Nucleosides and Nucleotides. 151. Conversion of (*Z*)-2′-(Cyanomethylene)-2′-deoxyuridines into Their (*E*)-Isomers *via* Addition of Thiophenol to the Cyanomethylene Moiety Followed by Oxidative *Syn*-elimination Reactions[1]

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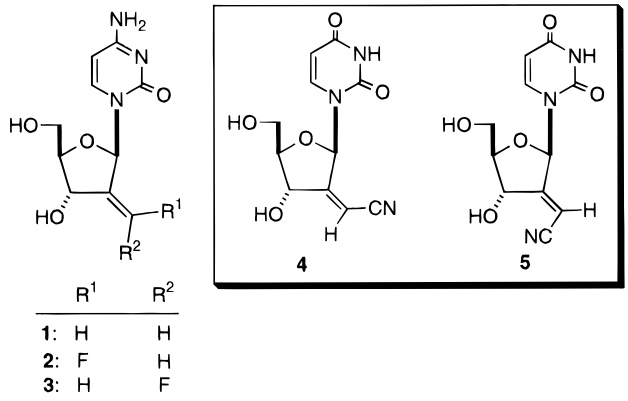
The Wittig reaction of 1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*erythro*-pentofuranos-2-ulosyl]uracil (**6**) with $Ph_3P{=}CHCN$ afforded (*Z*)-2′-cyanomethylene derivative **7** exclusively. The (*E*)-isomer was accessed from its (*Z*)-isomer through a sequence of addition of thiophenol to the 2′-cyanomethylene moiety of the (*Z*)-isomer from the α-face, selectively, and stereoselective oxidative *syn*-elimination of the resulting adduct. The diastereofacial selectivity of the benzenethiolate addition to the cyanomethylene moiety was found to be influenced by participation of the 2-carbonyl group at the base moiety and steric hindrance of the sugar protecting groups. Although nucleophilic addition reactions at the 2′-position of **6** have been well-known to occur from the α-face selectively, treatment of **7** with LiSPh in THF unexpectedly afforded a mixture of α- and β-phenylthio derivatives **8** and **9** in almost equal ratio. Furthermore, an unusual β-facial selective addition was observed on treatments of **7** with $PhSAlMe_2$ in CH_2Cl_2 or with LiSPh in the presence of $Mg(ClO_4)_2$ in THF. On the other hand, when (*Z*)-2′-(cyanomethylene)-5′-*O*-triisopropylsilyl derivative **10** was treated with LiSPh, the α-phenylthio derivative **13** was obtained predominantly (89:11). Oxidation of **8** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 and pyrolysis of the resulting sulfoxides afforded the (*Z*)-isomer **7** exclusively. Treatment of **13** with *m*-CPBA under the same conditions afforded the desired (*E*)-cyanomethylene derivatives **18** as a major product (*E*:*Z* = 14:1) in good yield. Deprotection of **18** by the standard procedures furnished (*E*)-2′-(cyanomethylene)-2′-deoxyuridine (**5**).

Introduction

2′-Deoxy-2′-methylenecytidine (DMDC, **1**; Chart 1)[2] has potent antiproliferative activity against a variety of human tumor cells both *in vitro* and *in vivo* and is now under clinical investigation in Japan. We and others have previously reported that the structural modifications of the 3′-allylic alcohol moiety of DMDC, *e.g.*, inversion,[3a] deoxygenation,[3b] and substitution with an amino[3c,d] or a fluoride group[3e] or by construction of an endocyclic allylic alcohol moiety at the 2′,3′-positions,[3f] resulted in nucleosides completely devoid of antitumor activity. These consequences emphasize the crucial role of both the 2′-*exo*-methylene group and the 3′-α-hydroxyl group of DMDC in its antitumor activity. The antitumor activity of DMDC is believed to be related to inhibition of DNA synthesis, since the 5′-triphosphate of DMDC strongly inhibited DNA polymerases from calf thymus[2d] and its 5′-diphosphate (DMDCDP) showed a time-dependent irreversible inactivation of ribonucleotide diphosphate reductase (RDPR) from *Escherichia coli*.[2f]

Chart 1



	R^1	R^2
1:	H	H
2:	F	H
3:	H	F

The synthesis of (*E*)- and (*Z*)-2′-deoxy-2′-(fluoromethylene)cytidines (dFMCyd; **2** and **3**) has been reported.[4a,b] The (*E*)-dFMCyd was more cytotoxic than the parent

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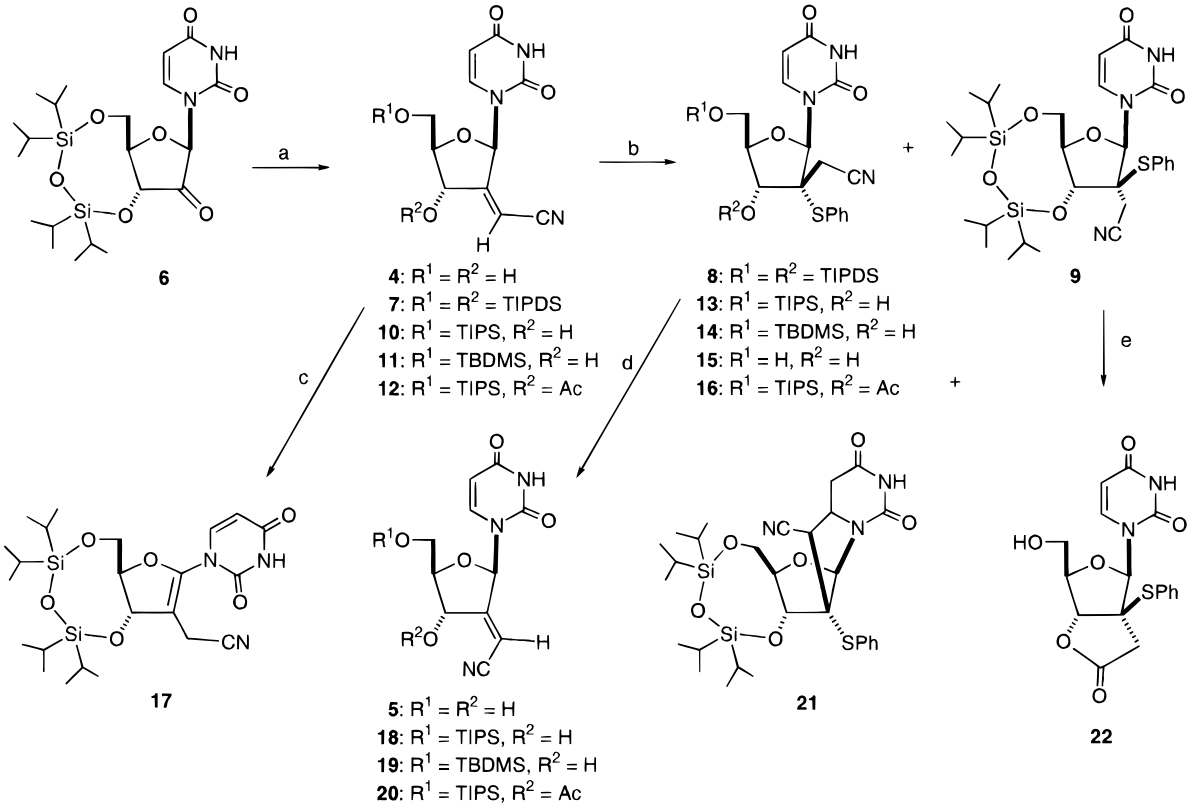
Scheme 1[a]



