.6)	benzene	80	69

[a] A mixture of the substrate, $(Me_3Sn)_2$ or $(Bu_3Sn)_2$, and AIBN in benzene or toluene was heated under reflux until the substrate disappeared on TLC. [b] The product was isolated as the 3′-*O*-TBS derivative **25**.

of the diphenylvinylsilyl-tethered substrate **18b** under both kinetic (entry 3) and thermodynamic (entry 4) conditions gave results similar to those of the 3′-*O*-dimethylvinylsilyl substrate **18a**.

These results were undesirable, since the yield of the 2′-deoxy-2′-*C*-(2-hydroxyethyl)uridine derivative **21**, which would probably be suitable for the further transformation to synthesize the target compounds, was low. It may be that hydrogen abstraction competed with the desired radical cyclization−ring-enlargement reaction, resulting in the low yield of **21**.[15] Deuterium labeling experiments with Bu_3SnD instead of Bu_3SnH under conditions identical to those in entries 1 and 2 were performed, and the positions and rates of deuterium incorporation into the products based on their ^1H NMR spectra are shown in Figure 3.[16] These deuterium-labeling results suggested that the radical reaction proceeded via the pathway shown in Scheme 1 and that such hydrogen abstraction was unlikely to occur during the radical reaction course.

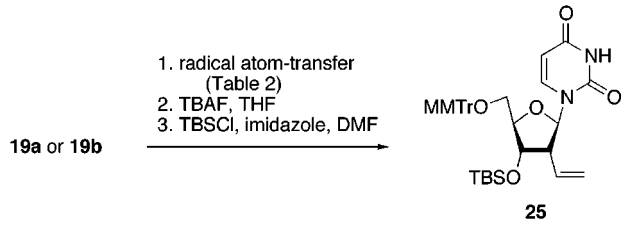
Radical Atom-Transfer Cyclization Reactions of the 3′-*O*-Vinylsilyl Ether Substrates. We investigated the straightforward introduction of a vinyl group at the 2′-position of 2′-deoxyuridine via a radical atom-transfer cyclization reaction[17] and subsequent fluoride ion treatment.[3e] The results are summarized in Table 2. First, the 2′-phenylseleno (**18a**) and the 2′-iodo substrates (**19a**)

(15) In radical cyclization reaction of D-glucose derivatives with a vinylsilyl tether, such a hydrogen abstraction by the 5-*exo*-cyclized radical occurred: see ref 11a.

(16) The configuration at the 2′-positono of **22-D** was determined by the NOE experiments.

(17) Curran, D. P.; Chang, C. *J. Org. Chem.* **1989**, *54*, 3140−3157.

Scheme 5



were irradiated with a high-pressure mercury lamp in the presence of $(Bu_3Sn)_2$ in benzene, which proved effective in our previous study,[3e] but the radical reaction was not initiated. However, when the 2′-iodo substrate **19a**[18] was heated under reflux with $(Bu_3Sn)_2$ (0.5 equiv) and AIBN (0.6 equiv) in benzene, the radical atom-transfer reaction proceeded, and the desired 2′-vinyl derivative was obtained as the 3′-*O*-silylated product **25** in 29% yield (Scheme 5), after treatment of the radical reaction product with TBAF in THF followed by TBSCl/imidazole in DMF (entry 1). Similar treatment of **19a** with $(Me_3Sn)_2$ (0.5, 0.7, or 1.0 equiv), instead of $(Bu_3Sn)_2$, successfully improved the yield of **25** (62−66%, entries 2−4). When the reaction was performed with 0.2 equiv of $(Me_3Sn)_2$, the yield decreased (entry 5). At 110 °C using toluene as a solvent, the yield was also lowered (entry 6). Treatment of the 3′-*O*-diphenylsilyl substrate **19b** under conditions identical to the entry 2 also gave **25** in good yield (entry 7). The 2′-stereochemistry of the radical reaction product **25** was confirmed by the NOE experiments of 2′-deoxy-2′-hydroxymethylcytidine (**11**), which was converted from **25** as described below, as shown in Figure 2.

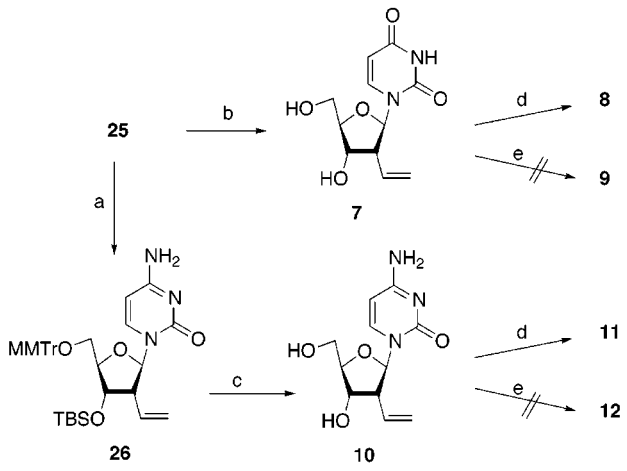
Thus, the radical atom-transfer reaction with a vinylsilyl group as a tether effectively occurred under thermal conditions with $(Me_3Sn)_2$ and AIBN, which is more convenient than the previous method by irradiation,[3e] especially for large-scale experiments.

Synthesis of the Target 2′-Deoxy-2′-Branched Pyrimidine Ribonucleosides. Conversion of the 2′-branched-2′-deoxyuridine derivatives prepared by the radical reaction into the target nucleosides was next investigated. We used 5′-*O*-MMTr-3′-*O*-TBS-2′-deoxy-2′-*C*-vinyluridine (**25**) for the synthesis of the targets, since it was obtained in rather good yield by the radical atom-transfer reaction and likely to be suitable for the desired functional group transformation at the 2′-position (Scheme 6).

The 2′-deoxy-2′-*C*-vinyluridine derivative **25** was treated with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl)/DMAP in MeCN followed by ammonolysis[19] to give the corresponding cytidine derivative **26** in 93% yield. Removal of the hydroxyl-protecting groups of **25** and **26** with HCl in MeOH afforded the 2′-deoxy-2′-*C*-vinyluridine (**7**) and -cytidine (**10**).

