Nucleic Acid Related Compounds. 73. Fluorination of Uridine 2'-Thioethers with Xenon Difluoride or (Diethylamino)sulfur Trifluoride. Synthesis of Stable 2'-[Alkyl(or Aryl)sulfonyl]-2'-deoxy-2'-fluorouridines[1]

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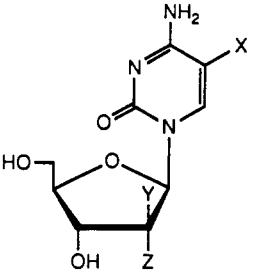
Treatment of 2,2'-anhydro-1-β-D-arabinofuranosyluracil with thiolate anions gave the 2'-*S*-alkyl(and aryl)-2'-thiouridines (1). Oxidation of 3',5'-di-*O*-acetyl-2'-*S*-alkyl(and aryl)-2'-thiouridines (2) with 3-chloroperoxybenzoic acid (MCPBA) gave the diastereomeric sulfoxides 4. Treatment of 2 with XeF_2 or 4 with (diethylamino)sulfur trifluoride/$SbCl_3$ gave the diastereomeric 3',5'-di-*O*-acetyl-2'-*S*-alkyl(and aryl)-2'-fluoro-2'-thiouridines (9). These α-fluoro thioethers were oxidized (MCPBA) to their stable sulfone derivatives 11 that are analogues of the biologically active 2'-deoxy-2',2'-difluoro nucleosides. Stereochemistry (2'*S*) and conformations of the major diastereomers were established by X-ray crystallography. Efficient conversions of 11 to the cytidine α-fluoro sulfones 14 were achieved.

The size and electronegativity of the fluorine atom make isosteres of important biological molecules in which hydrogen has been replaced by fluorine of significant interest.[2] Nucleosides substituted at C2' in the sugar moiety with fluorine, including the 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) analogues[3] of thymidine, 5-iodouridine, 5-iodocytidine (FIAC, A), and 5-ethyluridine, and a 2'-fluoroarabinofuranosyladenine analogue,[4] show anticancer and antiviral activity. Some 1-(2-deoxy-2-fluoro-β-D-ribofuranosyl) analogues of cytidine (B), 5-halouridine, and 5-(iodovinyl)uridine display similar activity.[5] Recently the preparation and anti-HIV activity of 2',3'-didehydro-2',3'-dideoxy-2'-fluoro analogues of cytidine, uridine, and thymidine have been reported,[6] and 2'-deoxy-2'(*S*)-fluoro ("arabino") analogues[7] of the anti-AIDS agents 3'-azido-3'-deoxythymidine (AZT) and 2',3'-dideoxycytidine (ddC) have been prepared. Fluoro sugar nucleosides usually have been synthesized by coupling fluoro sugar derivatives with heterocyclic bases or by transformations on intact nucleoside derivatives including: (i) epoxide cleavage, (ii) displacement of a sulfonyloxy group, or (iii) attack at the carbohydrate terminus of a sugar–base anhydro bond, with fluoride reagents. Syntheses of fluorinated-sugar nucleosides have been reviewed,[8] and recent applications of (diethylamino)sulfur trifluoride (DAST) have provided a number of fluoro[8-11] and difluoro analogues[10-12] from naturally occurring nucleosides.



A, X = I, Y = F, Z = H
B, X = Y = H, Z = F
C, X = H, Y = Z = F

Nucleoside analogues with *gem*-difluoro substitution in the ribose ring also have been prepared.[12,13] Treatment of a 3'-ketothymidine derivative with DAST was reported to give 3'-deoxy-3',3'-difluorothymidine in low yield.[12] The Eli Lilly group has pursued multistep syntheses of 2-deoxy-2,2-difluoro-D-ribose derivatives and couplings with pyrimidines (α/β ~4:1)[13a] and purines (α/β ~1:1)[13b] to obtain new and biologically fascinating nucleoside analogues. The β-anomer of 2'-deoxy-2',2'-difluorocytidine (dFdCyd, C) has potent anticancer activity against solid tumors that usually are refractory to chemotherapy, and C is in human clinical trials.[14] The inhibition of ribonucleotide reductase was inferred by biological studies with dFdCyd (C),[15] and very recently it was demonstrated that

