Nucleosides and Nucleotides. 156. Chelation-Controlled and Nonchelation-Controlled Diastereofacial Selective Thiophenol Addition Reactions at the 2′-Position of 2′-[(Alkoxycarbonyl)methylene]-2′-deoxyuridines: Conversion of (*Z*)-2′-[(Alkoxycarbonyl)methylene]-2′-deoxyuridines into Their (*E*)-Isomers[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 (**4**) with $Ph_3P{=}CHCO_2R$ (R = ethyl or *tert*-butyl) exclusively gave (*Z*)-2′-[(alkoxycarbonyl)methylene] derivatives **5** and **13**, respectively, in high yields. An unusual *β*-facial selectivity of thiophenol addition to the 2′-[(alkoxycarbonyl)methylene] moiety of **5** and **13** was observed, and this facial selectivity was found to be influenced by both the thiolate counter cation and the bulkiness of the alkoxy moiety. Treatment of 2′-[(ethoxycarbonyl)methylene] derivative **5** with LiSPh (1.5 equiv) in the presence of PhSH in THF selectively gave 2′*β*-(phenylthio) derivative **11** in high yield along with a trace of 2′α-(phenylthio) derivative **10**. On the other hand, when 2′-[(*tert*-butoxycarbonyl)methylene] derivative **13** was treated with KSPh in the presence of PhSH in dioxane/DMF, the facial selectivity was reversed to selectively give the 2′α-(phenylthio) adduct **14** (α:*β*, 77:23) in 90% yield. Oxidation of **14** with *m*-chloroperbenzoic acid in CH_2Cl_2 and subsequent pyrolysis of the resulting sulfoxides exclusively gave the (*Z*)-isomer **13** in 92% yield. The oxidative *syn*-elimination of the (2′*R*)-2′-[(*tert*-butoxycarbonyl)methyl]-2′-deoxy-2′-thiophenoxy-5′-*O*-(triisopropylsilyl)uridine (**17**), which was obtained from **14** in two steps, exclusively gave the desired (*E*)-[(*tert*-butoxycarbonyl)methylene] derivatives **18** in 90% yield. Deprotection of **18** gave the (*E*)-(carboxymethylene)-2′-deoxyuridine (**3**). The (*Z*)-(carboxymethylene)-2′-deoxyuridine (**2**) was synthesized from **13** in a similar manner.

Introduction

Ribonucleoside diphosphate reductase (RDPR), an essential enzyme in DNA synthesis, catalyzes the conversion of ribonucleoside diphosphates into their corresponding 2′-deoxyribonucleoside diphosphates.[2] The high activity of RDPR in tumor cells, in addition to the positive correlation between antitumor activity and inhibitory activity against RDPR,[2b,c] has led to intensive studies to find potent inhibitors of this enzyme.[2d] 2′-Deoxy-2′-methylenecytidine (DMDC, **1**)[3a] has potent antitumor activity against various solid tumors as well as leukemias and lymphomas.[3b−e] The time-dependent irreversible inhibition of RDPR by its 5′-diphosphate (DMDCDP)[3f] may be related to its antitumor activity, together with inhibition of DNA polymerases by its 5′-triphosphate.[3g] Based on the proposed mechanism of inactivation of RDPR by DMDCDP,[3f] the introduction of an electron-withdrawing substituent, such as a carboxy group,[4] at the terminus of the 2′-*exo*-methylene group may result in a stabilized allylic radical, which would increase its inhibitory effect on RDPR. We report here the synthesis of (*Z*)- and (*E*)-2′-(carboxymethylene)-2′-deoxyuridines (**2** and **3**) as potential mechanism-based inhibitors of RDPR. We previously described a facile method for conversion of the easily accessible (*Z*)-2′-(cyanomethylene)-2′-deoxy-5′-*O*-(triisopropylsilyl)uridine into its *E*-isomer *via* the sequential stereoselective addition of PhSH to the cyanomethylene moiety at the 2′-position from the α-face followed by a stereoselective oxidative *syn*-elimination reaction.[5] While using this method to convert (*Z*)-2′-deoxy-2′-[(ethoxycarbonyl)methylene] derivative **7** into its *E*-isomer, we encountered an unusual *β*-facial selectivity

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(4) Radical-stabilizing effect of carbonyl groups has been known: (a) Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem.* **1972**, *25*, 1081. (b) Julia, M. *Pure Appl. Chem.* **1967**, *15*, 167.

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(6) For references of the conjugate addition of thiolates to α,*β*-unsaturated esters see: (a) Kuwajima, I.; Murobushi, T.; Nakamura, E. *Synthesis* **1978**, 602. (b) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823. (c) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 363. (d) Kamimura, A.; Ono, N. *J. Chem. Soc., Chem. Commun.* **1988**, 1278. (e) Miyata, O.; Shinada, T.; Kawakami, N.; Taji, K.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K. *Chem. Pharm. Bull.* **1992**, *40*, 2579 and references cited therein.

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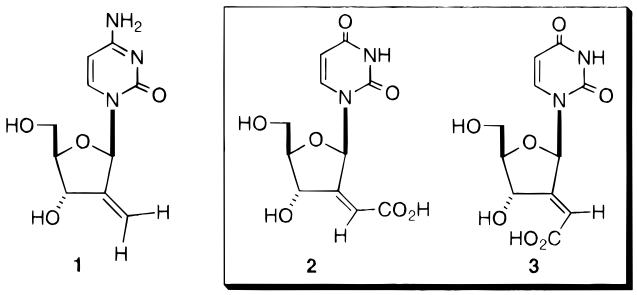
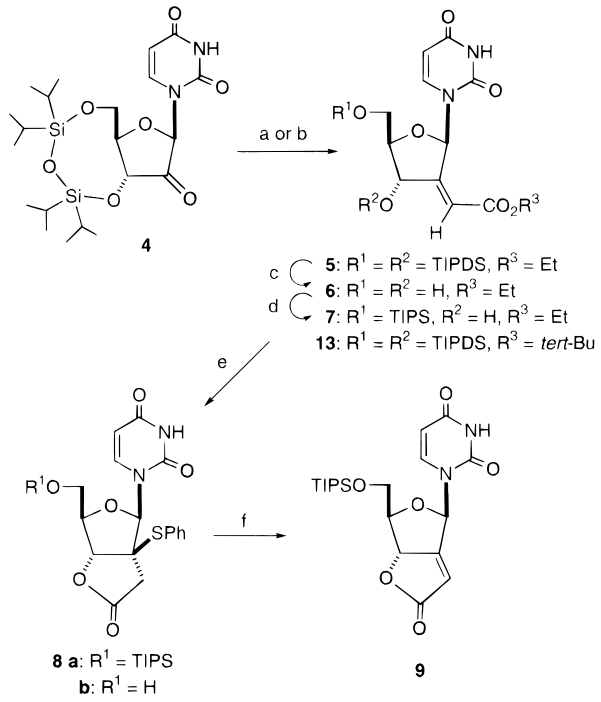
Chart 1



Scheme 1[a]



[a] (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2/THF, rt; (b) $Ph_3P{=}CHCO_2Bu^t$, THF, rt; (c) TBAF, AcOH, THF, 0 °C; (d) TIPSCl, imidazole, DMF, rt; (e) LiSPh, PhSH, THF, 0 °C - rt; (f) mCPBA , CH_2Cl_2, -78 °C - rt.

in the addition of benzenethiolate to its (*Z*)-[(2′-ethoxycarbonyl)methylene] moiety.[6] In this paper, we describe this unusual *β*-facial selectivity, its origin, and its reversal to the desired α-facial selective addition, as a key step in the preparation of the (*E*)-isomer.