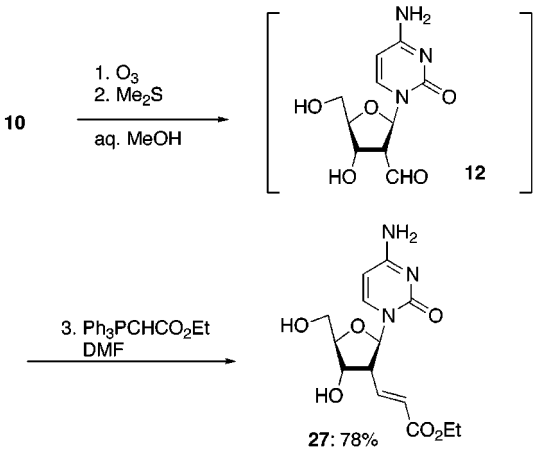
On the other hand, ozonolysis of the 2′-deoxy-2′-*C*-vinyluridine (**7**) and -cytidine (**10**) in aqueous MeOH at −78 °C, followed by reductive treatment with $NaBH_4$, successfully gave the desired 2′-deoxy-2′-*C*-hydroxymethyluridine (**8**) and -cytidine (**11**), respectively.

Scheme 6[a]



[a] Conditions: (a) TPSCl, DMAP, MeCN, then NH_4OH, 93%; (b) HCl, MeOH, 93%; (c) (1) HCl, MeOH, (2) Diaion PA 312 (HCO_3^-), 85%; (d) O_3, aq MeOH, then $NaBH_4$, **8** (62%), **11** (87%); (e) O_3, aq MeOH, then Me_2S.

Scheme 7



We next tried to synthesize the 2′-deoxy-2′-*C*-formyluridine (**9**) and -cytidine (**12**). Thus, **7** and **10** were successively treated with O_3 and Me_2S in aqueous MeOH, and the purification of the products by usual silica gel column chromatography and/or reverse-phase HPLC was attempted.[20] However, the desired 2′-*C*-formylnucleoside **9** or **12** was not obtained in pure form. When the reaction mixture of the ozonolysis of the 2′-deoxy-2′-*C*-vinylcytidine (**10**) was successively treated with Me_2S and a stable ylide $Ph_3P{=}CHCO_2Et$, the corresponding Wittig reaction product **27** was isolated in 78% yield as shown in Scheme 7. These experiments showed that although these 2′-*C*-formylnucleosides **9** and **12** could be produced under these conditions, they were too unstable to be isolated. As a result, it proved that 2′-*C*-formylnucleosides **9** and **12** could be not used as DNA strand-breaking agents.

Conclusion. The radical reactions of the 2′-deoxy-2′-phenylseleno- and the 2′-deoxy-2′-iodoridine derivatives **18** and **19**, bearing a vinylsilyl group as a temporary connecting tether at the 3-hydroxy group, were investigated. The 2′-deoxy-2′-*C*-(1-hydroxyethyl)uridine derivatives **20R** and **20S** and the 2′-deoxy-2′-*C*-vinyluridine

(18) It is recognized that alkyl iodides are more efficient as substrates for radical atom-transfer reactions than the corresponding phenylselenides or bromides: see ref 3e and references therein.

(19) Matsuda, A.; Okajima, H.; Masuda, A.; Kakefuda, A.; Yoshimura, Y.; Ueda, T. *Nucleosides Nucleotides* **1992**, *11*, 197−226.

(20) An ion peak at *m*/*z* 256 corresponding to the molecular-ion of 2′-deoxy-2′α-formylcytidine **12** was observed in the FABMS analysis of the reaction mixture.

derivative **25** were obtained via the reductive radical cyclization with Bu_3SnH and AIBN under kinetic conditions and via the radical atom-transfer cyclization with $(Me_3Sn)_2$ and AIBN, respectively. From **25**, 2′-deoxy-2′-*C*-vinyl- and 2′-deocy-2′-*C*-hydroxymethyluridines (**7** and **8**, respectively) and the corresponding 2′-deoxycytidine congeners (**10** and **11**, respectively), which were designed as potential antitumor and/or antiviral agents, were synthesized. However, the 2′-deoxy-2′-*C*-formyluridine (**9**) and -cytidine (**12**) were probably too unstable to be isolated, although it was clear that they had been produced since they could be transformed into further products.

Experimental Section

NMR chemical shifts are reported in ppm downfield from TMS (^{1}H and ^{13}C), and *J* values are given in hertz. Assignments of ^{1}H and ^{13}C NMR described for key compounds are based on COSY and/or DEPT spectra. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done with Merck silica gel 5715. Reactions were carried out under an argon atmosphere.

2,2′-Anhydro-1-[5-*O*-(4-methoxytrityl)-*β*-D-arabinofuranosyl]uracil (14). A mixture of 2,2′-anhydro-1-*β*-D-arabinofuranosyluracil[13] (**13**, 2.0 g, 8.8 mmol) and 4-methoxytrityl chloride (3.0 g, 9.7 mmol) in pyridine (88 mL) was stirred at room temperature for 94 h. After MeOH (2 mL) was added, the solution was evaporated, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 0−8% MeOH in $CHCl_3$) to give **14** (3.59 g, 82%) as white crystals: mp 161−163 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.93 (d, 1 H, J = 7.3), 7.29−6.82 (m, 14 H), 6.31 (d, 1 H, J = 5.3), 5.94 (d, 1 H, J = 4.6), 5.85 (d, 1 H, J = 7.3), 5.19 (d, 1 H, J = 5.3), 4.29 (m, 1 H), 4.21 (m, 1 H), 3.73 (s, 3 H), 2.95 (dd, 1 H, J = 4.0, 9.9), 2.80 (dd, 1 H, J = 7.3, 9.9); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 171.05, 159.43, 158.37, 144.19, 144.10, 136.88, 134.69, 129.96, 128.07, 127.95, 127.87, 127.07, 113.45, 109.06, 89.91, 88.61, 86.92, 85.85, 74.92, 63.10, 55.15; LRMS (FAB, positive) *m*/*z* 499 (MH^+). Anal. Calcd for $C_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62. Found: C, 69.74; H, 5.40; N, 5.57.