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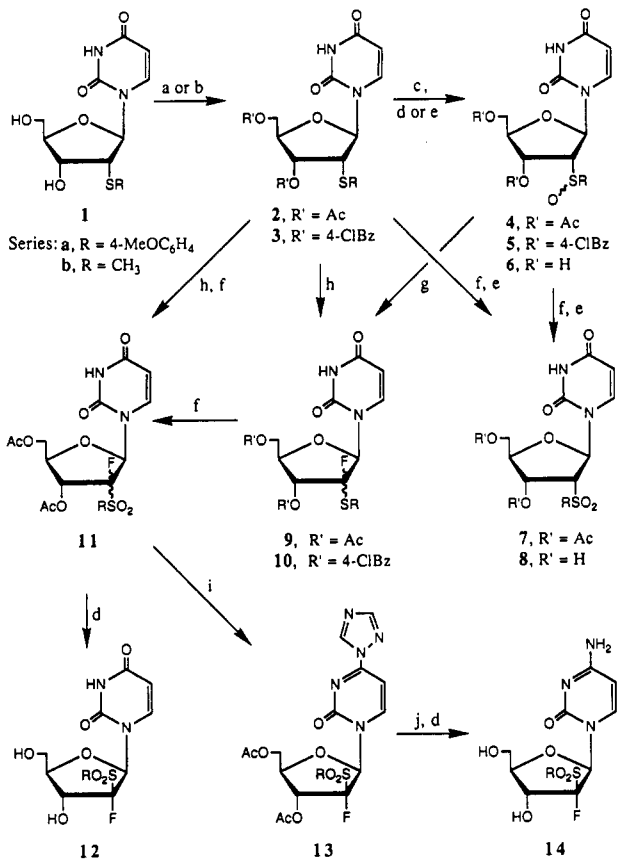
Scheme I[a]



[a] (a) Ac_2O/DMAP; (b) 4-ClC_6H_4COCl/pyridine; (c) MCPBA/CH_2Cl_2/−40 °C; (d) NH_3/MeOH; (e) HCl/MeOH; (f) MCPBA/CH_2Cl_2/ambient; (g) DAST/$SbCl_3$/CH_2Cl_2/ambient; (h) XeF_2/CH_2Cl_2/−35 °C to ambient; (i) $POCl_3$/triazole/Et_3N/MeCN; (j) NH_3/H_2O/dioxane.

its 5′-diphosphate (dFdCDP) functions as a potent mechanism-based inhibitor of the purified ribonucleoside diphosphate reductase (EC 1.17.4.1) from *Escherichia coli*.[16] We now report two methods for the conversion of uridine into 2′-*S*-alkyl(and aryl)-2′-deoxy-2′-fluoro-2′-thiouridine analogues and their transformation into stable 2′-[alkyl(and aryl)sulfonyl]-2′-deoxy-2′-fluorouridine and cytidine analogues of dFdUrd and dFdCyd (C). The first method utilized the conversion of sulfoxides to α-fluoro thioethers with DAST/$SbCl_3$.[17] The second employed transformations of thioethers to α-fluoro sulfides[18,19] with xenon difluoride.[18]

From available procedures,[20,21] we chose the Matsuda and Miyasaka method[21a] with our improved conditions[22] for the preparation of 2′-*S*-(4-methoxyphenyl)-2′-thiouridine (**1a**) and 2′-*S*-methyl-2′-thiouridine (**1b**) (Scheme I). As reported,[21a] heating 4-methoxybenzenethiol and 2,2′-anhydro-1-β-D-arabinofuranosyluracil[23] in DMF gave **1a**. Treatment of the cyclonucleoside[23] with alkyl or aryl thiolates in DMF (RSH/NaH/DMF)[22] also gave **1a** (81%) and **1b** (78%). Brown et al.[24a] and Furukawa et al.[24b] reported that its treatment with sodium ethanethiolate/DMF gave the xylo 3′-deoxy-3′-ethylthio derivative via a presumed 2′,3′-anhydro (ribo epoxide) intermediate.[24] However, our results agree with those of Matsuda and Miyasaka,[21a] Reese,[21b,e] and Ueda[21c,d] with direct substitution having occurred to give the expected ribo configuration at C2′. ^1H NMR spectra of **1a** and **1b** had upfield shifts of the H2′ peaks (δ 3.65 and 3.36, respectively) relative to that of uridine (δ 4.01). The $J_{1'-2'} \geq 8.5$ Hz coupling constants for **1a** and **1b** are indicative of trans configurations and are in harmony with literature values (2′-*S*-methyl ribo, $J_{1'-2'}$ = 8.3 Hz;[21c] arabino, $J_{1'-2'}$ = 6.8 Hz[21d]). Proof of the ribo configuration of **1a** was provided by X-ray crystallography of **6a**.