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 (**4**)[7] with $Ph_3P{=}CHCO_2Et$ in THF gave (*Z*)-2′-deoxy-2′-ethoxycarbonylmethyleneuridine derivative **5** as a single stereoisomer in a quantitative yield. Desilylation of **5** followed by the selective protection of the 5′-hydroxyl group of **6** by a triisopropylsilyl (TIPS) group gave substrate **7** of the addition reaction in high yield (Scheme 1). We previously reported that the steric effects of both the nucleobase and the 5′-*O*-TIPS group together with the alleviated steric hindrance at the α-face of (*Z*)-2′-(cyanomethylene)-2′-deoxy-5′-*O*-(TIPS)uridine lead to the conjugate addition of PhSH to the 2′-(cyanomethylene) selectively from the α-face.[4] However, the treatment of **7** with LiSPh (1.5 equiv) in the presence of an excess of PhSH in THF unexpectedly gave the lactone **8a** exclusively in 92% yield (Scheme 1). The structure of **8a** was confirmed by the absence of both the 3′-hydroxyl proton and ethyl protons of the ester moiety and the presence of a pair of methylene protons (H-2″) at 3.53 and 3.03 ppm in the ^{1}H NMR spectrum. Furthermore, the oxidative *syn*-elimination of **8a** with mCPBA gave the unsaturated lactone derivative **9** in high yield, thus confirming the structure of **8a**. However, attempts to cleave the lactone moiety of **9** under various conditions to obtain the target **3** were unsuccessful. We first considered that formation of the lactone **8a** might be mediated by an equilibration between the α-(phenylthio) and the *β*-(phenylthio) adducts, where the *β*-(phenylthio) adduct is irreversibly converted into the stable **8a** with the assistance of the 3′-hydroxyl group under basic reaction conditions. If this indeed occurs, treatment of the more hindered ester **5** with LiSPh would result in at least a mixture of the two diastereomers or the α-(phenylthio) adduct selectively. However, the reaction again selectively gave the *β*-(phenylthio) derivative **11**, along with a trace of the α-(phenylthio) derivative **10** (Scheme 2; Table 1, entry 1).[8] The adducts **10** and **11** could be separated on silica gel column chromatography, and their structures were confirmed by ^{1}H NMR spectra and NOE experiments. Moreover, the (*S*)-configuration at the 2′-position of **11** was confirmed by the facile formation of lactone **8b** upon deprotection of the silyl groups with tetrabutylammonium fluoride (TBAF) in THF followed by neutralization with AcOH and chromatography on silica gel. The observed *β*-facial selectivity of the thiophenol addition to the (*Z*)-2′-[(ethoxycarbonyl)methylene] moiety of **5**[9] and **7** contrasts with the well-known α-facial selectivity of nucleophilic additions at the trigonal center of 2′-ketonucleosides,[10,11] 2′-deoxy-2′-methyleneuridines,[12] and 2′,3′-didehydro-2′,3′-dideoxy-3′-(nitro, cyano, or sulfonyl)uridines[13] as well as our recent results with (*Z*)-2′-(cyanomethylene)-2′-deoxyuridine derivatives.[5] The fact that *β*-facial selectivity occurs in the 1,4-addition of benzenethiolate to **5**[14] and **7** suggests involvement of a chelated intermediate. To verify this proposition, the ^{13}C-NMR spectrum of **5** was measured in THF/C_6D_6 (10:1) in the presence of different molar ratios of $LiClO_4$.[15] A noteworthy feature of the spectra was the downfield

(7) Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125.

(8) However, upon treatment of **10** and **11** with LiSPh/PhSH in THF, neither interconversion between the two isomers nor the generation of the starting material **5** was observed in the ^{1}H NMR spectrum, even at elevated temperatures. This implies that this facial selectivity is not related to the thermodynamic stability of the two adducts.

(9) A preferential α-selective hydride attack at the (ethoxycarbonyl)-methylene moiety of **5** was observed upon treatment with NaBH4 in MeOH. See: Ueda, T.; Shuto, S.; Sato, M.; Inoue, H. *Nucleosides Nucleotides* **1985**, *4*, 401.

(10) For examples of the hydride reduction of **4** see: (a) ref 7. (b) Hansske, F.; Robins, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 6736.

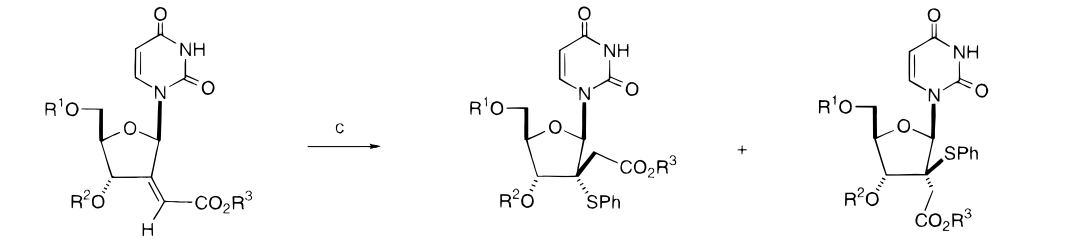
(11) For examples on the α-facial selective addition of carbon nucleophiles to 2′-keto-pyrimidine nucleosides see: (a) Matsuda, A.; Itoh, H.; Takenuki, K.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 945. (b) Awano, H.; Shuto, S.; Baba, M.; Kira, T.; Shigeta, S.; Matsuda, A. *BioMed. Chem. Lett.* **1994**, *4*, 367. (c) Iino, T.; Yoshimura, Y.; Matsuda, A. *Tetrahedron* **1994**, *50*, 10397. (d) Ueda, T.; Shuto, S.; Inoue, H. *Nucleosides Nucleotides* **1984**, *3*, 173. (e) Yoshimura, Y.; Saitoh, K.; Ashida, N.; Sakata, S.; Matsuda, A. *BioMed. Chem. Lett.* **1994**, *4*, 721. (f) Takenuki, K.; Itoh, H.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1990**, *38*, 2947.

(12) Cicero, D. O.; Neuner, P. J. S.; Franzese, O.; D'Onofrio, C.; Iribarren, A. M. *BioMed. Chem. Lett.* **1994**, *4*, 861.

(13) Hossain, N.; Garg, N.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 10061.

(14) ^{1}H NMR and MM2 calculations suggest that both **5** and the 2′-ketouridine derivative **4** have similar 3′-*endo*-puckering. This implies that the (ethoxycarbonyl)methylene moiety of **5** does not alter the sugar puckering to elevate the steric hindrance at the *β*-face of the 2′-position.

Scheme 2[a]



[a] (a) TBAF, AcOH, THF, 0 °C; (b) Dowex 50 (H^+), CH_3CN/H_2O (2:1), 90 -100 °C; (c) PhS^- (see Table 1); (h) $TIPDSCl_2$, pyridine, rt.