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-phenylseleno-*β*-D-ribofuranosyl]uracil (15). $NaBH_4$ (303 mg, 8.0 mmol) was slowly added to a solution of $(PhSe)_2$ (2.50 g, 8.0 mmol) in EtOH (15 mL) and THF (20 mL), and the mixture was heated under reflux for 30 min. To the mixture was added a suspension of **14** (1.00 g, 2.0 mmol) in EtOH (5 mL), and the whole was heated under reflux for 1 h. After cooling to room temperature, saturated aqueous NH_4Cl (40 mL) was added, and the resulting mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 33−86% AcOEt in hexane) to give **15** (1.18 g, 90%) as a pale yellow foam;^{1}H NMR (270 MHz, $CDCl_3$) δ 8.06 (br s, 1 H), 7.59 (d, 1 H, J = 7.9), 7.37−6.77 (m, 19 H), 6.38 (d, 1 H, J = 8.6), 5.20 (d, 1 H, J = 7.9), 4.48 (m, 1 H), 4.20 (m, 1 H), 3.91 (dd, 1 H, J = 8.6, 5.3), 3.80 (s, 3 H), 3.47 (dd. 1 H, J = 10.6, 2.6), 3.42 (dd. 1 H, J = 10.6, 2.0), 2.71 (d, 1 H, J = 3.3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 162.98, 158.78, 150.44, 143.67, 143.43, 139.71, 134.91, 134.39, 130.35, 129.51, 128.52, 128.28, 128.25, 128.00, 127.30, 126.83, 113.30, 102.62, 88.34, 87.51, 84.94, 73.23, 63.79, 55.20, 53.37; LRMS (FAB, positive) *m*/*z* 657 (MH^+). Anal. Calcd for $C_{35}H_{32}N_2O_6Se$: C, 64.12; H, 4.92; N, 4.27. Found: C, 64.14; H, 5.02; N, 4.27.

1-(2-Deoxy-2-iodo-*β*-D-ribofuranosyl)uracil (16). A mixture of $TsOH\cdot H_2O$ (285 mg, 1.5 mmol), NaI (223 mg, 1.5 mmol), and **13** (226 mg, 1.0 mmol) in acetone (10 mL) was stirred at 50 °C for 2.5 h. After cooling to room temperature, the resulting precipitates were filtered and washed with acetone, and the filtrate was evaporated. A small amount of acetone and saturated aqueous $Na_2S_2O_3$ (about 1 mL) was added and sonicated. After the color was faded, the solution was concentrated and purified by column chromatography (SiO_2, 33% MeOH in $CHCl_3$) to give **16** (349 mg, 98%) as a pale yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.41 (br s, 1 H), 7.85 (d, 1 H, J = 8.0), 6.20 (d, 1 H, J = 7.7), 5.97 (d, 1 H, J = 4.9), 5.69 (d, 1 H, J = 8.0), 5.18 (m, 1 H), 4.48 (m, 1 H), 3.94 (m, 1 H), 3.83 (m, 1 H), 3.58 (m, 2 H); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 162.99, 150.69, 139.84, 102.45, 89.23, 85.82, 70.37, 60.93, 32.55; HRMS (FAB, positive) calcd for $C_9H_{12}IN_2O_5$ 354.9791, found 354.9806 (MH^+).

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-iodo-*β*-D-ribofuranosyl]uracil (17). Compound **17** (5.62 g, 65%) was obtained as a pale yellow foam from **16** (4.92 g, 13.9 mmol) as described above for the synthesis of **14**, after purification by column chromatography (SiO_2, 0−2% MeOH in $CHCl_3$): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.17 (br s, 1 H), 7.76 (d, 1 H, J = 8.6), 7.38−6.85 (m, 14 H), 6.39 (d, 1 H, J = 5.9), 5.36 (d, 1 H, J = 8.6), 4.52 (m, 1 H, J = 5.9), 4.22 (ddd, 1 H, J = 4.0, 2.6, 2.0), 3.96 (m, 1 H), 3.81 (s, 3 H, OCH_3), 3.59 (dd, 1 H, J = 11.2, 2.6), 3.51 (dd, 1 H, J = 11.2, 2.0), 2.11 (d, 1 H, J = 4.6); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 162.84, 158.77, 150.08, 143.54, 143.33, 139.28, 134.28, 130.32, 128.25, 128.22, 128.06, 127.79, 127.75, 127.38, 113.35, 102.72, 90.36, 87.69, 83.58, 70.95, 62.41, 55.30, 33.86; HRMS (FAB, positive) calcd for $C_{29}H_{28}IN_2O_6$ 627.0992, found 627.1004 (MH^+)

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-phenylseleno-3-*O*-(dimethylvinylsilyl)-*β*-D-ribofuranosyl]uracil (18a). A mixture of **15** (1.97 g, 3.0 mmol), dimethylvinylchlorosilane (1.24 mL, 9.0 mmol), Et_3N (1.26 mL, 9.0 mmol), and DMAP (73 mg, 0.9 mmol) in toluene (30 mL) was stirred at room temperature for 1 h. The mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 25−50% AcOEt in hexane) to give **18a** (1.83 g, 83%) as a white foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.77 (br s, 1 H), 7.57−6.82 (m, 20 H), 6.52 (d, 1 H, J = 9.2), 6.09 (d, 1 H, J = 17.8), 6.06 (d, 1 H, J = 6.6), 5.79 (dd, 1 H, J = 17.8, 6.6), 5.05 (d, 1 H, J = 8.6), 4.62 (d, 1 H, J = 5.3), 4.04 (m, 1 H), 3.81 (s, 3 H), 3.78 (m, 1 H), 3.38 (dd, 1 H, J = 13.2, 2.6), 3.34 (dd, 1 H, J = 13.2, 2.0), 0.25 (s, 3 H), 0.20 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.55, 159.03, 150.15, 143.99, 143.73, 139.86, 136.84, 135.37, 134.73, 130.57, 129.50, 128.47, 128.30, 127.59, 127.32, 113.59, 102.61, 90.55, 87.78, 86.38, 75.47, 63.82, 55.60, 51.68, −1.25, −1.55; LRMS (FAB, positive) *m*/*z* 741 (MH^+). Anal. Calcd for $C_{39}H_{40}N_2O_6SeSi$: C, 63.32; H, 5.45; N, 3.79. Found: C, 63.15; H, 5.48; N, 3.69.