[a] (a) $Ph_3P{=}CHCN$, CH_2Cl_2/THF, rt; (b) PhS^- (see Table 1); (c) LiSPH, HMPA, THF, 0 °C to rt, or NaSePh; (d) *m*-CPBA or H_2O_2 (see Table 2); (e) TBAF, AcOH, THF, 0 °C.

nucleoside DMDC and (*Z*)-dFMCyd, and its 5′-diphosphate was also found to be a time-dependent irreversible inhibitor of RDPR.[4c] This together with the proposed mechanism of inactivation of RDPR by DMDCDP[2e] indicates that introduction of an electron-withdrawing group at the terminal of the *exo*-methylene moiety with (*E*)-geometry would elevate the activity of DMDC. Therefore, we selected a cyano group, which has good electron-withdrawing property and is not bulky, to be introduced at the terminus of the 2′-*exo*-methylene moiety. Herein, we describe an easy method for stereoselective conversion of the readily accessible (*Z*)-2′-deoxy-2′-(cyanomethylene)-uridine derivatives to their corresponding (*E*)-cyanomethylene derivatives through a sequence of a stereoselective addition of PhSH to the cyanomethylene moiety and stereoselective oxidative *syn*-elimination reactions of the resulting sulfoxides.

Results and Discussion

Treatment of 1-[3,5-*O*-[1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS)]-*β*-D-*erythro*-pentofuranos-2-ulosyl]uracil (**6**)[5] with the stable ylide $Ph_3P{=}CHCN$ in THF/CH_2Cl_2 afforded (*Z*)-2′-cyanomethylene derivative **7** as a single stereoisomer in quantitative yield (Scheme 1). The geometry of the terminal cyanomethylene group in **7** was confirmed by NOE experiments. Our strategy to build up a cyanomethylene group with (*E*)-geometry at the 2′-position is based on an addition of a benzeneselenolate or benzenethiolate group to the cyanomethylene moiety[6] of **7** stereoselectively from the α-face, followed by successive oxidation and stereoselective *syn*-elimination of the sulfoxide.[7] We envisioned that, if the 2′*β*-cyanomethyl group of the resulting adduct could adopt the conformation **A**, in which the cyano group is between the C-3′ and the 2′-SOPh, rather than **B** or **C** (Figure 1), the

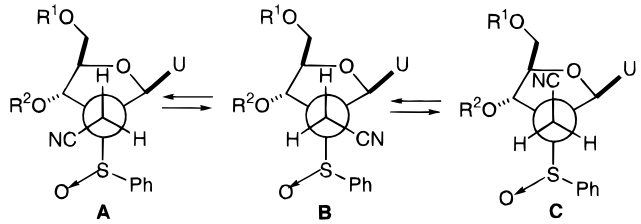


Figure 1. Newman projections of the rotamers around the C2′−C2″ bond.

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Table 1. Addition of Thiophenol to 7

entry	reagent (equiv)[a]	solvent	additives (equiv)	conditions	yield (%)[b]	ratio (**8**:**9**)[c]
1	LiSPh (0.1)	THF	none	rt, 25 h	85	55:45
2	LiSPh (1.5)	THF	none	rt, 3 h	95[d]	62:38
3	Me_2AlSPh (1.5)	CH_2Cl_2	none	rt, 3 days	80	17:83
4	LiSPh (1.5)	THF	$Mg(ClO_4)_2$ (**5**)	60 °C, 5 days	87	15:85
5	LiSPh (0.1)	THF	12-c-4 (10)	rt, 26 h	81	59:41
6	LiSPh (1.5)	THF	HMPA (5)	rt, 3 h	*e*	
7	NaSPh (2.5)	THF	none	rt, 2 h	68	60:40

[a] All reactions were done in the presence of 10 equiv of PhSH. [b] Yields after purification by silica gel chromatography. [c] Ratio of **8**:**9** was measured by ^{1}H NMR spectra. [d] The cycloadduct **21** was isolated in 4% yield. [e] Compound **17** was isolated in 91%.

syn-elimination of the corresponding sulfoxide would give rise to the corresponding (*E*)-cyanomethylene derivative.

Addition of benzeneselenolate to the cyanomethylene moiety of **7** was first attempted under various conditions; however, none of the addition products was obtained and only 1′,2′-didehydro-2′-cyanomethyl derivative **17** was isolated in good yield. On the other hand, treatment of **7** with LiSPh in the presence of an excess of PhSH in THF afforded unexpectedly a mixture of the α-phenylthio derivative **8**, the *β*-phenylthio derivative **9**, and the cycloadduct **21** (Table 1, entries 1 and 2). The structures of **8** and **9** were identified on the basis of ^{1}H NMR spectra and NOE experiments. Irradiation at H-1′ of **8** showed an NOE enhancement at the 2′-PhS protons (8.2%). On the other hand, irradiation at the 2′-cyanomethyl protons of **9** showed NOE enhancements at H-1′ (4.8% and 5.1%, respectively).

When the addition product **8** or **9** was further treated with LiSPh under the conditions described above, no interchange between the two diastereomers was observed, which suggested that the addition reaction was irreversible.

This nonselective *π*-facial addition of PhSH contrasts to the well-known α-facial selectivity of nucleophilic additions at the trigonal center of 2′-ketonucleosides.[8] For instance, $NaBH_4$[5] and $LiBHEt_3$[8a] as well as the carbon nucleophiles, such as MeMgBr,[8n−d] LiC≡CR,[8e] $NaCH_2NO_2$,[8f] and $(CH_3)_2S(O)=CH_2$,[8g] add to **6** from the α-face selectively. Moreover, α-facial selective benzenethiolate addition at the 2′-position of 2′,3′-didehydro-2′,3′-dideoxy-3′-nitrothymidine was reported.[9] However, we have previously encountered an exceptional example of the nonselective addition reaction at the 2′-position of 4-ethoxy-1-[3,5-*O*-(TIPDS)-*β*-D-*erythro*-2-pentofuranos-2-ulosyl]-2-(1*H*)-pyrimidinone upon treatment with MeMgBr in Et_2O.[8h] The unusual methyl addition reaction was interpreted to be a result of a chelation of the Grignard reagent between the relatively basic 2-carbonyl oxygen and the 2′-carbonyl oxygen, by which the methyl carbanion would be delivered from the sterically hindered *β*-face.[8h] To investigate whether the unusual *β*-facial nucleophilic attack is related to the aforementioned nucleobase participation or not, ^{13}C NMR of **7** was measured in THF/C_6D_6 (10:1) in the presence of different molar ratios of $LiClO_4$, as a monitor of changes in the electron density.[10,11] A noteworthy feature of the ^{13}C chemical shifts is the significant downfield shift of C-2 as well as C-6 and C-5 and the upfield shift of C-1′,[12] while the cyano carbon showed a slight upfield shift (Figure 2). The observed electron deficiency at the C-2 suggests a complexation of LiSPh with the 2-carbonyl oxygen. Further, when the addition reaction was done with a countercation of higher affinity for the carbonyl oxygen as in the aluminum thiophenoxy "ate" complex, $PhSAlMe_2$[13] (Table 1, entry 3) or LiSPh in the presence of $Mg(ClO_4)_2$ (Table 1, entry 4), the *β*-facial selective addition proceeded selectively. These results suggested that the nucleobase participation directs the *β*-facial attack of the thiolate anion at the 2′-cyanomethylene moiety of **7**. Attempts to elevate the α-facial selectivity through impeding the postulated 2-carbonyl participation by carrying out the reaction in the presence of 12-crown-4 ether[14] or HMPA, however, were unsuccessful (Table 1, entries 5 and 6).[15] Also, the use of NaSPh did not show any advantage over the use of LiSPh in respect to the facial selectivity (Table 1, entry 7).[16]