Table 1. Addition of Thiophenol to 5 and 13

entry	substrate	reagent (equiv)[a]	additives (equiv)	solvent	conditions	yield (%)	ratio (α: *β*)[b]
1	**5**	LiSPh (1.5)	none	THF	0 °C, 24 h	98	6:94
2	**5**	LiSPh (1.5)	12-C-4 (1.5)	THF	−10 °C, 0.5 h	98	13:87
3	**5**	LiSPh (1.5)	DABCO (2.0)	THF	rt, 5 days	91	6:94
4	**5**	NaSPh (1.5)	none	THF	rt, 9 h	45[c]	26:74
5	**5**	NaSPh (1.5)	18-C-6 (1.5)	THF	rt, 1 h	65[c]	31:69
6	**5**	KSPh (2.0)	18-C-6 (2.0)	THF	rt, 31 h	88	44:56
7	**5**	CsSPh (10)	none	THF/DMF	reflux, 48 h	sm[d]	−
8	**13**	LiSPh (1.5)	12-C-4 (1.5)	THF	−10 °C, 4 h	89	32:68
9	**13**	KSPh (1.5)	none	THF/DMF (6:1)	rt, 48 h	58	82:18
10	**13**	KSPh (1.5)	none	dioxane/DMF (5:1)	50 °C, 24 h	90	77:23

[a] All the reactions were performed in the presence of 10 equiv of PhSH, except for entry 10 (50 equiv). [b] The ratios were determined by the integration of the corresponding H-1′ in the ^1H NMR spectra. [c] The rest of the products was uracil. [d] The starting material was recovered.

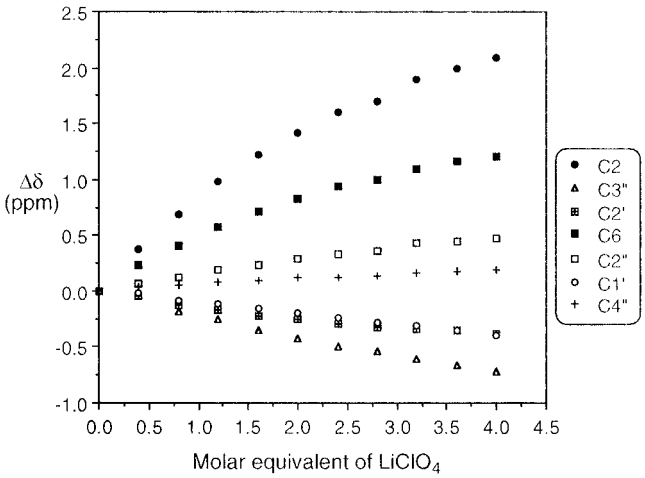


Figure 1. ^{13}C NMR chemical shift difference (Δδ) of **5** as a function of the molar equivalence of $LiClO_4$. ^{13}C NMR was measured at a concentration of 0.07 M in THF−C_6D_6 (10:1). Values were referenced to C_6D_6 at 128 ppm.

shifts of C-2, C-6, C-2″, and C-4″ and the upfield shift of the carbonyl carbon of the ester moiety (C-3″) and C-1′[16] with the addition of $LiClO_4$ (Figure 1).[17] The observed downfield shifts of both the C-2 and C-4″ in the ethyl ester moiety, which is consistent with electron depletion, suggests chelation of the LiSPh between the C-2 carbonyl oxygen in the uracil moiety and the ester moiety. This

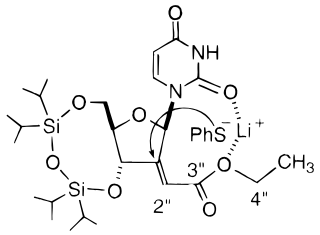


Figure 2. A possible explanation for the *β*-facial selectivity of the benzenethiolate addition at the 2′-ethoxycarbonylmethylene moiety of **5**.

chelation may be accompanied by the intramolecular delivery of the thiolate group from the sterically hindered *β*-face in the formation of **11** (Figure 2).

Attempts to selectively increase the α-facial addition *via* impeding the postulated chelation effect by performing the addition reaction in the presence of 12-crown-4 ether or DABCO[18] (Table 1, entries 2,3), or by conducting the addition reaction under high pressure in the absence of a base (data not shown), were unsuccessful. On the other hand, upon changing the countercation of the benzenethiolate to Na^+ or K^+, *β*-facial selectivity was lost (Table 1, entries 4−6). The ^{13}C NMR spectrum of **5** in the presence of $NaClO_4$ in THF/C_6D_6 showed a similar chemical shift difference pattern, but to a lesser degree than with $LiClO_4$ (data not shown). The similarity of the degree of ^{13}C chemical shifts of **5** in the presence of $LiClO_4$ and $NaClO_4$ with the observed facial selectivity, together with the unusual ^{13}C shift pattern of the ester moiety (an upfield shift of C-3″ and a downfield shift of C-4″) implied that the introduction of a bulky alkyl group at

(15) (a) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. (b) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Ibid.* **1982**, *60*, 809.

(16) Although an upfield shift was observed at C-1′ upon the addition of $LiClO_4$, it is not certain whether this shift is due to an increased electron density on C-1′ or to the dimensional anisotropic effect of the 2-carbonyl group.

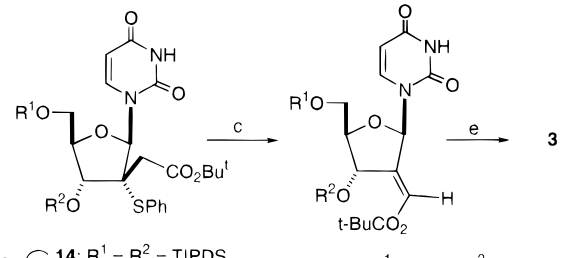
(17) Assignment of ^{13}C signals was based on DEPT and HSQC (heteronuclear single quantum coherence) experiments.

(18) Addition of thiophenol to **5** in the presence of counter cations incapable of chelation such as Et_3N, *i*-Pr_2NEt, or 1,1,3,3-tetramethylguanidine was attempted. However, decomposition or recovery of the starting material was observed.

the ester moiety would prevent chelate formation. Therefore, (*Z*)-2′-[(*tert*-butoxycarbonyl)methylene] derivative **13** was synthesized by the Wittig reaction of **4**, as a substrate for the thiophenol addition reaction. Treatment of **13** with an excess of PhSH in the presence of LiSPh in THF gave a mixture of the α-(phenylthio) derivative **14** and the *β*-(phenylthio) derivative **15** in a ratio of 32:68 (Table 1, entry 8). The ^{13}C NMR spectrum of **13** in the presence of $LiClO_4$ showed chemical shift differences at the nucleobase and the ester moiety similar to those in the [(ethoxycarbonyl)methylene] derivative **5** (data not shown), suggesting that the (*Z*)-2′-[(alkoxycarbonyl)methylene] moiety was likely to accommodate the aforementioned chelate even in the presence of the bulky *tert*-butyl group. On the other hand, treatment of **13** with an excess of PhSH in the presence of KSPh in dioxane/DMF selectively gave the desired 2′α-(phenylthio) derivative **14** (Table 1, entries 9, 10). In the reaction of **13**, the relatively softer K^+ would not form chelates probably due to the presence of the bulky *tert*-butyl group, to selectively give the α-addition product.[19] The (*E*)-2′-[(*tert*-butoxycarbonyl)methylene] derivatives **18** and **20** were synthesized as described below. When **20** was treated with LiSPh/PhSH in THF, none of the addition products was obtained even after a prolonged reaction time at elevated temperature. On the other hand, treatment of **18** with LiSPh under the same reaction conditions selectively gave the 2′α-(phenylthio) derivative **17** along with the lactone **8a** (87:13) in 83% yield. These results also imply the necessity of a chelated intermediate for the *β*-facial attack of the benzenethiolate, and the increased steric hindrance at the α-face would impede the α-facial attack of the benzenethiolate.