Catalytic amounts of 4-(dimethylamino)pyridine in acetic anhydride (DMAP/Ac_2O)[25] effected quantitative acetylation of **1a** to **2a**. Partial oxidation of **2a** (1.04 equiv of MCPBA/CH_2Cl_2/−50 °C) proceeded quantitatively to give the diasteromeric sulfoxides **4a** (~1:1) which were separated by chromatography. Deprotection of the more polar diastereomer and crystallization afforded **6a**[*S* at sulfur (*S*-S)] whose configurations at sulfur and C2′ were determined by X-ray crystallography. Sulfide **2a** and sulfoxides **4a** were oxidized to sulfone **7a** which was deprotected to give **8a** (81% for two steps).

Treatment of **4a** (~1:1) with DAST/$SbCl_3$/CH_2Cl_2 at ambient temperature gave the α-fluoro diastereomers **9a** (2′*R*/*S*, ~1:6.5; 56%) plus deoxygenated sulfide **2a** (20%). The **9a** diastereomers had ^{19}F NMR peaks (upfield from CCl_3F in Me_2SO) centered at δ −128.27 [dd, $^3J_{F-1'} \cong {}^3J_{F-3'} \cong 16.5$ Hz; **9a**(*S*)] and −139.26 [bs; **9a**(*R*)]. Treatment of **4a**(2′*R*-S) (18 h) and **4a**(2′*S*-S) (7 h) by the noted conditions gave the same ratio of **9a** (2′*R*/*S*, ~1:6.5) plus **2a** in similar yields. Thus the stereochemistry of this deoxygenative fluorination process does not depend on the configuration of the precursor sulfoxide, as also was noted with the 5′-fluorination of adenosine.[9a,b]

The preparation of **9a** directly[18] from **2a** gave similar results. Treatment of **2a** with $XeF_2/CH_2Cl_2/N_2$ at ambient temperature followed by aqueous workup gave **9a** (2′*R*/*S*, 1:4.5; 50%) and the sulfoxides **4a** (24%). This permits deletion of the oxidation step, which is especially advantageous when isolation of the sulfoxide in high yield is troublesome (e.g. **4b**). The unprotected α-fluoro thioethers were unstable and underwent decomposition during deprotection. However, oxidation of **9a**(2′*R*/*S*, ~1:4.5) with MCPBA (2.3 equiv) afforded the stable α-fluoro

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sulfones **11a**(2′*R*/*S*, ~1:4.4; 80%). Preparative HPLC separated a sample of the major diastereomer **11a**(2′*S*) whose configuration and molecular conformation were determined by X-ray crystallography. Deprotection gave **12a**(2′*S*) [^{19}F NMR δ −160.11 (dd, $^3J_{F-1'}$ = 21.5 Hz, $^3J_{F-3'}$ = 22.0 Hz)]. Formation of the major **9a**(2′*S*) isomer with fluorine in the ribo orientation might indicate attack by fluoride at the less hindered α-face of the sugar ring at C2′ of an intermediate sulfenium cation.[17a] An arylthio group in the arabino orientation permits parallel stacking of its benzene ring and the uracil base.