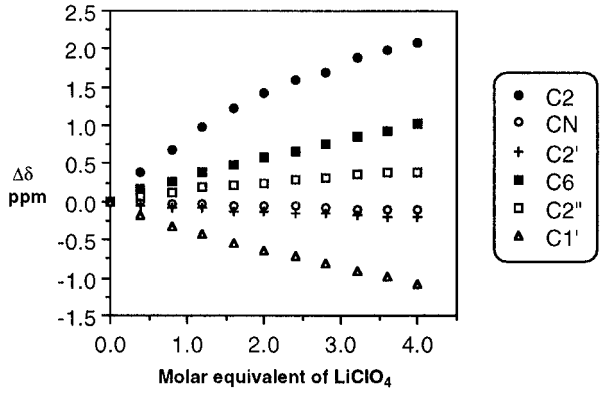

Figure 2. ^{13}C NMR chemical shift difference (Δδ) of **7** as a function of the molar equivalence of the $LiClO_4$. ^{13}C NMR was measured at a concentration of 0.07 M in THF−C_6D_6 (10:1). Values were referenced relative to C_6D_6 at 128 ppm.

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(12) Although an upfield shift was observed at the C-1′ upon addition of $LiClO_4$, it is not certain whether this shift is due to an increased electron density on C-1′ or to the dimensioned anisotropic effect of the 2-carbonyl group. However, ^{1}H NMR of **7** in the presence of 1 equiv of $LiClO_4$ (data not shown) showed a considerable downfield shift of the protons of the uracil moiety; H-6, H-5, H-N^3, and, unexpectedly, a slight downfield shift of H-1′ was also observed.

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(14) Loupy, A.; Seyden-Penne, J. *Tetrahedron* **1980**, *36*, 1937.

(15) Upon attempted addition of thiophenol to **7** in the presence of countercations incapable of chelation such as Et_3N, *i*-Pr_2NEt, or 1,1,3,3-tetramethylguanidine, however, decomposition or recovering of the starting material was observed.

Table 2. Oxidative *Syn*-elimination[a]

entry	substrate	R^1	R^2	reagent	solvent	conditions[b]	yield (%)[c]	ratio (*E*:*Z*)[d]
1	**8**	TIPDS		*m*-CPBA	CH_2Cl_2	rt, 11 h	79	1:99
2	**13**	TIPS	H	*m*-CPBA	CH_2Cl_2	rt, 1.5 h	82	93:7
3	**14**	TBDMS	H	*m*-CPBA	CH_2Cl_2	rt, 7 h	85	84:16
4	**15**	H	H	*m*-CPBA	CH_2Cl_2/THF	rt, 19 h	96	75:25
5	**16**	TIPS	Ac	*m*-CPBA	CH_2Cl_2	rt, 20 h	80	52:48
6	**13**	TIPS	H	H_2O_2	AcOH	60 °C, 2 h	85	59:41
7	**9**	TIPDS		*m*-CPBA	CH_2Cl_2	90 °C, 72 h	37	1:99

[a] All reactions were done using 1.2 equiv of the oxidant. [b] Oxidation with *m*-CPBA was completed within 30 min at −78 °C. [c] Yields after purification by silica gel chromatography. [d] The *E*:*Z* ratios were identified by ^{1}H NMR spectra.

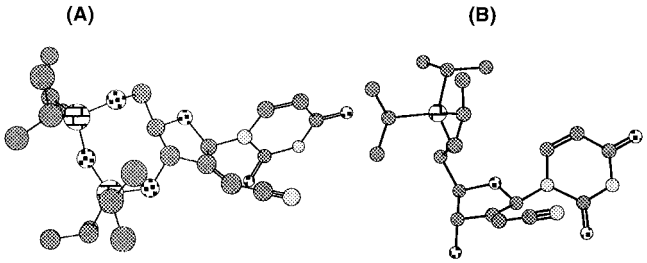

Figure 3. Molecular structures of **7** (A) and **10** (B). Hydrogen atoms and lone pairs are omitted for clarity. Global minimal optimizations were done by using MM2 implemented in MacroModel program version 4.5.

The addition reaction was next done with 5′-*O*-(triisopropylsilyl (TIPS))-2′-(cyanomethylene)uridine (**10**) as the substrate, in which the α-face of the sugar moiety would be sterically hindered due to the bulky 5′-TIPS group so that *β*-selective nucleophilic attack at the 2′-potition might proceed. Deprotection of the 3′,5′-protecting groups of **7**, followed by selective protection of the 5′-hydroxyl by the bulky TIPS group, furnished **10** (Scheme 1). When **10** was treated with LiSPh, the desired α-phenylthio derivative **13** was obtained predominantly along with the *β*-phenylthio derivative in a ratio of 89:11 in 91% yield, from which **13** was isolated in a pure form by crystallization. ^{1}H NMR spectra of **7** and **10** gave information about the sugar-puckering difference between the two nucleosides, where $J_{3',4'}$ of **10** (7.7 Hz) implies a less 3′-*endo* puckered conformation than that of **7** (8.4 Hz). We also carried out molecular mechanics calculations[17] on the two nucleosides. A 2′-*exo*,3′-*endo* conformational preference was observed for **7**, while a 2′-*endo*,3′-*exo* conformational preference was observed for **10** (Figure 3). The latter conformation might result in alleviation of the steric hindrance at the α-face of the 2′-position due to both the 5′-*O*-TIPS group and the uracil base. The participation of the 2-carbonyl in the reaction of **7** may also be indicated by the result of treatment of **10** with $PhSAlMe_2$ in CH_2Cl_2 which did not give any addition product, but recovery of **10**.

The oxidative *syn*-elimination of the α-phenylthio derivatives **8** and **13** was next investigated. First, **8** was treated with *m*-CPBA in CH_2Cl_2 at −78 °C, followed by stirring the reaction mixture at room temperature for further 11 h. However, none of the desired (*E*)-cyanomethylene derivative was obtained, but the (*Z*)-isomer **7** was isolated in 79% yield (Table 2, entry 1). On the contrary, treatment of **13** with *m*-CPBA in CH_2Cl_2 under these conditions gave the desired (*E*)-cyanomethylene derivative **18** (*E*:*Z* = 93:7) in 82% yield (Table 2, entry 2). Similarly, the *m*-CPBA oxidation of 5′-*O*-TBDMS derivative **14** also afforded the corresponding (*E*)-derivative **19** selectively (Table 2, entry 3). The contradiction in the geometrical selectivity of the oxidative *syn*-elimination between **8** and **13** may imply a substantial difference in the conformations of the 2′*β*-cyanomethyl moiety upon changing the sugar protecting groups.