Treatment of **14** with mCPBA in CH_2Cl_2 at −78 °C, followed by warming the reaction mixture to room temperature with stirring for a further 72 h, gave the anticipated (*Z*)-[(*tert*-butoxycarbonyl)methylene] derivative **13** in 92% yield. This *Z*-selectivity is consistent with the previously observed reliance of the geometrical selectivity of the oxidative *syn*-elimination reaction on the conformation of the 2′*β*-(cyanomethyl) moiety.[5] We previously reported that a highly stereoselective oxidative *syn*-elimination of the (2′*R*)-2′-(cyanomethyl)-2′-(phenylthio) derivative into the corresponding (*E*)-(cyanomethylene) was achieved upon maximizing the steric effects at the 5′-position and allowing the cooperative coordination effect[20] of the 3′-hydroxyl. Therefore, **14** was converted into its 5′-*O*-TIPS derivative **17** after de-*O*-silylation of **14** and subsequent selective protection of the 5′-hydroxyl group in **16**. Treatment of **17** with mCPBA in CH_2Cl_2 at −78 °C followed by warming the mixture to room temperature exclusively gave the desired (*E*)-[(*tert*-butoxycarbonyl)methylene] derivative **18** in high yield (Scheme 3). Deprotection of **18** by TBAF in the presence of AcOH[21] in THF gave **19** in high yield. The Dowex 50 (H^+)-catalyzed hydrolysis[22] of the *tert*-butoxy ester group

Scheme 3[a]



[a] (a) TBAF, AcOH, THF, 0 °C; (b) TIPSCl, imidazole, DMF, rt; (c) mCPBA , CH_2Cl_2, -78 °C - rt; (d) TIPDS, imidazole, DMF, rt; (e) Dowex 50 (H^+), CH_3CN/H_2O (2:1), 90 -100 °C.

of **19** in CH_3CN/H_2O gave the (*E*)-2′-(carboxymethylene)-2′-deoxyuridine (**3**) in 95% yield. The (*Z*)-2′-(carboxymethylene)-2′-deoxyuridine (**2**) was synthesized from **13** in a similar manner.

In conclusion, phenylsulfenylation of (*Z*)-2′-[(alkoxycarbonyl)methylene]uridine derivatives proceeded smoothly by 1,4-addition. The diastereofacial selectivity of the reaction could be controlled by chelation- and nonchelation manner to selectively produce either the 2′α-(phenylthio) or 2′*β*-(phenylthio) derivatives. *β*-Facial selectivity was achieved by using a small 2′-[(alkoxycarbonyl)-methylene] moiety, such as **5** and **7**, and a hard cation, in this case Li^+, that can chelate strongly with the 2-carbonyl oxygen at the uracil moiety and the alkoxy oxygen of the 2′-[(alkoxycarbonyl)methylene] moiety. The α-facial selectivity was attained by using a bulky *tert*-butoxy group, as in **14**, and KSPh as a thiolate source. Dehydrophenylsulfenylation of the 2′α-(phenylthio) derivative **17** proceeded stereoselectively to give (*E*)-2′-[(*tert*-butoxycarbonyl)methylene]-2′-deoxyuridine (**18**), which is difficult to synthesize by Wittig-related reactions.

Experimental Section

General. Melting points are uncorrected. NMR spectra were recorded at 270, 400, or 500 MHz (^1H) and at 100 or 125 MHz (^{13}C), and are reported in ppm downfield from TMS. Mass spectra were obtained by fast-atom bombardment. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done with YMC gel 60 A (70−230 mesh).

(*Z*)-2′-Deoxy-2′-ethoxycarbonylmethylene-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (5). A solution of $Ph_3P{=}CHCO_2Et$ (2.6 g, 6.8 mmol) in CH_2Cl_2 (10 mL) was added to **4** (3.0 g, 6.2 mmol) in THF (15 mL) dropwise at 0 °C. The mixture was stirred at room temperature for 4.5 h and then quenched with aqueous saturated NH_4Cl. Aqueous workup and silica gel column chromatography with 20% EtOAc/hexane gave **5** (3.6 g, 96% as a colorless foam): ^{13}C NMR [THF−C_6D_6 (10:1), ^{13}C signals were assigned on the basis of DEPT and HSQC experiments] *δ* 165.0 (C4), 163.0 (C2), 160.4 (C3″), 150.2 (C2′), 145.3 (C6), 115.4 (C2″), 101.2 (C5), 88.0 (C1′), 82.4 (C4′), 75.2 (C3′), 63.9 (C5′), 60.7 (C4″), 17.3 (*i*-Pr), 17.5 (*i*-Pr), 17.4 (*i*-Pr), 17.3 (*i*-Pr), 17.2 (*i*-Pr), 17.0 (*i*-Pr), 14.0 (*i*-Pr), 13.8 (*i*-Pr), 13.6 (*i*-Pr), 13.2 (*i*-Pr), 13.1 (*i*-Pr); ^1H NMR ($CDCl_3$) *δ* 8.28 (s, 1H, H-N3), 7.32 (d, 1H, H-6, J = 8.0 Hz), 6.45 (d, 1H, H-1′, J = 1.7 Hz), 6.10 (t, 1H, H-2″, J = 2.2 Hz), 5.66 (dd, 1H, H-5, J = 1.7, J = 8.0 Hz), 5.32 (dt, 1H, H-3′, J = 2.2, J = 8.2 Hz), 4.21−4.09 (m, 3H, CH_2 and H-5′a), 4.06 (dd, 1H, H-5′b, J = 2.9, J = 12.6 Hz), 3.65 (ddd, 1H, H-4′, J = 8.2, J = 2.9, J = 4.6 Hz), 1.26 (t, 3H, CH_3, J = 7.1 Hz), 1.13−0.90 (m, 28H, H-isopropyl); NOE: irradiate H-2″, observe H-1′ (0.6%), H-3′ (2.0%), and isopropyl-H (8.2%); irradiate H-3′, observe H-2″ (3.0%), H-1′ (0.4%), H-4′ (3.0%), H-5′ (4.3%), and

(19) Due to solubility problems, the ^{13}C NMR spectrum of **5** in the presence of $KClO_4$ in THF/C_6D_6 could not be measured.

(20) For examples of the cooperative coordination to mCPBA see: (a) Johnson, 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.

(21) Azuma, A.; Nakajima, Y.; Nishizono, N.; Minakawa, N.; Suzuki, M.; Hanaoka, K.; Kobayashi, T.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1993**, *36*, 4183.

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H-6 (3.5%); irradiate CH_3, observe CH_2 (4.9%) and no other NOE enhancement was observed; FABMS *m*/*z* 555 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{42}N_2O_8Si_2$: C, 54.12; H, 7.63; N, 5.05. Found: C, 54.39; H, 7.56; N, 4.86.