Acetylation of the 2′-methylthio analogue **1b** gave **2b** quantitatively. Partial oxidation of **2b** (MCPBA, 1.03 equiv) gave low isolated yields of the diastereomers of **4b** (~22%) owing to their high polarity. [We later found that chromatographic purification without aqueous workup gave good yields of **4b**.] Oxidation of **2b** (MCPBA, 2.4 equiv) afforded **7b** which was deprotected to give methyl sulfone **8b** (57%, two steps). Treatment of **2b** with XeF_2 gave the unstable **9b** diastereomers (2′*R*/*S*, 1.5:1; 22%), sulfoxides **4b**, and unchanged **2b**. The fluoro nucleoside fraction **9b** had an inverted diastereomer ratio relative to the conversion of **2a** to **9a**, but the instability of **9b** made this ratio suspect. Fluorination of **2b** (XeF_2) and direct oxidation of the crude mixture (MCPBA, 2.08 equiv) gave **7b** plus the α-fluoro sulfones **11b**(2′*R*/*S*, ~1:4.6; 46%). This diastereomer ratio and yield was consistent with that for the transfomation of **2a** to **11a** with XeF_2. Recrystallization of the **11b** mixture afforded the major isomer (higher field ^{19}F resonance) whose *S* configuration at C2′ was confirmed by X-ray crystallography. Deprotection of **11b**(2′*S*) gave the stable α-fluoro sulfone **12b**(2′*S*).

It is noteworthy that fluorination was not observed on the methyl group of **2b** in contrast with fluorinations of methionine, methionylglycine, and cytsteine derivatives with XeF_2 that were reported to occur exclusively on the methyl carbon.[18c,e] Fluorinations of 2′,3′-di-*O*-acetyl-5′-*S*-methyl-5′-thioadenosine with XeF_2[9e] and its sulfoxide with DAST[9a,d] gave regioisomeric mixtures of the 5′-*S*-(fluoromethyl)thio compound and 5′-fluoro-5′-*S*-methylthio diasteromers. Steric and electronic effects at the vicinal aminacetal carbon (C1′) might control the apparently regiospecific fluorination of **2b** at C2′ in the present case.

The regiochemistry of the sulfoxide/DAST/$SbCl_3$ route with methylthio at C2′ also was evaluated. Protection of **1b** with 4-chlorobenzoyl chloride gave the 3′,5′-diester **3b** that was oxidized (MCPBA) to sulfoxides **5b** (~3:1, 85% from **1b**). Recrystallization afforded **5b** (~5:1) whose major diasteromer was tentatively assigned (*R*-S) by comparison of its ^{1}H NMR spectrum with those of the known **4a** sulfoxides. Signals for H1′ of sulfoxides **4a** and **5b** (*R*-S) resonate at lower field (>0.2 ppm) and those for H2′ at higher field (>0.2 ppm) relative to those of their diastereomers (*S*-S) (Table I). Deprotection of **5b** (~5:1) and crystallization afforded **6b**(*R*-S). Treatment of **5b** with DAST/$SbCl_3$ and chromatography gave **10b** (2′*R*/*S*, 1:7; 61%) which was recrystallized to give **10b**(2′*S*). The absence of ^{19}F NMR peaks in the region of δ −180 to −185[9a,d] in the crude mixture or purified fractions indicated that fluorination did not occur at the methyl carbon. In contrast, treatment of methyl ethyl sulfoxide with DAST gave (fluoromethyl)thioethane.[17a] Fluorination of **3b** with XeF_2 under the usual conditions gave **10b** in low isolated yields.

The α-fluoro sulfones **11a**(2′*S*) and **11b**(2′*S*) were converted to their cytidine counterparts **14a**(2′*S*) and **14b**(2′*S*) by the procedure of Divakar and Reese.[26] Treatment of

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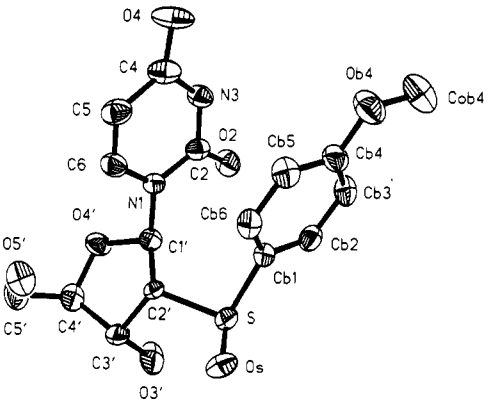

Figure 1. X-ray crystal structure of **6a**(*S*-S) drawn with SHELXTL PLUS.[28] Hydrogen atoms were omitted for clarity.