To verify the importance of the remote effects of the bulky 5′-*O*-TIPS group on the conformational preference of the 2′*β*-cyanomethyl group, and consequently on the geometrical selectivity of the oxidative *syn*-elimination, the 3′,5′-unprotected derivative **15** was prepared and subjected to the oxidative elimination reaction. As a result, the (*E*)-cyanomethylene derivative **5** was obtained predominantly (Table 2, entry 4) while the selectivity was reduced compared with those of the reaction with **13** or **14**. These results suggested that the geometrical selectivity does not depend only on bulkiness of the protecting group at the 5′-position. Therefore, we next investigated the role of the 3′-hydroxyl group in the stereoselective *syn*-elimination of the sulfoxide. The 3′-hydroxyl of **13** was acetylated to give **16**, which was then subjected to the oxidative elimination reaction. However, the (*E*)-selectivity was lost (**20**:**12** = 52:48) (Table 2, entry 5). When the oxidative *syn*-elimination of **13** was carried out using an oxidizing reagent incapable of coordinative interaction[18] with the 3′-hydroxyl such as H_2O_2, the *E*:*Z* ratio was 59:41 (Table 2, entry 6). Therefore, it appears that both the cooperative coordination effect of the 3′-hydroxyl group and the steric effects of both the 5′-protecting group and the nucleobase would be synchronized to direct the oxidative *syn*-elimination *via* the conformation **A** (Figure 1) to produce **18** selectively. Although the configuration of the sulfoxides would also be an important determinant of the stereoselectivity of the *syn*-elimination reactions, it was difficult to isolate these sulfoxides due to their fragmentations to the corresponding cyanomethylene derivatives on silica gel column chromatography. Attempts to identify the sulfoxide configuration by doing the reaction in an NMR tube in CD_2Cl_2 at −60 °C, however, were unsuccessful due to low resolution of the ^{1}H NMR spectra. It is also worth noting that the oxidative *syn*-elimination of the *β*-phenylthio derivative **9** afforded only the (*Z*)-cyanomethylene derivative **7** (Table 2, entry 7). Since attempted desilylation of **9**, however, gave the lactone **22**, we could not study further the effects of the protecting groups on the geometrical selectivity as described above.

(16) A ^{13}C NMR spectrum of **7** in THF/C_6D_6 in the presence of $NaClO_4$ (data not shown) showed a shift pattern similar to that measured in the presence of $LiClO_4$, but in a smaller degree than that of $LiClO_4$.

(17) Global minimal optimizations were carried out by using MM2 force field implemented in MacroModel version 4.5; default parameters were used.

(18) For examples of directive coordination to *m*-CPBA, see: (a) Jonson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347. (b) Clayden, J.; Collington, E. W.; Egert, E.; McElroy, A. B.; Warran, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2801. (c) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311. (d) Jenmalm, A.; Berts, W.; Luthman, K.; Csöregh, I.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 1026.

Finally, desilylation of **18** and **7** by NH_4F in MeOH[19] furnished (*E*)- and (*Z*)-2′-deoxy-2′-(cyanomethylene)-uridines **5** and **4**, respectively.

In conclusion, phenylsulfenylation of the cyanomethylene moiety proceeded smoothly in a conjugate manner. The diastereofacial selectivity of this benzenethiolate addition can be controlled by the thiolate countercation and/or manipulation of the sugar protecting groups to produce stereoselectively either the 2′α-phenylthio or 2′β-phenylthio derivatives. Dehydrophenylsulfenylation of the α-phenylthio derivatives **13** and **14** proceeded stereoselectively providing an access to the synthesis of the (*E*)-2′-(cyanomethylene)-2′-deoxyuridine (**5**), which is difficult to attain by Wittig and related reactions. Application of this method to the synthesis of cytidine derivatives is now in progress.

Experimental Section

General. Melting points are uncorrected. NMR spectra were recorded at 270, 400, or 500 MHz (^{1}H) and at 100 or 125 MHz (^{13}C) and are reported in ppm downfield from TMS. Mass spectra were obtained by fast atom bombardment (FAB) mode. Silica gel chromatography was done with YMC gel 60 A (70−230 mesh).

(*Z*)-2′-(Cyanomethylene)-2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (7). A solution of $Ph_3P{=}CHCN$ (1.7 g, 5.6 mmol) in CH_2Cl_2 (10 mL) was added to a solution of **6** (1.0 g, 2.1 mmol) in THF (15 mL) dropwise at 0 °C. The mixture was stirred at room temperature for 3 h, and the reaction was then quenched with aqueous 1 M NH_4-Cl. The volatile was evaporated, and the residue was partitioned between EtOAc and H_2O. The organic phase was washed with brine and H_2O, dried (Na_2SO_4), and evaporated. The residue was purified on a silica gel column with EtOAc/hexane (1:3) to give **7** (1.0 g, 93% as a colorless foam): IR ν_{max} (neat)/cm^{-1} 2220 (CN); ^{1}H NMR ($CDCl_3$) δ 8.17 (br s, 1H, NH), 7.20 (d, 1H, H-6, J = 8.1 Hz), 6.14 (d, 1H, H-1′, J = 2.2 Hz), 5.75 (dd, 1H, H-5, J = 2.2, J = 8.1 Hz), 5.64 (t, 1H, H-2″, J = 2.2 Hz), 5.30 (dt, 1H, H-3′, J = 2.2, J = 8.3 Hz), 4.12 (dd, 1H, H-5′a, J = 4.5, J = 12.7 Hz), 4.06 (dd, 1H, H-5′b, J = 3.1, J = 12.7 Hz), 3.73 (ddd, 1H, H-4′, J = 8.3, J = 3.1, J = 4.5 Hz), 1.11−0.90 (m, 28 H, *i*-Pr); NOE, irradiate H-1′, observe H-2″ (0.7%), H-3′ (0.3%), H-4′ (3.8%), and H-6 (14.6%); irradiate H-2″, observe H-1′ (0.2%), H-3′ (2.1%), and isopropyl-H (7.6%); irradiate H-3′, observe H-2″ (2.3%), H-1′ (0.2%), and H-6 (2.2%); ^{13}C NMR [THF/C_6D_6 (10:1)] δ 166.6, 162.7, 150.1, 143.5, 114.6, 102.8, 94.6, 87.7, 83.2, 74.9, 63.4, 17.4, 17.3, 17.2, 17.1, 16.9, 13.8, 13.5, 13.2, 13.1; FABMS *m/z* 508 [M$^+$ + 1]; HR FABMS calcd for $C_{23}H_{38}N_3O_6Si_2$ 508.2299, found 508.2272.

(*Z*)-2′-(Cyanomethylene)-2′-deoxyuridine (4). A mixture of **7** (500 mg, 0.99 mmol), and NH_4F (500 mg, 12.5 mmol) in MeOH (15 mL) was heated at 65 °C for 2.5 h. After the mixture was cooled to room temperature and the insoluble material was removed by filtration, the filtrate was evaporated and purified on a silica gel column with 5% MeOH/$CHCl_3$ to give **4** (250 mg, 96% as a white solid, which was crystallized from EtOH/hexane); mp 197−199 °C; IR ν_{max} (film)/cm^{-1} 2240 (CN); ^{1}H NMR (DMSO-d_6) δ 11.51 (br s, 1H, NH), 7.61 (d, 1H, H-6, J = 8.0 Hz), 6.59 (t, 1H, H-1′, J = 2.2 Hz), 6.15 (d, 1H, 3′-OH, J = 6.9 Hz), 5.97 (t, 1H, H-2″, J = 2.5 Hz), 5.72 (d, 1H, H-5, J = 8.0 Hz), 4.96 (t, 1H, 5′-OH, J = 5.6 Hz), 4.70 (m, 1H, H-3′, J = 2.3, J = 8.0 Hz), 3.74 (m, 1H, H-5′a), 3.67 (m, 1H, H-5′b), 3.55 (m, 1H, H-4′); NOE, irradiate H-1′, observe H-2″ (1.1%), H-4′ (3.3%), and H-6 (9.1%); irradiate H-2″, observe H-1′ (0.9%) and 3′-OH (2.2%); irradiate H-3′, observe H-1′ (0.5%), H-2″ (4.7%), H-6 (3.8%), and 3′-OH (12.0%). Anal. Calcd for $C_{11}H_{11}N_3O_5{\cdot}0.6H_2O$: C, 47.86; H, 4.60; N, 15.22. Found: C, 47.99; H, 4.36; N, 15.16.