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-phenylseleno-3-*O*-(diphenylvinylsilyl)-*β*-D-ribofuranosyl]uracil (18b). Compound **18b** (901 mg, 98%) was obtained as a white foam from **15** (695 mg, 1.1 mmol) as described above for the synthesis of **18a** with diphenylvinylchlorosilane (0.59 mL, 2.7 mmol) instead of dimethylvinylchlorosilane, after purified by column chromatography (SiO_2, 33% AcOEt in hexane): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.74 (br s, 1 H), 7.67−6.79 (m, 30 H), 6.66 (d, 1 H, J = 8.6), 6.49 (dd, 1 H, J = 19.8, 14.5), 6.33 (dd, 1 H, J = 14.5, 4.0), 5.98 (dd, 1 H, J = 19.8, 4.0), 4.96 (d, 1 H, J = 8.6), 4.87 (m, 1 H), 4.07 (m, 1 H), 3.85 (m, 1 H), 3.82 (s, 3 H), 3.19 (dd, 1 H, J = 10.6, 2.6), 3.01 (dd, 1 H, J = 10.6, 2.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.65, 143.61, 143.28, 139.62, 138.36, 135.11, 135.09, 135.05, 134.24, 132.86, 132.68, 132.65, 130.38, 130.23, 129.19, 128.15, 127.99, 127.94, 127.22, 127.20, 127.06, 113.23, 102.22, 90.31, 87.45, 85.65, 77.21, 76.18, 63.42, 55.27, 51.46; LRMS (FAB, positive) *m*/*z* 865 (MH^+). Anal. Calcd for $C_{49}H_{44}N_2O_6SeSi$: C, 68.12; H, 5.13; N, 3.24. Found: C, 68.17; H, 5.13; N, 3.23.

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-iodo-3-*O*-(dimethylvinylsilyl)-*β*-D-ribofuranosyl]uracil (19a). Compound **19a** (286 mg, 84%) was obtained as a white foam from **17** (301 mg, 0.48 mmol) as described above for the synthesis of **18a**, after purified by column chromatography (SiO_2, 33% AcOEt in hexane): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.16 (br s, 1 H), 7.82 (d, 1 H, J = 8.6), 7.37−6.84 (m, 14 H), 6.38 (d, 1 H, J = 5.9), 6.11 (d, 1 H, J = 15.2), 6.04 (d, 1 H, J = 8.6), 5.78 (dd, 1 H, J = 15.2, 8.6), 5.33 (d, 1 H, J = 8.6), 4.35 (m, 1 H), 4.12 (m, 1 H), 3.88 (m, 1 H), 3.81 (s, 3 H), 3.56 (dd, 1 H, J = 11.2, 3.3), 3.39 (dd, 1 H, J = 2.0, 11.2), 0.23 (s, 3 H), 0.18 (s, 3 H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 162.67, 158.77, 149.98, 143.43, 143.24, 139.28, 136.27, 134.70, 134.26, 130.33, 128.29, 128.00, 127.36, 113.27, 102.58, 91.11, 87.54, 84.61, 77.20, 70.99, 61.76, 55.29, 32.48, −1.60, −1.68; LRMS (FAB, positive) *m*/*z* 711 (MH^+). Anal. Calcd for $C_{33}H_{35}IN_2O_6Si$: C, 55.78; H, 4.96; N, 3.94. Found: C, 55.64; H, 4.86; N, 3.87.

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-iodo-3-*O*-(diphenylvinylsilyl)-*β*-D-ribofuranosyl]uracil (19b). Compound **19b** (2.19 g, 88%) was obtained as a pale yellow foam from **17** (1.88 g, 3.0 mmol) as described above for the synthesis of **18a** with diphenylvinylchlorosilane (1.66 mL, 7.5 mmol) instead of dimethylvinylchlorosilane, after purification by column chromatography (SiO_2, 20−33% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1 H), 7.70 (d, 1 H, J = 8.1) 7.62−6.80 (m, 24 H), 6.46 (d, 1 H, J = 5.6), 6.40 (dd, 1 H, J = 14.9, 20.2), 6.25 (dd, 1 H, J = 3.7, 14.9), 5.89 (dd, 1 H, J = 3.7, 20.2), 5.19 (d, 1 H, J = 8.1), 4.28 (m, 1 H, J = 5.6), 4.21 (m, 1 H), 4.12 (m, 1 H), 3.80 (s, 3 H), 3.45 (m, 1 H), 3.24 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.29, 158.43, 149.63, 143.11, 142.88, 138.94, 138.38, 134.86, 133.88, 132.27, 132.23, 130.22, 130.18, 130.12, 128.11, 128.06, 127.74, 127.72, 127.10, 127.06, 112.99, 102.27, 90.85, 87.42, 84.17, 71.74, 61.76, 55.13, 31.57; HRMS (FAB, positive) calcd for $C_{43}H_{40}IN_2O_6Si$ 835.1701, found 835.1686 (MH^+)