(*Z*)-2′-Deoxy-2′-ethoxycarbonylmethyleneuridine (6). A THF solution of TBAF (1 M, 13.5 mL) was added to **5** (3.0 g, 5.4 mmol) in THF (25 mL) at 0 °C. The mixture was stirred for 30 min and then neutralized with AcOH, and the solvent was evaporated. The residue was purified on a silica gel column with 6% EtOH/$CHCl_3$ to give **6** (1.64 g, 97% as a pale gray solid): ^{1}H NMR (DMSO-d_6) δ 11.30 (s, 1H), 7.50 (s, 1H, J = 8.3 Hz), 6.60 (s, 1H), 6.02 (s, 1H, J = 2.2 Hz), 6.01 (d, 1H, J = 6.6 Hz), 5.55 (d, 1H, J = 8.3 Hz), 4.87 (t, 1H, J = 5.5 Hz), 4.69 (br m, 1H, became d after addition of D_2O, J = 8.2 Hz), 4.06 (q, 2H, J = 7.1 Hz), 3.72 (m, 1H), 3.51 (m, 2H), 1.14 (t, 3H); FABMS *m*/*z* 313 [$M^+ + 1$]. Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.80; H, 5.21; N, 9.16.

(*Z*)-2′-Deoxy-2′-ethoxycarbonylmethylene-5′-*O*-(triisopropylsilyl)uridine (7). Triisopropylsilyl chloride (0.44 mL, 2.04 mmol) was added to a mixture of **6** (400 mg, 1.27 mmol) and imidazole (139 mg, 2.04 mmol) in DMF (8 mL) at 0 °C. The mixture was stirred for 24 h at room temperature. Aqueous workup and silica gel column chromatography with 30% EtOAc/hexane gave **7** (526 mg, 90% as a white solid): ^{1}H NMR ($CDCl_3$) δ 8.33 (br s, 1H), 7.25 (d, 1H, J = 8.0 Hz), 6.55 (t, 1H, J = 1.8 Hz), 6.21 (t, 1H, J = 2.2 Hz), 5.65 (dd, 1H, J = 8.0, J = 2.3 Hz), 5.11 (m, 1H, became dt after addition of D_2O, J = 8.2, J = 2.0 Hz), 4.15 (m, 2H), 4.09 (dd, 1H, J = 4.8, J = 10.1 Hz), 3.95 (dd, 1H, J = 6.2, J = 10.1 Hz), 3.74 (ddd, 1H, J = 4.8, J = 6.2, J = 8.2 Hz), 2.56 (br s, 1H), 1.25 (t, 3H, J = 7.2 Hz), 1.18−0.97 (m, 21H); FABMS *m*/*z* 469 [$M^+ + 1$]. Anal. Calcd for $C_{22}H_{36}N_2O_7Si$: C, 56.39; H, 7.74; N, 5.98. Found: C, 56.42; H, 7.80; N, 5.82.

(2′*S*)-2′-Deoxy-2′-(carboxymethyl)-2′-(phenylthio)-5′-*O*-(triisopropylsilyl)uridine-3′,2′-γ-lactone (8a). Compound **7** (550 mg, 1.17 mmol) was treated with a THF solution of LiSPh (0.58 M, 3.0 mL, 1.74 mmol) and PhSH (1.2 mL, 12 mmol) in THF (15 mL) at 0 °C. The mixture was stirred for 2 h and then neutralized with aqueous AcOH. Aqueous workup and silica gel column chromatography with 25% EtOAc/hexane gave **8a** (571 mg, 92% as a colorless foam): ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.72 (d, 1H, J = 8.2 Hz), 7.47−7.34 (m, 5H), 6.16 (s, 1H), 5.73 (dd, 1H, J = 8.2, J = 2.1 Hz), 5.03 (d, 1H, J = 3.9 Hz), 4.19 (m, 1H), 4.13 (dd, 1H, J = 11.0, J = 4.9 Hz), 4.10 (dd, 1H, J = 11.0, J = 4.2 Hz), 3.53 (d, 1H, J = 18.9 Hz), 3.03 (d, 1H, J = 18.9 Hz), 1.26−0.99 (m, 21H); FABMS *m*/*z* 533 [$M^+ + 1$]. Anal. Calcd for $C_{26}H_{36}N_2O_6SSi$: C, 58.62 H, 6.81; N, 5.26. Found: C, 58.42; H, 6.92; N, 5.20.

2′-Deoxy-2′-(carboxymethylene)-5′-*O*-(triisopropylsilyl)uridine-3′,2′-γ-lactone (9). Compound **8a** (590 mg, 1.11 mmol) in CH_2Cl_2 (10 mL) was treated with mCPBA (213 mg, 1.23 mmol) in CH_2Cl_2 (3 mL) at −78 °C. The mixture was stirred for 15 min and then warmed gradually to room temperature. The mixture was neutralized with saturated aqueous $NaHCO_3$, and the solvent was removed under reduced pressure. The residue was taken in EtOAc and the solution washed with H_2O and brine. The organic phase was dried (Na_2SO_4) and evaporated. The residue was dissolved in toluene and heated under reflux for 1 h. The solvent was removed under reduced pressure, and the residue was purified on a silica gel column with 50% EtOAc/hexane to give **9** (418 mg, 89% as a white solid): ^{1}H NMR ($CDCl_3$) δ 8.88 (br s, 1H), 7.97 (d, 1H, J = 8.2 Hz), 6.56 (s, 1H), 6.42 (d, 1H, J = 2.0 Hz), 5.74 (d, 1H, J = 8.2 Hz), 5.62 (dd, 1H,J = 8.4 Hz), 4.24 (dd, 1H, J = 1.4, J = 12.0 Hz), 4.05 (dd, 1H, J = 1.4, J = 12.0 Hz), 3.75 (dt, 1H, J = 8.4, J = 1.4 Hz), 1.21−0.96 (m, 21H); FABMS *m*/*z* 423 [$M^+ + 1$]. Anal. Calcd for $C_{20}H_{30}N_2O_6Si$: C, 56.85; H, 7.16; N, 6.63. Found: C, 56.82; H, 7.08; N, 6.69.