2′-(Cyanomethyl)-2′-deoxy-1′,2′-didehydro-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (17). Method A. A solution of **7** (102 mg, 0.2 mmol), PhSH (0.2 mL, 1.9 mmol), and HMPA (0.18 mL, 1 mmol) in THF (4 mL) was treated with a THF solution of LiSPh (0.58 M, 0.5 mL, 0.3 mmol) at −15 °C. The mixture was stirred for 3 h and then neutralized with AcOH and evaporated. The residue was washed with brine and H_2O, dried (Na_2SO_4), and evaporated. The residue was purified on a silica gel column with 30% EtOAc/hexane to give **17** (93 mg, 91% as a white solid, which was crystallized from EtOAc/hexane): mp 153−155 °C, IR ν_{max} (film)/cm^{-1} 2250 (CN); UV λ_{max} (MeOH) 258, 214 nm, ^{1}H NMR ($CDCl_3$) δ 8.48 (br s, 1H), 7.30 (d, 1H, J = 8.3 Hz), 5.84 (dd, 1H, J = 2.4, J = 8.3 Hz), 5.33 (d, 1H, J = 4.9 Hz, appeared as a singlet on irradiation at 4.53 ppm), 4.53 (ddd, 1H, J = 4.9, J = 9.8, J = 10.7 Hz), 4.17 (dd, 1H, J = 4.8, J = 11.2 Hz), 3.80 (dd, 1H, J = 11.2, J = 10.7 Hz), 3.23 (d, 1H, J = 18.6 Hz), 3.17 (d, 1H, J = 18.6 Hz), 1.25 (m, 28H); FABMS 508 [M$^+$ + 1], 464 [M$^+$ − *i*-Pr]. Anal. Calcd for $C_{23}H_{37}N_3O_6Si_2$: C, 54.41; H, 7.35; N, 8.28. Found: C, 54.29; H, 7.35; N, 8.07. **Method B.** Sodium borohydride (40 mg, 0.8 mmol) was added to a solution of $(PhSe)_2$ (410 mg, 1.3 mmol) in EtOH (5 mL) at room temperature. The mixture was stirred for 15 min until the solution turned clear. Compound **7** (416 mg, 0.82 mmol) in EtOH (2 mL) was added to the mixture and was heated at 60 °C for 8 h. The mixture was neutralized with AcOH, and the solvent was evaporated. The residue was partitioned between EtOAc and H_2O. The water phase was evaporated, and the residue was purified on a silica gel column to give 34 mg (37%) of uracil as a white solid. The organic phase was washed with brine and H_2O, dried (Na_2SO_4), and evaporated. The residue was purified on a silica gel column with 25% EtOAc/hexane to give **17** (254 mg, 61% as a white solid).

(2′*S*)-2′-(Cyanomethyl)-2′-deoxy-2′-(phenylthio)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (8), (2′*R*)-2′-(Cyanomethyl)-2′-deoxy-2′-(phenylthio)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (9), and (2′*R*)-2′-Deoxy-2′-(phenylthio)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6,2′-(cyanomethano)-5,6-dihydrouridine (21). A THF solution of LiSPh (0.58 M, 17.6 mL, 10.2 mmol) in THF was added to a mixture of **7** (3.45 g, 6.8 mmol) and PhSH (7 mL, 68 mmol) in THF (40 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. The mixture was neutralized with AcOH, and the whole was taken in EtOAc, which was washed with brine and H_2O, dried (Na_2SO_4), and evaporated. The residue was purified on a silica gel column with 15% EtOAc/hexane to give **21** (168 mg, 4% as a white solid, which was crystallized from hexane), with 20% EtOAc/hexane to give **8** (2.48 g, 59% as a white solid, which was crystallized from EtOAc/hexane), and then with 25% EtOAc/hexane to give **9** (1.51 g, 36% as a white solid, which was crystallized from EtOAc/hexane). The physical data of **8**: mp 131−132 °C; IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 8.22 (br s, 1H, NH), 7.96 (d, 1H, H-6, J = 8.2 Hz), 7.64 (dd, 2H, SPh, J = 1.7, J = 6.6 Hz), 7.45 (m, 3H, SPh), 6.05 (s, 1H, H-1′), 5.71 (dd, 1H, H-5, J = 1.7, J = 8.2 Hz), 4.66 (d, 1H, H-3′, J = 8.8 Hz), 4.57 (dd, 1H, H-4′, J = 2.2, J = 8.8 Hz), 4.32 (d, 1H, H-5′a, J = 14.3 Hz), 4.12 (dd, 1H, H-5′b, J = 14.3, J = 2.2 Hz), 3.15 (d, 1H, $CH_{2a}CN$, J = 17.0 Hz), 3.00 (d, 1H, $CH_{2b}CN$, J = 17.0 Hz), 1.12−1.02 (m, 28H, *i*-Pr); NOE, irradiate H-1′, observe $CH_{2b}CN$ (1.5%) and SPh (8.2%); irradiate $CH_{2a}CN$, observe H-3′ (2.4%), $CH_{2b}CN$ (23.9%), and SPh (2.7%); irradiate $CH_{2b}CN$, observe H-1′ (4.3%), H-3′ (1.3%), $CH_{2a}CN$ (22.3%), and SPh (6.8%); FABMS *m/z* 618 [M$^+$ + 1]. Anal. Calcd for $C_{29}H_{43}N_3O_6SSi_2$: C, 56.37; H, 7.01; N, 6.80. Found: C, 56.14; H, 7.05; N, 6.90. The physical data of **9**: mp 147−148 °C; IR ν_{max} (film)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 8.19 (br s, 1H, NH), 7.66 (d, 1H, H-6, J = 8.2 Hz), 7.47−7.31 (m, 5H, SPh), 6.19 (s, 1H, H-1′), 5.84 (dd, 1H, H-5, J = 2.8, J = 8.2 Hz), 4.43 (d, 1H, H-3′, J = 6.1 Hz), 4.17 (m, 2H, H-5′a,b), 4.11 (ddd, 1H, H-4′, J = 6.1, J = 4.4 Hz), 2.96 (d, 1H, CH_{2a}-CN, J = 17.0 Hz), 2.84 (d, 1H, $CH_{2b}CN$, J = 17.0 Hz), 1.14−0.94 (m, 28H, *i*-Pr); NOE, irradiate H-1′, observe H-6 (1.7%), $CH_{2a}CN$ (1.7%), and $CH_{2b}CN$ (1.9%); irradiate $CH_{2a}CN$, observe H-1′ (5.1%), $CH_{2b}CN$ (11.5%), and SPh (3.7%); irradiate $CH_{2b}CN$, observe H-1′ (4.8%), $CH_{2a}CN$ (14.4%), and SPh (5.2%); FABMS *m/z* 618 [M$^+$ + 1]. Anal. Calcd for $C_{29}H_{43}N_3O_6SSi_2$: C, 56.37; H, 7.01; N, 6.80. Found: C, 56.09; H, 7.09; N, 6.83. The physical data of **21**: mp 108−109 °C; IR ν_{max} (neat)/cm^{-1}

(19) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177.