Radical Reaction of 18a and 18b under Reductive Conditions. Method A. Entry 1: A mixture of **18a** (148 mg, 0.20 mmol), Bu_3SnH (65 μL, 0.24 mmol), AIBN (20 mg, 0.12 mmol) in benzene (2 mL) was heated under reflux for 1 h, and then the solvent was evaporated. The residue was partitioned between CH_3CN and hexane, and the CH_3CN layer was evaporated. A mixture of the residue, $KHCO_3$ (20 mg, 0.20 mmol), KF (23 mg, 0.24 mmol), and 30% aqueous H_2O_2 (227 μL, 2.0 mmol) in MeOH/THF (1:1, 5 mL) was stirred at room temperature for 19 h. Saturated aqueous $Na_2S_2O_3$ was added, and the resulting mixture was filtered through Celite. The filtrate was evaporated, and the residue was partitioned between $CHCl_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (SiO_2, 50−75% AcOEt in hexane) to give a mixture of the products. The mixture was further purified by flash column chromatography (SiO_2, 2−4% MeOH in $CHCl_3$) to give a mixture of **20R** and **22** (31 mg) as a white solid and **20S** (52 mg, 48%) as a white solid. **(1-[5-*O*-(4-methoxytrityl)-2-deoxy-2-(*S*-1-hydroxyethyl)-*β*-D-*ribo*-pentofuranosyl]uracil (20S)**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (br s, 1 H), 7.49 (d, 1 H, J = 8.3), 7.39−6.90 (m, 14 H), 6.16 (d, 1 H, J = 8.3), 5.39 (d, 1 H, J = 8.3), 5.31 (d, 1 H, J = 5.1), 4.41 (d, 1 H, J = 5.1), 4.10 (m, 1 H), 3.90 (m, 2 H), 3.74 (s, 3 H), 3.22 (dd, 1 H, J = 4.9, 10.3), 3.11 (dd, 1 H, J = 3.9, 10.3), 2.10 (m, 1 H), 1.12 (d, 3 H, J = 6.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.90, 158.10, 150.32, 144.12, 143.90, 141.18, 134.64, 130.04, 127.91, 126.91, 113.26, 101.34, 86.53, 86.13, 84.86, 71.83, 64.22, 63.71, 55.20, 53.00, 22.95; HRMS (FAB, positive) calcd for $C_{31}H_{33}N_2O_7$ 545.2288, found 545.2286 (MH^+). Entry 3: using **18b** (173 mg, 0.20 mmol) as a substrate, the experiment was carried out as described above for the entry 1 to give a mixture of **20R** and **22** (17 mg) as a white solid and another mixture of **20S** and **21** (38 mg) as a white solid. **Method B.** Entry 2: To a refluxing solution of **18a** (148 mg, 0.20 mmol) in benzene (10 mL) was added a mixture of Bu_3SnH (65 μL, 0.20 mmol) and AIBN (20 mg, 0.12 mmol) in benzene (10 mL) slowly over 4 h, and then the resulting mixture was evaporated. The residue was partitioned between CH_3CN and hexane, and the CH_3CN layer was evaporated. The residue was treated under Tamao oxidation conditions and purified by the procedure as described above in the Method A to give a mixture of **20R** and **22** (10 mg) as a white solid and another mixture of **20S** and **21** (43 mg) as a white solid. Entry 4: using **18b** (173 mg, 0.20 mmol) as a substrate, the experiment was carried out as described above for the entry 2 to give **21**, which was further purified after silylation. A solution of the solid obtained, TBDPSCl (41 μL, 0.16 mmol), and imidazole (21 mg, 0.31 mmol) in DMF (2 mL) were stirred at room temperature for 20 h. After addition of MeOH, the mixture was evaporated, the residue was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 0−2% MeOH in $CHCl_3$) to give **1-[5-*O*-(4-methoxytrityl)-2-deoxy-2-[2-(*tert*-butyldiphenylsilyloxy)-ethyl]-*β*-D-*ribo*-pentofuranosyl]uracil (24)** (45 mg, 29% overall yield): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.03 (br s, 1 H, NH-3), 7.73−6.82 (m, 25 H, MMTr, $SiPh_2$, H-6), 6.10 (d, 1 H, H-1′, J = 8.6), 5.35 (dd, 1 H, H-5, J = 2.0, 8.6), 4.77 (m, 1 H, H-3′), 4.23 (m, 1 H, H-4′), 3.79 (s, 3 H, MMTr-OCH_3), 3.64 (m, 2 H, $-CH_2CH_2$OTBDPS), 3.52−3.37 (m, 3 H, H-5′a,b, OH-3′), 2.32 (m, 1 H, H-2′), 2.18 (m, 1 H, $-CH_2CH_2$OTBDPS), 1.64 (m, 1 H, $-CH_2CH_2$OTBDPS), 1.08 (s, 9 H, *tert*-butyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.65, 158.35, 150.21, 143.67, 143.31, 139.84, 135.07, 135.04, 134.41, 131.76, 131.53, 129.99, 129.79, 129.74, 127.94, 127.91, 127.71, 127.67, 126.91, 113.03, 102.36, 88.05, 86.97, 85.04, 73.45, 64.10, 63.64, 55.09, 50.65, 26.65, 26.39, 18.84; HRMS (FAB, positive) calcd for $C_{47}H_{51}N_2O_7Si$ 783.3466, found 783.3450 (MH^+).

Acetonide 23R. A solution of the mixture of **20R** and **22** (26 mg, 0.048 mmol) obtained in the entry 1 (Table 1) in HCl/MeOH (2.6% w/v, 500 μL) was stirred at room temperature for 5 min, and then the mixture was evaporated. A solution of the residue, $TsOH\cdot H_2O$ (1.2 mg, 0.006 mmol), and 2,2-dimethoxypropane (7.9 μL, 0.064 mmol) in acetone (500 μL) was stirred at room temperature for 24 h. After neutralization with 25% NH_4OH, the resulting mixture was evaporated, and the residue was purified by column chromatography (SiO_2, 5−15% MeOH in $CHCl_3$) to give **23R** (10 mg, 67%) as a white solid and 2′-deoxyuridine (3 mg). **23R**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (d, 1 H, H-6, $J_{6,5}$ = 8.3), 6.11 (d, 1 H, H-1′, $J_{1',2'}$ = 7.6), 5.74 (d, 1 H, H-5, $J_{5,6}$ = 8.3), 4.39 (m, 1 H, H-3′), 4.04 (m, 1 H, H-4′, $J_{4',5'a}$ = 3.4, $J_{4',5'b}$ = 3.2), 3.95 (m, 1 H, CH-2′, $J_{CH-2',2'}$ = 15.6, $J_{CH-2',CH3'}$ = 6.4), 3.75 (ddd, 2 H, H-5′a,b, $J_{5'a,4'}$ = 3.4, $J_{5'b,4'}$ = 3.2, $J_{5a',\ 5b'}$ = 12.0), 2.27 (m, 1 H, H-2′), 1.37 (s, 3 H, isop-CH_3), 1.36 (s, 3 H, isop-CH_3), 1.12 (d, 3 H, CH_3, $J_{CH3,CH-2'}$ = 6.4); ^{13}C NMR (100 MHz, CD_3OD) δ 165.36, 151.83, 142.14, 103.28, 101.42, 89.04, 85.88, 73.42, 66.63, 63.03, 56.00, 24.97, 24.39, 20.91; HRMS (FAB, positive) calcd for $C_{14}H_{21}N_2O_6$ 313.1400, found 313.1384 (MH^+); NOE (400 MHz, CD_3OD): irradiated H-1′, observed 2′-C*H*(O-)CH_3 (9.7%); irradiated H-2′, observed 2′-CH(O-)C*H*$_3$ (3.1%).

Acetonide 23S. Compound **23S** (19 mg, 94%) was obtained as a white solid from **20S** (36 mg, 0.066 mmol) as described above for the synthesis of **23R** after purified by column chromatography (SiO_2, 5% MeOH in $CHCl_3$): ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, 1 H, H-6, $J_{6,5}$ = 8.3), 6.48 (d, 1 H, H-1′, $J_{1',2'}$ = 9.3), 5.74 (d, 1 H, H-5, $J_{5,6}$ = 8.3), 4.62 (m, 1 H, H-3′), 4.37 (m, 1 H, H-4′), 3.93 (m, 1 H, CH-2′), 3.71 (m, 2 H, H-5′a,b), 2.43 (m, 1 H, H-2′, $J_{2',1'}$ = 9.3), 1.50 (s, 3 H, isop-CH_3), 1.39 (s, 3 H, isop-CH_3), 1.03 (d, 3 H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 165.44, 151.88, 142.71, 103.40, 99.63, 86.49, 84.60, 75.18, 63.64, 63.30, 45.90, 30.12, 19.50, 18.54; HRMS (FAB, positive) calcd for $C_{14}H_{21}N_2O_6$ 313.1400, found 313.1387 (MH^+); NOE (400 MHz, CD_3OD): irradiated H-1′, observed 2′-CH(O-)C*H*$_3$ (2.1%); irradiated H-2′, observed 2′-C*H*(O-)CH_3 (6.7%).