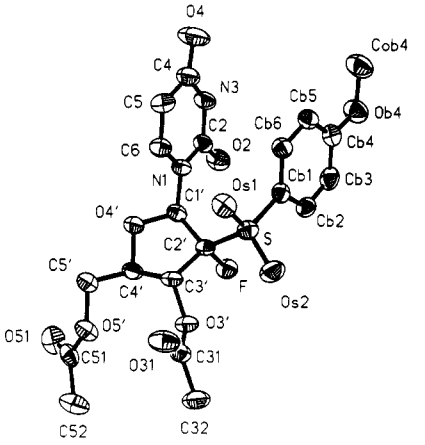

Figure 2. X-ray crystal structure of **11a**(2′*S*) drawn with SHELXTL PLUS.[28] Hydrogen atoms were omitted for clarity.

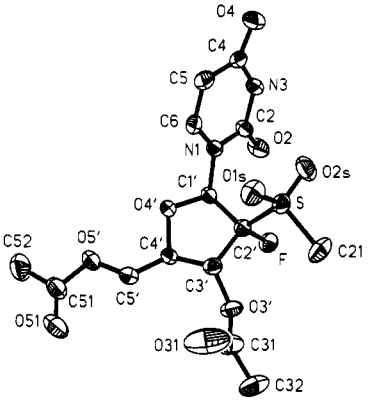

Figure 3. X-ray crystal structure of **11b**(2′*S*) drawn with SHELXTL PLUS.[28] Hydrogen atoms were omitted for clarity.

11a(2′*S*) with $POCl_3/Et_3N$/triazole gave the 4-(1,2,4-triazol-1-yl)pyrimidin-2-one derivative **13a**(2′*S*) that was treated with NH_3/H_2O/dioxane and then NH_3/MeOH to give **14a**(2′*S*) (76% for three steps). Similarly, **11b**(2′*S*) gave **14b**(2′*S*) (61%). The ^{13}C NMR peaks for C2′ of the α-fluoro sulfones **11–14** are shifted downfield to δ ~107 (d, $^1J_{C2'-F}$ = ~230 Hz) (Table II), approaching the range of the reported signal for C2′ of dFdCyd (C) at δ 123.77.[13a] Attempts to convert **11a** and **11b** into 2′-deoxy-2′,2′-difluorouridine derivatives resulted in recovery of starting material and/or formation of complex reaction mixtures.

The absolute configurations and conformations of **6a**-(*S*-S), **11a**(2′*S*), and **11b**(2′*S*) are shown in Figures 1–3, respectively. Positional and thermal parameters plus bond lengths and angles for non-hydrogen atoms, important torsion angles for the sugars, and hydrogen bonding

Table I. ^{1}H NMR Spectral Data[a,b]