2240 (CN); ^{1}H NMR ($CDCl_3$) δ 7.79 (m, 2H, SPh), 7.69 (br s, 1H, NH), 7.42−7.30 (m, 3H, SPh), 5.75 (s, 1H, H-1′), 4.33 (ddd, 1H, H-6, J = 6.6, J = 6.1 Hz), 4.29 (d, 1H, H-3′, J = 7.8 Hz), 3.96 (dd, 2H, H-5′a,b, J = 3.2 Hz), 3.85 (ddd, 1H, H-4′, J = 7.8, J = 3.2 Hz), 3.58 (d, 1H, H-2″, J = 6.6 Hz), 2.82 (dd, 2H, H-5a,b, J = 6.2, J = 11.5 Hz), 1.13−1.05 (m, 28H, *i*-Pr); NOE, irradiate H-1′, observe H-4′ (3.6%), H-6 (0.7%), isopropyl (3.7%), and SPh (9.7%); irradiate H-2″, observe H-1′ (0.5%), H-5′a (0.9%), H-5′b (1.7%), H-6 (18.9%), isopropyl (5.3%), and SPh (1.8%); FABMS *m*/*z* 618 [M^+ + 1]. Anal. Calcd for $C_{29}H_{43}N_3O_6SSi_2$: C, 56.37; H, 7.01; N, 6.80. Found: C, 56.02; H, 7.03; N, 6.59.

Other Experiments in Table 1. Entry 3. The reaction of **7** (102 mg, 0.2 mmol) with Me_3AlSPh [prepared from 31 μL (0.30 mmol) of PhSH and Me_3Al (0.99 M in hexane, 0.30 mL)] in CH_2Cl_4 (4 mL) gave a mixture of **8** and **9** [17:83 (determined by the H-1′ integration ratio in the ^{1}H NMR spectrum), 98 mg, 80%]. **Entry 4.** The reaction of **7** (102 mg, 0.2 mmol) with a mixture of LiSPh (0.58 M, 0.52 mL, 0.3 mmol) and PhSH (0.2 mL, 2 mmol) in the presence of $Mg(ClO_4)_2$ (223 mg, 1 mmol) in THF (6 mL) gave a mixture of **8** and **9** (15:85, 108 mg, 87%). **Entry 5.** The reaction of **7** (102 mg, 0.2 mmol) with LiSPh (0.58 M, 52 μL, 0.03 mmol) and PhSH (0.2 mL, 2 mmol) in the presence of 12-crown-4 (0.5 mL, 3 mmol) in THF (4 mL) gave a mixture of **8** and **9** (59:41, 100 mg, 81%). **Entry 7.** The reaction of **7** (102 mg, 0.2 mmol) with NaSPh (66 mg, 0.5 mmol) and PhSH (0.2 mL, 2 mmol) in THF (3 mL) gave a mixture of **8** and **9** in a ratio of 60:40 (84 mg, 68%).

(*Z*)-2′-(Cyanomethylene)-2′-deoxy-5′-*O*-(triisopropylsilyl)uridine (10). A mixture of **4** (150 mg, 0.57 mmol), imidazole (62 mg, 0.91 mmol), and triisopropylsilyl chloride (0.20 mL, 0.93 mmol) was dissolved in DMF (5 mL) at 0 °C. The mixture was stirred for 17 h at room temperature. After water workup, the residue was purified on a silica gel column with 2% EtOH/$CHCl_3$ to give **10** (267 mg, 94% as a white solid, which was crystallized from EtOH/EtOAc): mp >245 °C (dec); ^{1}H NMR ($CDCl_3$) δ 7.91 (br s, 1H), 7.20 (d, 1H, J = 8.1 Hz), 6.34 (dd, 1H, J = 2.2, J = 1.8 Hz), 5.77 (t, 1H, J = 2.2 Hz), 5.77 (dd, 1H, J = 8.1, J = 2.2 Hz), 5.11 (dd, 1H, J = 7.7, J = 2.2 Hz), 4.08 (dd, 1H, J = 4.2, J = 10.3 Hz), 3.96 (dd, 1H, J = 5.8, J = 10.3 Hz), 3.83 (ddd, 1H, J = 4.2, J = 5.8, J = 7.7 Hz), 2.50 (br d, 1H), 1.11−1.01 (m, 21H); ^{13}C NMR [THF/C_6D_6 (10:1)] δ 167.4, 162.7, 150.2, 142.1, 114.5, 103.1, 95.4, 85.9, 84.2, 71.7, 63.0, 17.9, 17.4, 12.4; FABMS *m*/*z* 422 [M^+]. Anal. Calcd for $C_{20}H_{32}N_3O_5Si$: C, 56.85; H, 7.63; N, 9.94. Found: C, 56.92; H, 7.44; N, 9.97.

(*Z*)-2′-(Cyanomethylene)-2′-deoxy-5′-*O*-(*tert*-butyldimethylsilyl)uridine (11). A mixture of **4** (42 mg, 0.16 mmol), imidazole (17 mg, 0.25 mmol), and *tert*-butyldimethylsilyl chloride (39 mg, 0.26 mmol) was dissolved in DMF (2 mL) at 0 °C. The mixture was stirred for 14 h at room temperature and then quenched with H_2O. The whole was taken in EtOAc, which was washed with brine and H_2O. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column with 25% EtOAc/hexane to give **11** (32 mg, 53% as a white solid, which was crystallized from EtOAc/hexane): mp 205−206 °C; IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$ + D_2O) δ 8.61 (br s, 1H), 7.23 (d, 1H, J = 8.2 Hz), 6.36 (br dd, 1H, J = 2.1 Hz), 5.79 (dd, 1H, J = 2.2, J = 2.8 Hz), 5.76 (d, 1H, J = 8.2 Hz)], 5.04 (dt, 1H, J = 7.7 Hz), 3.95 (m, 2H, J = 11.0, J = 4.4, J = 5.0 Hz), 4.83 (ddd, 1H, J = 7.7, J = 4.4, J = 5.0 Hz), 0.90 (m, 9H), 0.10 (s, 3H), 0.09 (s, 3H); FABMS *m*/*z* 380 [M^+ + 1]. Anal. Calcd for $C_{17}H_{25}N_3O_5Si$: C, 53.81; H, 6.64; N, 11.07. Found: C, 53.56; H, 6.57; N, 10.97.

(*Z*)-3′-*O*-Acetyl-2′-(cyanomethylene)-2′-deoxy-5′-*O*-(triisopropylsilyl)uridine (12). Triethylamine (26 μL, 0.19 mmol) was added to a mixture of **10** (72 mg, 0.17 mmol) and Ac_2O (20 μL, 0.19 mmol) in MeCN (3 mL) at 0 °C. The mixture was stirred for 15 min. After water workup, the residue was purified on a silica gel column with 15% EtOAc/hexane to give **12** (61 mg, 77% as a white solid, which was crystallized from EtOAc): mp 182−183 °C; IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 8.20 (br s, 1H), 7.40 (d, 1H, J = 8.2 Hz), 6.75 (dd, 1H, J = 1.7, J = 2.2 Hz), 5.98 (dt, 1H, J = 2.2, J = 5.0 Hz), 5.82 (t, 1H, J = 2.2 Hz), 5.75 (dd, 1H, J = 8.2, J = 2.2 Hz), 4.16 (ddd, 1H, J = 5.0, J = 2.8, J = 3.3 Hz), 4.02 (dd, 1H, J = 11.5, J = 2.8 Hz), 3.97 (dd, 1H, J = 11.5, J = 3.3 Hz), 2.15 (s, 3H), 1.16−1.03 (m, 21H); FABMS *m*/*z* 464 [M^+ + 1]; HR FABMS calcd for $C_{22}H_{34}N_3O_6Si$ 464.2217, found, 464.2245.