Deuterium-Labeling Experiment of 18a with Bu_3SnD under Kinetic Conditions. The experiment was carried out by the procedure identical to the entry 1 in Table 1 described above, with Bu_3SnD (65 μL, 0.24 mmol) instead of Bu_3SnH. Compounds **20R-D** (8 mg, 7%), **20S-D** (23 mg, 21%), and **22D** (3 mg, 3%) were obtained from **18a** (148 mg, 0.20 mmol) in pure forms after HPLC purification (YMC Pack D-ODS-5-A, 20 × 250 mm; 90% aqueous MeOH, 9.9 mL/min; room temperature; 260 nm). **20R-D**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 7.63 (d, 1 H, J = 8.1) 7.38−6.84 (m, 14 H), 6.36 (d, 1 H, J = 9.0), 5.47 (d, 1 H, J = 8.1), 4.67 (m, 1 H), 4.29 (br s, 1 H), 4.20 (m, 2 H), 3.80 (s, 3 H), 3.48−3.38 (m, 3 H), 2.24 (m, 1 H, J = 9.0), 1.40 (d, 2 H, J = 6.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.32, 158.41, 150.65, 143.38, 143.15, 139.41, 134.19, 130.01, 127.94, 127.72, 127.00, 113.04, 102.76, 87.13, 86.52, 85.48, 73.91, 64.44, 63.75, 55.13, 54.65, 21.24 (t, J = 19.2); HRMS (FAB, positive) calcd for $C_{31}H_{31}DN_2O_7Na$ 568.2170, found 568.2180 (MNa^+). **20S-D**: ^{1}H NMR (400 MHz, DMSO) δ 11.21 (br s, 1 H), 7.49 (d, 1 H, J = 8.1), 7.39−6.90 (m, 14 H),

6.16 (d, 1 H, J = 8.5), 5.39 (d, 1 H J = 8.1), 5.31 (d, 1 H, J = 5.4), 4.40 (d, 1 H, J = 4.9), 4.10 (m, 1 H), 3.92 (m, 2 H), 3.74 (s, 3 H), 3.22 (dd, 1 H, J = 5.1, 10.3) 3.12 (dd, 1 H, J = 3.7, 10.3), 2.10 (m, 1 H), 1.10 (d, 2 H, J = 6.3); ^{13}C NMR (100M Hz, $CDCl_3$) δ 162.91, 158.11, 150.33, 144.13, 143.90, 141.18, 134.65, 130.04, 127.92, 126.92, 113.26, 101.35, 86.54, 86.14, 84.88, 71.83, 64.24, 63.68, 55.21, 52.99, 22.66 (t, J = 19.2); HRMS (FAB, positive) calcd for $C_{31}H_{32}DN_2O_7$ 546.2350, found 546.2352 (MH^+). **22-D**:^{1}H NMR (270 MHz, $CDCl_3$) δ 8.13 (br s, 1 H, NH-3), 7.78 (d, 1 H, H-6, J = 8.1) 7.40−6.83 (m, 14 H, MMTr), 6.30 (d, 1 H, H-1′, J = 6.1), 5.39 (d, 1 H, H-5, J = 8.1), 4.56 (m, 1 H, H-3′), 4.00 (m, 1 H, H-4′), 3.81 (s, 3 H, OMe), 3.50 (dd, 1 H, H-5′a J = 3.2, 10.7), 3.45 (dd, 1 H, H-5′b, J = 3.2, 10.7), 2.26 (m, 1 H, H-2′, J = 6.1), 1.86 (br s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.23, 158.42, 149.49, 143.41, 143.24, 139.72, 134.27, 130.05, 128.00, 127.72, 127.02, 113.02, 101.91, 87.17, 85.58, 84.62, 71.14, 62.66, 55.13; HRMS (FAB, positive) calcd for $C_{29}H_{28}DN_2O_6$ 502.2089, found 502.2061 (MH^+); NOE (400 MHz, CD_3OD): irradiated H-2′, observed H-3′ (6.5%) H-6 (5.0%).

Deuterium-Labeling Experiment of 18a with Bu_3SnD under Thermodynamic Conditions. The radical reaction and subsequent Tamao oxidation were carried out by the procedure identical to the entry 2 in Table 1, with Bu_3SnD (65 μL, 0.24 mmol) instead of Bu_3SnH to give a mixture of the reaction products as a solid. A solution of the solid obtained, TBDPSCl (36 μL, 0.18 mmol) and imidazole (24 mg, 0.36 mmol) in DMF (2 mL) was stirred at room temperature for 24 h. After addition of MeOH, the mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 0−2% MeOH in $CHCl_3$) to give crude **24-D** (52 mg), which was further purified by HPLC (YMC Pack D-ODS-5-A, 20 × 250 mm; 90% aqueous MeOH, 9.9 mL/min; room temperature; 260 nm) to give **24-D** in a pure form (30 mg, 19% from **18a**) as a solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.45 (br s, 1 H), 7.69−6.81 (m, 25 H), 6.10 (d, 1 H, J = 8.6), 5.36 (d, 1 H, J = 7.9), 4.76 (m, 1 H), 4.23 (m, 1 H), 3.79 (s, 3 H), 3.76 (m, 2 H), 3.52−3.37 (m, 3 H), 2.31 (m, 1 H), 2.16 (m, 0.6 H), 1.63 (m, 0.4 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.66, 158.36, 150.21, 143.68, 143.31, 139.85, 135.08, 135.04, 134.41, 131.77, 131.54, 130.00, 129.79, 129.75, 127.94, 127.92, 127.72, 127.68, 126.91, 113.04, 102.37, 88.05, 86.98, 85.05, 73.46, 64.10, 63.60, 55.10, 50.59, 26.66, 26.40, 18.85; HRMS (FAB, positive) calcd for $C_{47}H_{49}DN_2O_7SiNa$ 806.3348, found 806.3327 (MNa^+).