(2′*R*)-2′-Deoxy-2′-ethoxycarbonylmethyl-2′-(phenylthio)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (10) and (2′*S*)-2′-deoxy-2′-ethoxycarbonylmethyl-2′-(phenylthio)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (11). Compound **5** (1.80 g, 3.25 mmol) was treated with a THF solution of LiSPh (0.58 M, 8.4 mL, 4.9 mmol) and PhSH (3.35 mL, 32.5 mmol) in THF at 0 °C under the same conditions as described for the synthesis of **8a**. Aqueous workup and silica gel column chromatography with 10% EtOAc/hexane gave **10** (130 mg, 6%, as a white solid which was crystallized from EtOAc/hexane) and then with 12% EtOAc/hexane gave **11** (1.98 g, 92% as a white solid, which was crystallized from EtOAc/hexane). The physical data of **10**: mp 185−187 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H, H-N3), 7.81 (d, 1H, H-6, J = 8.3 Hz), 7.68 (m, 2H, 2′-SPh), 7.47−7.38 (m, 3H, 2′-SPh), 6.12 (s, 1H, H-1′), 5.56 (dd, 1H, H-5, J = 2.4, J = 8.3 Hz), 5.47 (d, 1H, H-3′, J = 9.3 Hz), 4.57 (dd, 1H, H-4′, J = 2.4, J = 9.3 Hz), 4.25 (d, 1H, H-5′a, J = 13.7 Hz), 4.11 (dd, 1H, H-5′b, J = 13.7, J = 2.9 Hz), 4.00 (dq, 1H, CH_2CH3, J = 14.2, J = 7.3 Hz), 3.74 (dq, 1H, CH_2CH$_3$, J = 14.2, J = 7.3 Hz), 3.01 (d, 1H, 2′-CH_2aCO$_2$Et, J = 16.1 Hz), 2.89 (d, 1H, 2′-CH_2bCO$_2$Et, J = 16.1 Hz), 1.13−0.94 (m, 31H, CH$_2$CH_3, and H-isopropyl); NOE: irradiate H-1′, observe H-6 (1.3%), SPh (7.9%), H-3′ (0.5%), H-4′ (1.8%), CH$_2$a (1.2%), and no NOE enhancement was observed at CH$_2$b signal; irradiate CH$_2$a, observe SPh (8.3%), H-1′ (4.9%), CH$_2$b (24.8%), and no NOE enhancement was observed at H-3′; irradiate CH$_2$b, observe SPh (2.0%), H-3′ (3.3%), CH$_2$b (26.0%), and no NOE enhancement was observed at H-1′; FABMS *m*/*z* 665 [$M^+ + 1$]. Anal. Calcd for $C_{31}H_{48}N_2O_8SSi_2$: C, 55.99; H, 7.28; N, 4.21. Found: C, 55.74; H, 7.24; N, 4.14. The physical data of **11**: mp 146−146.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H, H-N3), 7.74 (d, 1H, H-6, J = 8.3 Hz), 7.38−7.30 (m, 5H, 2′-SPh), 6.88 (s, 1H, H-1′), 5.81 (dd, 1H, H-5, J = 2.4, J = 8.3 Hz), 4.35 (d, 1H, H-3′, J = 6.8 Hz), 4.16−4.03 (m, 5H, H-4′, H-5′a,b, and 2′-CH_2CH$_3$, J = 6.8, J = 3.4, J = 10.7 Hz), 2.99 (d, 1H, 2′-CH_2aCO$_2$Et, J = 16.6 Hz), 2.91 (d, 1H, 2′-CH_2bCO$_2$Et, J = 16.6 Hz), 1.21 (t, 3H, CH$_2$CH_3, J = 7.3 Hz), 1.14−1.00 (m, 28H, H-isopropyl); NOE: irradiate H-1′, observe H-6 (2%), H-3′ (1%), H-4′ (5.6%), CH$_2$a (2.7%), CH$_2$b (0.4%), isopropyl-H (1.5%), and no NOE enhancement was observed at SPh signal; irradiate CH$_2$a, observe SPh (4.3%), H-1′ (9.3%), CH$_2$b (11.7%), H-4′ (0.7%), isopropyl-H (2.7%); irradiate CH$_2$b, observe SPh (7.4%), H-3′ (0.9%), H-4′ (2.6%), CH$_2$b (15.0), isopropyl-H (4.6%); FABMS *m*/*z* 665 [$M^+ + 1$]. Anal. Calcd for $C_{31}H_{48}N_2O_8SSi_2$: C, 55.99; H, 7.28; N, 4.21. Found: C, 55.73; H, 7.22; N, 4.17.

(2′*S*)-2′-Deoxy-2′-ethoxycarbonylmethyl-2′-(phenylthio)uridine (12) and (2′*S*)-2′-(Carboxymethyl)-2′-deoxy-2′-(phenylthio)uridine-3′,2′-γ-lactone (8b). A THF solution of TBAF (1 M, 5.2 mL) was added to a solution of **11** (1.38 g, 2.10 mmol) in THF (15 mL) at 0 °C. The mixture was stirred at room temperature for 1.5 h and then neutralized with AcOH. The solvent was evaporated, and the residue was purified on a silica gel column with 1% EtOH/$CHCl_3$ to give **12** (0.11 g, 12%, as a white solid) and then with 2% EtOH/$CHCl_3$ to give **8b** (0.51 g, 65% as a colorless foam). The physical data of **12**: ^{1}H NMR (DMSO-d_6) δ 11.11 (s, 1H), 8.18 (br d, 1H), 7.64−7.40 (m, 5H), 6.27 (s, 1H), 5.72 (d, 1H, J = 3.8 Hz), 5.50 (d, 1H, J = 8.1 Hz), 5.40 (br s, 1H), 4.97 (br dd, 1H, J = 9.1 Hz), 4.18 (dd, 1H, J = 9.1 Hz), 3.98 (m, 1H), 3.88−3.80 (m, 2H), 3.69 (br dd, became dd after addition of D_2O, 1H, J = 2.0, J = 12.0 Hz), 2.80 (d, 1H, J = 15.5 Hz), 2.62 (d, 1H, J = 15.5 Hz), 1.13 (t, 3H, J = 7.2 Hz); FABMS *m*/*z* 423 [$M^+ + 1$]. Anal. Calcd for $C_{19}H_{22}N_2O_7S$: C, 54.02; H, 5.25; N, 6.63. Found: C, 53.83; H, 5.24; N, 6.44. The physical data of **8b**: ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H), 7.87 (d, 1H, J5,6 = 8.1 Hz), 7.48−7.35 (m, 5H), 6.27 (s, 1H), 5.70 (d, 1H, $J_{5,6}$ = 8.1 Hz), 5.33 (br t, 1H), 4.91 (d, 1H, $J_{3',4'}$ = 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.

(*Z*)-2′-[(*tert*-Butoxycarbonyl)methylene]-2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (13). Compound **13** (4.6 g, 95% as a colorless foam) was obtained by the reaction of **4** (4.0 g, 8.3 mmol) with $Ph_3P{=}CHCO_2Bu^t$ (6.2 g, 17 mmol) in THF (50 mL) by the method described for the synthesis of **5**: ^{13}C NMR [THF−C_6D_6 (10:1), ^{13}C signals were assigned on the basis of DEPT and HSQC experiments] δ 164.7 (C4), 163.1 (C2), 159.5 (C3″), 150.2 (C2′), 145.3 (C6), 117.1 (C2″), 101.0 (C5), 87.9 (C1′), 82.5 (C4′), 81.1 (C4″), 75.1 (C3′), 63.9 (C5′), 27.7 (CH$_3$) 17.5 (*i*-Pr), 17.4 (*i*-Pr), 17.3 (*i*-Pr), 17.2 (*i*-Pr), 17.0 (*i*-Pr), 14.0 (*i*-Pr), 13.9 (*i*-Pr), 13.6 (*i*-Pr), 13.2

(*i*-Pr), 13.1 (*i*-Pr); ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 7.23 (d, 1H, J = 8.1 Hz), 6.47 (t, 1H,J = 1.8 Hz), 6.01 (t, 1H, J = 2.2 Hz), 5.64 (dd, 1H, J = 2.4, J = 8.1 Hz), 5.27 (dt, 1H, J = 2.0, J = 8.3 Hz), 4.11 (dd, 1H, J = 5.0, J = 12.6 Hz), 4.05 (dd, 1H, J = 3.0, J = 12.6 Hz), 3.65 (ddd, 1H, J = 8.3, J = 3.0, J = 5.0 Hz), 1.42 (s, 9H), 1.13−0.99 (m, 28H); FABMS m/z 583 [M^+ + 1]. Anal. Calcd for $C_{27}H_{46}N_2O_8Si_2$: C, 55.64; H, 7.96; N, 4.81. Found: C, 55.61; H, 7.89; N, 4.67.