(2′*S*)-2′-(Cyanomethyl)-2′-deoxy-2′-(phenylthio)-5′-*O*-(triisopropylsilyl)uridine (13). Method A. Compound **10** (285 mg, 0.68 mmol) was treated with a THF solution of LiSPh (0.58 M, 1.8 mL, 1.0 mmol) and PhSH (1.4 mL, 14 mmol) in THF (5 mL) under the same conditions as described for the synthesis of **8** to give a mixture of **17** and its 2′-diastereomer in a ratio of 89:11 (327 mg, 91%), from which **13** was separated as a white powder from hot EtOAc/hexane. **Method B.** Compound **15** (150 mg, 0.40 mmol) was treated with triisopropylsilyl chloride under the same conditions as described for the synthesis of **10** to give **13** (150 mg, 71%): IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 8.25 (br s, 1H, NH), 8.23 (d, 1H, H-6, J = 8.2 Hz), 7.71 (m, 2H, SPh), 7.52−7.44 (m, 3H, SPh), 6.27 (s, 1H, H-1′), 5.66 (dd, 1H, H-5, J = 1.9, J = 8.2 Hz), 4.66 (dd, 1H, H-3′, J = 9.1, J = 7.1 Hz), 4.32 (dt, 1H, H-4′, J = 9.1, J < 1 Hz), 4.24 (d, 1H, H-5′a, J = 12.1 Hz), 4.04 (d, 1H, H-5′b, J = 12.1 Hz), 2.88 (d, 1H, H-2″a, J = 17.2 Hz), 2.67 (br d, 1H, 3′-OH), 2.60 (d, 1H, H-2″b, J = 17.2 Hz), 1.26−0.80 (m, 21H, *i*-Pr); NOE, irradiate H-1′, observe CH_{2b}CN (0.7%) and SPh (7.2%); irradiate H-3′, observe CH_{2a}CN (2.4%) and 3′-OH (3.0%); irradiate CH_{2a}CN, observe H-1′ (1.1%) and SPh (5.3%); irradiate CH_{2b}CN, observe H-1′ (1.6%) and H-3′ (4.0%); FABMS *m*/*z* 532 [M^+ + 1]. Anal. Calcd for $C_{26}H_{37}N_3O_5SSi$: C, 58.73; H, 7.01; N, 7.90. Found: C, 58.73; H, 7.04; N, 7.94.

(2′*S*)-2′-(Cyanomethyl)-2′-deoxy-2′-(phenylthio)uridine (15). A mixture of **8** (513 mg, 0.83 mmol) and NH_4F (310 mg, 8.4 mmol) was dissolved in MeOH (10 mL) and heated at 65 °C for 2 h. The mixture was cooled to room temperature, and the solvent was evaporated. The residue was suspended in EtOH, and the insoluble material was removed by filtration. The filtrate was evaporated and purified on a silica gel column with 5% MeOH/$CHCl_3$ to give **15** (221 mg, 71% as a white solid, which was crystallized from EtOH/EtOAc): mp >205 °C (dec); IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR (DMSO-d_6) δ 11.15 (br s, 1H), 8.29 (d, 1H, J = 8.2 Hz), 7.65 (m, 2H), 7.38 (m, 3H), 6.25 (d, 1H, J = 5.5 Hz), 6.00 (s, 1H), 5.55 (d, 1H, J = 8.2 Hz), 5.48 (br s, 1H), 4.42 (dd, 1H, J = 8.8, J = 5.5 Hz), 4.19 (br d, 1H, J = 8.8 Hz), 3.90 (ddd, 1H, J = 12.6, J = 2.2 Hz), 3.71 (ddd, 1H, J = 12.6 Hz), 3.08 (d, 1H, J = 17.0 Hz), 2.94 (d, 1H, J = 17.0 Hz); FABMS *m*/*z* 376 [M^+ + 1]; HR FABMS calcd for $C_{17}H_{18}N_3O_5S$ 376.0967, found 376.0953.

(2′*S*)-2′-(Cyanomethyl)-2′-deoxy-2′-(phenylthio)-5′-*O*-(*tert*-butyldimethylsilyl)uridine (14). Compound **14** (130 mg, 86% as a white solid) was synthesized from **15** (116 mg, 0.31 mmol) by the method described for the synthesis of **11**: IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 8.42 (br s, 1H), 8.24 (d, 1H, J = 8.2 Hz), 7.72 (m, 2H), 7.55 (m, 3H), 6.27 (d, 1H, J = 2.2 Hz), 5.67 (d, 1H, J = 8.2 Hz), 4.55 (dd, 1H, J = 8.8, J = 5.5 Hz), 4.31 (dd, 1H, J = 8.8, J = 2.0 Hz), 4.18 (dd, 1H, J = 12.1, J = 1.7 Hz), 3.95 (d, 1H, J = 12.1 Hz), 2.88 (d, 1H, J = 17.0 Hz), 2.60 (d, 1H, J = 17.0 Hz), 0.95 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); FABMS *m*/*z* 490 [M^+ + 1]. Anal. Calcd for $C_{23}H_{31}N_3O_5SSi$: C, 56.42; H, 6.38; N, 8.58. Found: C, 56.56; H, 6.49; N, 8.24.

(2′*S*)-3′-*O*-Acetyl-2′-(cyanomethyl)-2′-deoxy-2′-(phenylthio)-5′-*O*-(triisopropylsilyl)uridine (16). Triethylamine (0.1 mL, 0.7 mmol) was added to a mixture of **13** (186 mg, 0.35 mmol) and Ac_2O (66 μL, 0.7 mmol) in MeCN (5 mL) at 0 °C and stirred for 1 h. After water workup, the residue was purified on a silica gel column with 25% EtOAc/hexane to give **16** (182 mg, 91% as a white solid): IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 8.32 (d, 1H, J = 8.0 Hz), 7.70 (br s, 1H), 7.54−7.45 (m, 5H), 6.26 (s, 1H), 5.86 (d, 1H, J = 9.4 Hz), 5.69 (d, 1H, J = 8.0 Hz), 4.63 (br dt, 1H, J = 9.4 Hz), 4.23 (dd, 1H, J = 11.5, J = 1.2 Hz), 3.87 (dd, 1H, J = 11.5, J = 1.5 Hz), 2.94 (d, 1H, J = 11.5 Hz), 2.66 (d, 1H, J = 11.5 Hz), 2.19 (s, 3H), 1.18−1.07 (m, 21H); FABMS *m*/*z* 574 [M^+ + 1]. Anal. Calcd for $C_{28}H_{39}N_3O_6SSi$: C, 58.61; H, 6.85; N, 7.32. Found: C, 58.41; H, 6.98; N, 7.05.

Oxidative *Syn*-Elimination: General Procedure. The sulfide derivatives **8**, **9**, and **13**−**16** in CH_2Cl_2 were treated with *m*-CPBA (1.2 equiv) at −78 °C under argon. The oxidation to the corresponding sulfoxide(s) was completed within 10−30 min as monitored by TLC. The mixtures were then allowed to warm gradually to room temperature. Stirring was further continued for appropriate times at temperatures depicted in Table 2 until the *syn*-elimination was completely finished (monitored by TLC). Neutralization by 5% $NaHCO_3$ and water workup followed by silica gel column chromatography provided the corresponding cyanomethylene derivatives. **Entry 1.** The reaction of **8** (510 mg, 0.825 mmol) with *m*-CPBA (171 mg, 0.99 mmol) in CH_2Cl_2 (18 mL) gave **7** (331 mg, 79% as a colorless foam). **Entry 4.** The reaction of **15** (205 mg, 0.55 mmol) with *m*-CPBA (114 mg, 0.66 mmol) in CH_2Cl_2/THF (5:1, 12 mL) gave a mixture of **4** and **5** [25:75 (measured by the H-1′ integration ratio in the ^{1}H NMR spectrum), 140 mg, 96% as a white solid]. **Entry 6.** To a solution of **13** (106 mg, 0.2 mmol) in AcOH (4 mL) was added 30% H_2O_2 (30 μL), and the mixture was heated at 60 °C for 2 h. The solvent was evaporated, and the residue was purified on a silica gel column to give a mixture of **4** and **5** in a ratio of 41:59 (45 mg, 85%). **Entry 7.** The reaction of **9** (210 mg, 0.34 mmol) with *m*-CPBA (70 mg, 0.41 mmol) in CH_2Cl_2 (6 mL) gave **7** (64 mg, 37% as a colorless foam).