General Procedure for Radical Atom-Transfer Reaction of 19a or 19b for the Synthesis of 1-[5-*O*-(4-methoxytrityl)-2-deoxy-2-vinyl-3-*O*-(*tert*-butyldimethylsilyl)-β-D-*ribo*-pentofuranosyl]uracil (25). A mixture of **19a** or **19b** (0.20 mmol), $(Me_3Sn)_2$ (29 μL, 0.14 mmol), and AIBN (20 mg, 0.12 mmol) in benzene (2 mL) was heated under reflux for 5 h, and then the solvent was evaporated. A mixture of the residue and TBAF (400 μL, 0.4 mmol) in THF (2 mL) was stirred at room temperature for 1 h. The mixture was evaporated, and the residue was purified by column chromatography (SiO_2, 50−100% AcOEt in Et_2O) to give the corresponding desilylated compound as a solid. A mixture of the solid, TBSCl (90 mg, 0.60 mmol), Et_3N (84 μL, 0.60 mmol), and DMAP (5 mg, 0.04 mmol) in toluene (2 mL) was stirred at room temperature for 20 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 25−33% AcOEt in hexane) to give **25** as a white foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.99 (br s, 1 H, NH-3), 7.70 (d, 1 H, H-6, $J_{6,5}$ = 8.6) 7.42−6.84 (m, 14 H, MMTr), 6.22 (d, 1 H, H-1′, $J_{1',2'}$ = 8.6), 5.90 (m, 1 H, -CH=CH_2), 5.43 (d, 1 H, H-5, $J_{5,6}$ = 8.6), 5.23 (d, 1 H, −CH=CH_2, J = 10.6), 5.16 (d, 1 H, −CH=CH_2, J = 17.2), 4.33 (m, 1 H, H-3′), 4.05 (m, 1 H, H-4′), 3.81 (s, 3 H, OCH_3), 3.44 (dd, 1 H, H-5′a, J = 10.6, 3.3), 3.38 (dd, 1 H, H-5′b, J = 10.6, 2.6), 2.90 (m, 1 H, H-2′), 0.86 (s, 9 H, *tert*-butyl), 0.03 (s, 3 H, Si−CH_3), −0.03 (s, 3 H, Si−CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.70, 158.71, 150.20, 143.68, 143.48, 139.99, 134.50, 131.04, 130.28, 128.23, 127.97, 127.26, 120.05, 113.25, 102.51, 87.43, 87.30, 86.63, 75.70, 63.51, 55.28, 54.94, 30.35, 25.77, 18.16, 0.08, −4.65; LRMS (EI) m/z 640 (M^+). Anal. Calcd for $C_{37}H_{44}N_2O_6Si$: C, 69.35; H, 6.92; N, 4.37. Found: C, 69.37; H, 6.95; N, 4.20.

1-[5-*O*-(4-Methoxytrityl)-2-deoxy-2-vinyl-3-*O*-(*tert*-butyldimethylsilyl)-β-D-*ribo*-pentofuranosyl]cytosine (26). A mixture of **25** (4.46 g, 7.0 mmol), TPSCl (4.22 g, 14 mmol), DMAP (1.70 g, 14 mmol), and Et_3N (1.94 mL, 14 mmol) in CH_3CN (70 mL) was stirred at room temperature for 4 h. Aqueous NH_4OH (25%, 70 mL) was added, and the resulting mixture was stirred at the same temperature for 2 h. The mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 2−5% MeOH in $CHCl_3$) to give **26** (4.14 g, 93%) as a pale yellow foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.86 (d, 1 H, H-6, J = 7.3) 7.44−6.83 (m, 14 H, MMTr), 6.35 (d, 1 H, J = 7.3), 5.95 (ddd, 1 H, J = 17.2, 10.6, 8.6), 5.41 (d, 1 H, J = 7.3), 5.20 (d, 1 H, J = 10.6), 5.17 (d, 1 H, J = 17.2), 4.33 (m, 1 H), 4.03 (m, 1 H), 3.80 (s, 3 H), 3.49 (dd, 1 H, J = 3.0, 11.2), 3.31 (dd, 1 H, J = 3.0, 11.2), 2.86 (m, 1 H, J = 7.3), 0.82 (s, 9 H), −0.01 (s, 3 H), −0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.18, 158.62, 155.80, 143.80, 143.71, 141.27, 134.80, 131.73, 130.32, 128.34, 127.88, 127.12, 119.35, 113.17, 94.30, 88.15, 87.11, 85.56, 74.81, 63.15, 55.28, 55.16, 25.75, 18.11, 0.08, −4.60, −4.73; LRMS (EI) m/z 639 (M^+). Anal. Calcd for $C_{37}H_{45}N_3O_5Si$: C, 69.45; H, 7.09; N, 6.57. Found: C, 69.23; H, 6.97; N, 6.46.

1-(2-Deoxy-2-*C*-vinyl-β-D-*ribo*-pentofuranosyl)uracil (7). A solution of **25** (417 mg, 0.65 mmol) in HCl/MeOH (2.6% w/v, 10 mL) was stirred at room temperature for 5 h, and then the mixture was evaporated. After coevaporation with MeOH several times, the residue was purified by column chromatography (SiO_2, 2−12% MeOH in $CHCl_3$) to give **7** (153 mg, 93%) as a white solid: ^{1}H NMR (400 MHz, D_2O) δ 7.81 (d, 1 H, H-6, J = 8.1), 6.15 (d, 1 H, H-1′, J = 9.0), 5.86 (d, 1 H, H-5, J = 8.1), 5.84 (m, 1 H, −CH=CH_2), 5.24 (d, 1 H, −CH=CH_2, J = 10.5), 5.22 (d, 1 H, −CH=CH_2, J = 17.6), 4.31 (m, 1 H, H-3′), 4.08 (m, 1 H, H-4′), 3.76 (dd, 1 H, H-5′a, J = 12.7, 3.9), 3.72 (dd, 1 H, H-5′b, J = 12.7, 5.1), 3.06 (m, 1 H, H-2′, J = 9.0); ^{13}C NMR (100 MHz, D_2O) δ 166.30, 152.22, 141.95, 130.08, 121.27, 103.22, 87.52, 86.92, 73.94, 62.09, 52.76; HRMS (EI) calcd for $C_{11}H_{14}N_2O_5$ 254.0902, found 254.0901 (M^+).