(2′*R*)-2′-[(*tert*-Butoxycarbonyl)methyl]-2′-deoxy-2′-(phenylthio)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (14) and (2′*S*)-2′-[(*tert*-Butoxycarbonyl)methyl]-2′-deoxy-2′-(phenylthio)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (15). A mixture of **13** (8.0 g, 14 mmol), KSPh (3.1 g, 21 mmol), and PhSH (71 mL, 6.9 mol) was dissolved in dioxane/DMF (5:1, 100 mL) and was heated for 24 h at 50 °C. The mixture was cooled to room temperature and neutralized with aqueous AcOH. Aqueous workup and silica gel column chromatography with 25% EtOAc/hexane gave a mixture of **14** and **15** (8.6 g, 90% as a white solid, in a **14**/**15** ratio of 77:23, determined by HPLC). Crystallization of the mixture from EtOAc/hexane provided **14** (4.4 g, as a white crystals). The physical data of **14**: mp 189−190 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 1H, J = 8.1 Hz), 7.80 (s, 1H), 7.69 (m, 2H), 7.48−7.39 (m, 3H), 6.07 (s, 1H), 5.75 (d, 1H, J = 8.1 Hz), 5.58 (d, 1H, J = 9.0 Hz), 4.58 (br d, 1H), 4.27 (d, 1H, J = 13.5 Hz), 4.11 (dd, 1H, J = 13.5, J = 1.6 Hz), 3.04 (d, 1H, J = 18.3 Hz), 2.92 (d, 1H, J = 18.3 Hz), 1.26 (s, 9H), 1.14−0.95 (m, 28H); FABMS m/z 694 [M^+ + 1]. Anal. Calcd for $C_{33}H_{52}N_2O_8SSi_2$: C, 57.19; H, 7.56; N, 4.04. Found: C, 57.07; H, 7.54; N, 4.12. The physical data of **15**: ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 1H), 7.73 (d, 1H, J = 8.2 Hz), 7.38−7.28 (m, 5H), 6.84 (s, 1H), 5.79 (d, 1H,J = 8.2 Hz), 4.33 (d, 1H, J = 7.4 Hz), 4.17 (ddd, 1H, J = 7.4, J = 3.6, J = 3.7 Hz), 4.09 (m, 2H), 2.86 (d, 1H, J = 16.5 Hz), 2.82 (d, 1H, J = 16.5 Hz), 1.42 (s, 9H), 1.14−0.95 (m, 28H).

(2′*R*)-2′-[(*tert*-Butoxycarbonyl)methyl]-2′-deoxy-2′-(phenylthio)uridine (16). A THF solution of TBAF (1 M, 12.6 mL) was added to a mixture of **14** (3.5 g, 5.1 mmol) and AcOH (0.72 mL) in THF (25 mL) at 0 °C. The mixture was stirred for 2 h and then the solvent was evaporated. The residue was purified on a silica gel column with 2% MeOH/$CHCl_3$ to give **16** (2.16 g, 95% as a white solid): ^{1}H NMR (DMSO-d_6) δ 11.10 (s, 1H), 8.20 (br d, 1H), 7.64 (m, 2H), 7.44 (m, 3H), 6.10 (br s, 1H), 5.52−5.49 (m, 2H, J = 8.2 Hz), 5.40 (br s, 1H), 4.84 (dd, 1H, J = 8.9 Hz), 4.17 (d, 1H, J = 8.9 Hz), 3.87 (br d, 1H, J = 12.4 Hz), 3.68 (br d, 1H, J = 12.4 Hz), 2.67 (d, 1H, J = 16.0 Hz), 2.54 (d, 1H, J = 16.0 Hz), 1.39 (s, 9H); FABMS m/z 451 [M^+ + 1]. Anal. Calcd for $C_{21}H_{26}N_2O_7S$: C, 55.99; H, 5.82; N, 6.22. Found: C, 55.86; H, 5.90; N, 6.05.

(2′*R*)-2′-[(*tert*-Butoxycarbonyl)methyl]-2′-deoxy-2′-(phenylthio)-5′-*O*-(triisopropylsilyl)uridine (17). Triisopropylsilyl chloride (0.88 mL, 4.1 mmol) was added to a mixture of **16** (1.6 g, 3.4 mmol) and imidazole (290 mg, 4.2 mmol) in DMF (10 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. Aqueous workup and silica gel column chromatography with 30% EtOAc/hexane gave **17** (1.9 g, 91% as a colorless foam): ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1H, J = 8.1 Hz), 7.85 (br s, 1H), 7.71−7.42 (m, 5H), 6.17 (s, 1H), 5.61 (dd, 1H, J = 8.1, J = 1.7 Hz), 4.89 (br s, 1H), 4.65 (d, 1H, J = 9.0 Hz), 4.47 (d, 1H, J = 9.0 Hz), 4.23 (d, 1H, J = 11.6 Hz), 4.05 (d, 1H, J = 11.6 Hz), 2.94 (d, 1H, J = 15.4 Hz), 2.18 (d, 1H, J = 15.4 Hz), 1.57 (s, 9H), 1.20−0.71 (m, 21H); FABMS m/z 607 [M^+ + 1]. Anal. Calcd for $C_{30}H_{46}N_2O_7SSi$: C, 59.38; H, 7.64; N, 4.62. Found: C, 59.15; H, 7.64; N, 4.39.

Addition of Thiophenol to 18. A THF solution of LiSPh (0.58 M, 0.52 mL, 0.3 mmol) was added to a mixture of **18** (100 mg, 0.2 mmol) and PhSH (0.21 mL, 2 mmol) in THF (3 mL) at 0 °C. The mixture was stirred at room temperature for 20 h and then neutralized with AcOH. Aqueous workup and silica gel column chromatography gave **17** and **8a** (100 mg, 84% in a **17**/**8a** ratio of 83:17, determined by the integration of the H-1′ in the ^{1}H NMR spectrum).

Oxidative *Syn*-Elimination of 14. mCPBA (60 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **14** (200 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) at −78 °C. The mixture was stirred for 15 min and then warmed to room temperature, and the mixture was stirred for further 72 h. The mixture was neutralized with 5% aqueous $NaHCO_3$ and diluted with EtOAc, and the organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography with 20% EtOAc/hexane to give **13** (156 mg, 92% as a colorless foam).