(*E*)-2′-(Cyanomethylene)-2′-deoxy-5′-*O*-(triisopropylsilyl)uridine (18). Compound **13** (220 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) was treated with *m*-CPBA (86 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) under the above-described conditions to give a mixture of **18** and **10** in a ratio of 93:7 (143 mg, 82% as a white solid, from which **18** was separated by crystallization from hexane): mp 156−157 °C; IR ν_{max} (film)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 8.82 (br s, 1H), 7.62 (d, 1H, J = 8.1 Hz), 6.68 (br t, 1H), 5.84 (dd, 1H, J = 2.1, J = 1.9 Hz), 5.70 (d, 1H, J = 8.1 Hz), 5.18 (m, 1H, J = 6.9 Hz), 4.12 (dd, 1H, J = 11.6, J = 2.2 Hz), 4.05−3.97 (m, 2H), 3.35 (d, 1H, J = 5.6 Hz), 1.25−0.95 (m, 21H); NOE, irradiate H-1′, observe H-2″ (3.6%) and H-6 (1.4%); irradiate H-2″, observe H-1′ (3.8%), and H-6 (0.8%); FABMS m/z 422 [M$^+$ + 1]. Anal. Calcd for $C_{20}H_{31}N_3O_5Si$: C, 56.98; H, 7.41; N, 9.97. Found: C, 56.98; H, 7.21; N, 9.80.

(*E*)-2′-(Cyanomethylene)-2′-deoxy-5′-*O*-(*tert*-butyldimethylsilyl)uridine (19). The reaction of **14** (100 mg, 0.20 mmol) with *m*-CPBA (42 mg, 0.24 mmol) in CH_2Cl_2 (4 mL) gave a mixture of **19** and **11** in a ratio of 84:26 (64 mg, 83% as a colorless foam), from which an analytical sample of **19** (as a foam) was obtained by preparative TLC. The physical data of **19**: IR ν_{max} (film)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 9.21 (br s, 1H), 7.67 (d, 1H, J = 7.8 Hz), 6.70 (t, 1H, J = 2.0 Hz), 5.82 (dd, 1H, J = 2.0, J = 2.4 Hz), 5.72 (d, 1H, J = 7.8 Hz), 5.09 (m, 1H), 4.03−3.92 (m, 3H), 3.68 (d, 1H, J = 5.9 Hz), 0.93−0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); FABMS m/z 380 [M$^+$ + 1]; HR FABMS $C_{17}H_{26}N_3O_5Si$ 380.1642, found 380.1657.

(*E*)-3′-*O*-Acetyl-2′-(cyanomethylene)-2′-deoxy-5′-*O*-(triisopropylsilyl)uridine (20). The reaction of **15** (100 mg, 0.17 mmol) with *m*-CPBA (36 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) gave a mixture of **20** and **12** (52:48, 65 mg, 80%), from which an analytically pure sample of **20** was obtained by preparative TLC (hexane/EtOAc, 2:1). The physical data of **20**: IR ν_{max} (film)/cm^{-1} 2240 (CN); ^{1}H NMR ($CDCl_3$) δ 9.18 (br s, 1H), 7.71 (d, 1H, J = 8.1 Hz), 6.83 (br t, 1H), 6.17 (dt, 1H, J = 5.3, J = 2.2 Hz), 5.75 (t, 1H), 5.73 (d, 1H, J = 8.1 Hz), 4.08 (dd, 1H, J = 5.3 Hz), 4.02 (dd, 1H, =11.7, J = 1.5 Hz), 3.97 (dd, 1H, J = 11.7, J = 1.7 Hz), 2.20 (s, 3H), 1.17−1.01 (m, 21H); FABMS m/z 464 [M$^+$ + 1]; HR FABMS calcd for $C_{22}H_{34}N_3O_6Si$ 464.2217, found 464.2214.

(*E*)-2′-(Cyanomethylene)-2′-deoxyuridine (5). Compound **5** was synthesized from **18** (100 mg, 0.24 mmol) by the same method as described for the synthesis of **4** to give **5** (50 mg, 79% as a white solid, which was crystallized from EtOH/hexane): mp 209−211 °C; IR ν_{max} (neat)/cm^{-1} 2240 (CN); ^{1}H NMR (DMSO-d_6) δ 11.42 (br s, 1H, NH), 7.54 (d, 1H, H-6, J = 8.1 Hz), 6.52 (t, 1H, H-1′, J = 1.9 Hz), 6.16 (d, 1H, 3′-OH, J = 7.8 Hz), 6.06 (t, 1H, H-2″, J = 2.4 Hz), 5.66 (d, 1H, H-5, J = 8.1 Hz), 4.98 (t, 1H, 5′-OH, J = 5.5 Hz), 4.73 (m, 1H, H-3′, J = 2.4, J = 7.3 Hz), 3.76 (ddd, 1H, H-4′, J = 7.3, J = 2.6, J = 1.1 Hz), 3.69 (ddd, 1H, H-5′a, J = 2.6, J = 5.3, J = 12.1 Hz), 3.56 (ddd, 1H, H-5′b, J = 1.1, J = 5.3, J = 12.1 Hz); NOE, irradiate H-1′, observe H-2″ (7.0%), H-4′ (2.6%), and H-6 (5.5%); irradiate H-2″, observe H-1′ (3.5%) and H-6 (1.2%); irradiate H-3′, observe H-1′ (0.6%), H-2″ (0.7%), and H-6 (2.6%). Anal. Calcd for $C_{11}H_{11}N_3O_5 \cdot 0.4H_2O$: C, 48.49; H, 4.37; N, 15.42. Found: C, 48.60; H, 4.27; N, 15.18.

(2′*R*)-2′-*C*-(Carboxymethyl)-2′-deoxy-2′-(phenylthio)uridine 2′,3′-Lactone (22). A THF solution of TBAF (1 M, 2.7 mL, 2.7 mmol) was added to a mixture of **9** (680 mg, 1.10 mmol) and AcOH (0.16 mL, 2.8 mmol) in THF at 0 °C. The mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the residue was purified on a silica gel column with 2% EtOH/$CHCl_3$ to give **22** (282 mg, 68% as a white solid): ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H), 7.87 (d, 1H, J = 8.1 Hz), 7.48−7.35 (m, 5H), 6.27 (s, 1H), 5.70 (d, 1H), 5.33 (br t, 1H), 4.91 (d, 1H, J = 5.5 Hz), 4.12 (br dd, 1H), 3.80−3.71 (m, 2H), 3.62 (d, 1H, J = 19.2 Hz), 3.02 (d, 1H, J = 19.2 Hz); FABMS m/z 377 [M$^+$ + 1]. Anal. Calcd for $C_{17}H_{16}N_2O_6S$: C, 54.25; H, 4.28; N, 7.44. Found: C, 54.22; H, 4.47; N, 7.23.

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