1-(2-Deoxy-2-*C*-vinyl-β-D-*ribo*-pentofuranosyl)cytosine (10). A solution of **26** (1.0 g, 1.6 mmol) in HCl/MeOH (2.6% w/v, 15 mL) was stirred at room temperature for 20 h, and then the mixture was evaporated. After coevaporation with MeOH several times, the residue was partitioned between H_2O and $CHCl_3$. The aqueous layer was evaporated and applied to a column of Diaion PA-312 resin (HCO_3^- form, packed with water). The column was eluted with water, and the appropriate fractions were evaporated to give **10** (336 mg, 85%) as a white solid: mp 239−240 °C (MeOH−EtOH); ^{1}H NMR (270 MHz, CD_3OD) δ 7.94 (d, 1 H, H-6, J = 7.9), 6.28 (d, 1 H, H-1′, J = 9.2), 5.97 (ddd, 1 H, −CH=CH_2, J = 2.0, 17.8, 10.6), 5.91 (d, 1 H, H-5, J = 7.9), 5.16 (d, 1 H, −CH=CH_2, J = 10.6), 5.14 (d, 1 H, −CH=CH_2, J = 17.8), 4.26 (dd, 1 H, H-3′, J = 5.3, 1.3), 4.00 (m, 1 H, H-4′, J = 1.3), 3.74 (m, 2 H, H-5′a, H-5′b), 2.93 (m, 1 H, H-2′); ^{13}C NMR (125 MHz, CD_3OD) δ 168.16, 159.34, 143.87, 133.53, 120.74, 97.36, 90.13, 89.27, 76.37, 64.23, 56.33; LRMS (FAB, positive) m/z 254 (MH^+). Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 51.99; H, 5.90; N, 16.61.

1-(2-Deoxy-2-*C*-hydroxymethyl-β-D-*ribo*-pentofuranosyl)uracil (8). Ozone-containing oxygen was bubbled into a solution of **7** (51 mg, 0.20 mmol) in MeOH/H_2O (3:1, 2 mL) at −78 °C for 5 min, where disappearance of the starting material was checked by HPLC (J'sphere ODS M80, 4 × 250 mm, YMC Co., Ltd.; 2% aqueous MeCN, 1.0 mL/min; room temperature, 260 nm). After addition of $NaBH_4$ (15 mg, 0.40 mmol) at the same temperature, the resulting solution was stirred at room temperature for 2 h. The mixture was neutralized with saturated aqueous NH_4Cl, evaporated, and purified by preparative HPLC (YMC Pack D-ODS-5-A, 20 × 250 mm; 15% aqueous CH_3CN, 9.9 mL/min; room temperature; 260 nm) to

give **8** (32 mg, 62%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, 1 H, H-6, $J_{6,5} = 7.9$), 6.13 (d, 1 H, H-1′, $J_{1',2'} = 7.9$), 5.72 (d, 1 H, H-5, $J_{5,6} = 7.9$), 4.41 (dd, 1 H, H-3′, $J_{3',2'} = 5.9$, $J_{3',4'} = 2.6$), 3.98 (m, 1 H, H-4′), 3.94−3.68 (m, 4 H, CH_2-2′, H-5′a,b), 2.49 (m, 1 H, H-2′); ^{13}C NMR (100 MHz, D_2O) δ 165.80, 152.20, 142.56, 102.82, 88.90, 88.47, 73.32, 63.22, 58.83, 52.18; HRMS (FAB, positive) calcd for 259.0930, found 259.0937 (MH^+).

1-(2-Deoxy-2-*C*-hydroxymethyl-*β*-D-*ribo*-pentofuranosyl)cytosine (11). Compound **11** (47 mg, 87%) was obtained as a white solid from **10** (51 mg, 0.20 mmol) as described above for the synthesis of **8**, after purification by preparative HPLC (YMC Pack D-ODS-5-A, 20 × 250 mm; 15% aqueous CH_3CN, 9.9 mL/min; room temperature; 270 nm): mp 221−222 °C (MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (d, 1 H, H-6, J = 7.6), 6.03 (d, 1 H, H-1′, J = 7.8), 5.81 (d, 1 H, H-5, J = 7.6), 4.30 (dd, 1 H, H-3′, J = 6.3, 2.9), 3.89 (ddd, 1 H, H-4′, J = 3.4, 3.2, 2.9), 3.85−3.60 (m, 4 H, CH_2-2′, H-5′a, H-5′b), 2.32 (m, 1 H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.25, 155.33, 141.26, 94.31, 87.05, 86.59, 71.29, 61.91, 56.67; LRMS (FAB, positive) m/z 258 (MH^+); NOE (400 MHz, CD_3OD): irradiated H-2′, observed H-3′ (15.8%) H-6 (11.4%). Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.29; H, 5.96; N, 16.33.

1-(2-Deoxy-2-*C*-*E*-ethoxycarbonylvinyl-*β*-D-*ribo*-pentofuranosyl)cytosine (27). Ozone-containing oxygen was bubbled into a solution of **10** (51 mg, 0.20 mmol) in MeOH/H_2O (3:1, 2 mL) at −78 °C for 5min. After addition of Me_2S (59 μL, 0.40 mmol) at the same temperature, the resulting solution was stirred at room temperature for 2 h. The mixture was evaporated, and the residue was coevaporated with benzene. A mixture of the residue and Ph_3PCHCO_2Et (139 mg, 0.40 mmol) in DMF (2 mL) was stirred for 16 h, and then solvent was evaporated. The residue was purified by preparative HPLC (YMC Pack D-ODS-5-A, 20 × 250 mm; 15% aqueous CH_3CN, 9.9 mL/min; room temperature; 270 nm) to give **27** (51 mg, 78%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, 1 H, J = 7.6), 7.08 (dd, 1 H, J = 8.6, 15.9), 6.34 (d, 1 H, J = 8.5), 5.95−5.91 (m, 2 H), 4.35 (dd, 1 H, J = 5.6), 4.15 (q, 2 H, J = 7.1), 4.04 (m, 1 H), 3.78 (dd, 1 H, J = 12.0, 3.4), 3.74 (dd, 1 H, J = 12.0, 3.4), 3.13 (m, 1 H, J = 8.5, 8.6 Hz), 1.25 (t, 3 H, J = 7.1); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.25, 165.06, 155.14, 143.06, 140.99, 123.58, 94.86, 87.00, 86.13, 73.91, 61.83, 60.12, 51.24, 14.39; HRMS (FAB, positive) calcd for 326.1352, found 326.1379 (MH^+).

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Supporting Information Available: ^{1}H NMR spectral charts of **7**, **8**, **14**, **16**, **17**, **19b**, **20R-D**, **20S**, **20S-D**, **22D**, **23R**, **23S**, **24**, **24-D**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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