(*Z*)-2′-[(*tert*-Butoxycarbonyl)methylene]-2′-deoxyuridine (21). A THF solution of TBAF (1 M, 15.9 mL) was added to a mixture of **13** (3.7 g, 6.35 mmol) and AcOH (0.9 mL, 16 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 1 h. The solvent was evaporated, and the residue was purified on a silica gel column with 2% EtOH in $CHCl_3$ to give **21** (2.0 g, 91% as a white solid): ^{1}H NMR (DMSO-d_6) δ 11.29 (s, 1H),7.46 (d, 1H, J = 8.0 Hz), 6.60 (t, 1H, J = 1.8 Hz), 5.95 (t, 1H, J = 2.3 Hz), 5.93 (d, 1H, J = 6.8 Hz), 5.56 (d, 1H, J = 8.0 Hz), 4.85 (t, 1H, J = 5.1 Hz), 4.63 (m, became dt after addition of D_2O, 1H, J = 8.2 Hz), 3.70 (m, 1H, J = 10.2, J = 5.1 Hz), 3.53−3.39 (m, 2H), 1.35 (s, 9H); FABMS m/z 341 [M^+ + 1]. Anal. Calcd for $C_{15}H_{20}N_2O_7$: C, 52.94; H,5.92; N, 8.23. Found: C, 52.86; H, 5.97; N, 8.23.

(*E*)-2′-[(*tert*-Butoxycarbonyl)methylene]-5′-*O*-(triisopropylsilyl)uridine (18). Compound **17** (1.8 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was treated with mCPBA (614 mg, 3.56 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The mixture was stirred for 15 min and then warmed gradually to room temperature, and the stirring was continued for further 10 h. Aqueous workup and silica gel column chromatography gave **18** (1.33 g, 90% as a colorless foam): ^{13}C NMR ($CDCl_3$) δ 166.2, 162.8, 160.3, 150.4, 140.5, 120.4, 103.3, 84.6, 84.5, 83.0, 68.6, 61.8, 28.0, 17.9, 11.9; ^{1}H NMR ($CDCl_3$) δ 8.66 (br s, 1H), 7.51 (d, 1H, J = 8.1 Hz), 6.75 (t, 1H, J = 1.7 Hz), 5.94 (t, 1H, J = 2.0 Hz), 5.70 (dd, 1H, J = 8.1, J = 2.0 Hz), 5.18 (dt, 1H, J = 6.6, J = 2.0 Hz), 4.96 (br s, 1H), 4.13 (m, 1H), 4.05 (dt, 1H, J = 6.6, J = 2.1 Hz), 4.00 (dd, 1H, J = 2.1, J = 11.0 Hz), 1.49 (s, 9H), 1.27−0.94 (m, 21H); HR FABMS calcd for $C_{24}H_{41}N_2O_7Si$ 497.2682, found 497.2680.

(*E*)-2′-[(*tert*-Butoxycarbonyl)methylene]-2′-deoxyuridine (19). A THF solution of TBAF (1 M, 1.4 mL) was added to a mixture of **18** (560 mg, 1.13 mmol) and AcOH (1 M, 1.4 mL) in THF (7 mL) at 0 °C. The mixture was stirred for 1 h and then the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column with 2% EtOH/$CHCl_3$ to give **19** (350 mg, 91% as a colorless foam): ^{13}C NMR (DMSO-d_6) δ 164.1, 163.1, 156.9, 150.8, 141.5, 118.5, 102.9, 86.0, 84.1, 80.9, 68.7, 61.2, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 27.7; ^{1}H NMR (DMSO-d_6) δ 11.36 (s, 1H), 7.52 (d, 1H, J = 8.1 Hz), 6.59 (s, 1H), 5.74 (s, 1H), 5.66 (dd, 1H, J = 8.1, J = 1.3 Hz), 5.42 (d, 1H, J = 5.5 Hz), 5.02 (br m, 1H), 4.96 (t, 1H, J = 5.2 Hz), 3.88 (ddd, 1H, J = 7.7, J = 3.1, J = 4.4 Hz), 3.63 (m, 1H, became dd after addition of D_2O, J = 12.0, J = 3.1 Hz), 3.58 (m, became dd after addition of D_2O, 1H, J = 12.0, J = 4.4 Hz), 1.45 (s, 9H); HR FABMS calcd for $C_{15}H_{21}N_2O_7$ 341.1348, found 341.1320.

(*E*)-2′-[(*tert*-Butoxycarbonyl)methylene]-2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (20). 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (120 μL, 0.37 mmol) was added to **19** (100 mg, 0.29 mmol) in pyridine (3 mL) at 0 °C. The mixture was stirred at room temperature for 12 h. The solvent was evaporated and coevaporated with toluene. The residue was purified on a silica gel column with 20% EtOAc/hexane to give **20** (93 mg, 55% as a colorless foam): ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.04 (d, 1H, J = 8.2 Hz), 6.69 (s, 1H), 5.77 (d, 1H, J = 8.2 Hz), 5.70 (br s, 1H), 5.53 (m, 1H), 4.13−4.07 (m, 2H), 3.75 (dd, 1H, J = 11.2 Hz), 1.47 (s, 9H), 1.25−0.93 (m, 28H); HR FABMS calcd for $C_{27}H_{47}N_2O_8Si_2$ 583.2870, found 583.2879.

(*Z*)-2′-(Carboxymethylene)-2′-deoxyuridine (2). A suspension of **21** (1.07 g, 3.14 mmol) and Dowex 50 (ca. 1 g, H^+) in CH_3CN-H_2O (1:2, 20 mL) was heated at 100 °C for 9 h. The mixture was cooled to room temperature and the resin was removed by filtration. The filtrate was evaporated and coevaporated with MeOH. The residual syrup was purified on a silica gel column with 45% MeOH/$CHCl_3$ to give **2** (0.85 g, 95% as a white powder): ^{13}C NMR (DMSO-d_6) δ 169.0, 163.6, 151.5, 150.2, 143.9, 123.7, 100.7, 84.6, 82.9, 70.7, 61.0; ^{1}H NMR (DMSO-d_6 + D_2O) δ 7.43 (d, 1H, J = 8 Hz), 6.66 (s,

1H), 5.98 (s, 1H), 5.54 (d, 1H, $J = 8$ Hz), 4.59 (dt, 1H, $J = 7.5$ Hz), 3.57−3.50 (m, 3H); HR FABMS calcd for $C_{11}H_{11}N_2O_7$ 283.0566, found 283.0552.

(*E*)-2′-(Carboxymethylene)-2′-deoxyuridine (3). A suspension of **20** (120 mg, 0.35 mmol) and Dowex 50 (ca. 120 mg, H^+) in CH_3CN-H_2O (1:2, 5 mL) was heated at 50 °C for 24 h. The mixture was cooled to room temperature, and the resin was filtered off. The filtrate was evaporated and coevaporated with MeOH. The residual syrup was purified on a silica gel column with 45% MeOH/$CHCl_3$ to give **3** (91 mg, 91% as a white powder): ^{13}C NMR (DMSO-d_6) δ 170.3, 163.0, 151.5, 150.6, 141.7, 127.1, 102.5, 84.4, 84.1, 69.4, 60.7; ^{1}H NMR (DMSO-d_6 + D_2O): δ 7.46 (d, 1H, $J = 8$ Hz), 6.44 (s, 1H), 5.76 (s, 1H), 5.66 (d, 1H, $J = 8$ Hz), 4.73 (br dd, 1H), 3.74−3.68 (m, 2H), 3.56 (m, 1H); HR FABMS calcd for $C_{11}H_{11}N_2O_7$ 283.0566, found 283.0577.

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Supporting Information Available: Copies of ^{1}H NMR spectra of **2**, **3**, **18**, **19**, and **20** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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