compd	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[e] ($J_{3'-4'}$)	H4′[f] ($J_{4'-5',5''}$)	H5′,5″[f,g] ($J_{5'-5''}$)	H5[c] (J_{5-6})	H6[c]	NH[h]	aromatic[c] (J_{A-B})	others[i]
1a	6.17 (9.0)	3.65 (5.0)	4.29 (1.0)	3.84–3.89	3.50–3.57	5.40 (8.0)	7.50	11.15	7.29, 6.78 (8.5)	5.83[c] (5.4,[j] OH3′) 5.08[k] (5.5,[l] OH5′) 3.70 (MeO)
1b	6.06 (8.5)	3.36 (5.5)	4.21 (2.0)	3.82–3.89	3.51–3.59	5.72 (8.0)	7.88	11.40		5.64[c] (5.0,[j] OH3′) 5.12[k] (4.5,[l] OH5′) 2.02 (MeS)
2a	6.12 (9.0)	4.11 (6.0)	5.35[d] (1.6)	4.17–4.22	4.23–4.27	5.49 (8.0)	7.41	11.32	7.34, 6.83 (8.8)	3.74 (MeO) 2.13, 2.05 (Ac's)
2b	5.98 (9.0)	3.80 (6.0)	5.31[d] (2.0)	4.21–4.26	4.21–4.26	5.78 (8.0)	7.71	11.52		2.12, 2.06 (Ac's) 2.06 (MeS)
3b	6.12 (8.5)	4.06 (6.0)	5.72[d] (2.5)	4.56–4.64	4.56–4.64	5.75 (8.0)	7.80	11.55	8.03, 8.00 7.66, 7.61 (8.8)	2.11 (MeS)
4a(*R*-S)	6.25 (6.0)	4.08–4.13[f] (8.0)	5.56[d] (5.5)	4.24–4.31	4.08–4.13	5.42 (8.0)	7.34	11.28	7.55, 7.05 (8.8)	3.78 (MeO) 2.18, 2.00 (Ac's)
4a(*S*-S)	6.05 (9.0)	4.46 (6.0)	5.54[d] (2.0)	4.23–4.30 (5.0)	4.23–4.30 4.19[d] (11.0)	5.43 (8.0)	7.28	11.18	7.65, 7.00 (8.8)	3.78 (MeO) 2.20, 2.05 (Ac's)
4b(*R*/*S*)[m]	6.45 (4.0) 6.14 (6.7)	3.98–4.33[f]	5.56 (7.8)	3.98–4.33	3.98–4.33	5.72 (8.0) 5.76 (8.0)	7.82 7.72	11.48		2.58 (MeSO) 2.02, 2.12 (Ac's) 2.64 (MeSO) 2.04, 2.12 (Ac's)
5b(*R*/*S*)[m]	6.52 (4.0) 6.27 (6.5)	4.24 (8.6) 4.44 (8.5)	6.07[d] (8.4)	4.39[e] (4.0, 5.3)	4.63,[d] 4.54[d] (12.0)	5.71 (8.0) 5.76 (8.0)	7.98 7.82	11.53	7.96–8.02[f] 7.64, 7.56 (8.8)	2.60 (MeSO) 2.70 (MeSO)
6a(*R*-S)	6.34 (7.5)	3.58 (7.0)	4.29 (6.0)	3.71–3.76 (4.5, 5.0)	3.50,[e] 3.40[e] (12.5)	5.40 (8.0)	7.43	11.10	7.52, 7.01 (9.0)	6.08[c] (5.0,[j] OH3′) 4.82[k] (5.0,[l] OH5′) 3.74 (MeO)
6a(*S*-S)	6.13 (9.0)	3.88 (5.0)	4.58 (1.5)	3.92–3.96	3.48–3.58	5.34 (8.0)	7.44	10.98	7.54, 6.93 (9.0)	6.40[c] (5.0,[j] OH3′) 5.20[k] (OH5′) 3.76 (MeO)
6b(*R*-S)	6.49 (5.0)	3.41–3.62[f] (7.0)	4.46 (6.0)	3.66–3.73	3.41–3.62	5.64 (8.0)	7.72	11.45		5.98[c] (5.0,[j] OH3′) 4.97[k] (5.3,[l] OH5′) 2.55 (MeSO)
7a	6.30 (8.0)	4.86 (7.0)	5.53[d] (2.5)	4.04–4.23	4.04–4.23	5.44 (8.0)	7.35	11.38	7.69, 7.03 (9.0)	3.78 (MeO) 2.02, 1.99 (Ac's)
7b	6.34 (6.6)	4.62 (7.3)	5.56[d] (5.1)	4.19–4.30 (7.0)	4.19–4.30 4.10[d] (12.5)	5.70 (8.0)	7.69	11.45		3.10 ($MeSO_2$) 2.04, 1.99 (Ac's)
8a	6.50 (9.2)	4.23 (5.4)	4.52 (2.0)	3.84–3.90	3.44–3.52	5.47 (8.0)	7.53	11.30	7.73, 7.05 (8.8)	6.06[c] (6.4,[j] OH3′) 5.16[k] (OH5′) 3.83 (MeO)
8b	6.49 (8.4)	4.00 (5.6)	4.49 (2.5)	3.90–3.98	3.45–3.60	5.75 (8.0)	7.79	11.45		6.32[c] (5.5,[j] OH3′) 5.21[k] (5.4,[l] OH5′) 3.13 ($MeSO_2$)
9a(2′*S*)[n,o]	6.25[p] (16.5[q])		5.72[h]	4.15–4.22	4.23–4.31	5.62 (8.0)	7.72[h]	11.42	7.33, 6.95 (8.8)	3.78 (MeO) 2.05, 1.86 (Ac's)
9a(2′*R*)[n,r]	6.38 (17.4[q])		5.06[d] (2.6, 15.0[s])	4.15–4.45	4.15–4.45	5.63[d] (8.0, 2.2[t])	7.34	8.70	7.36, 6.82 (8.8)	3.78 (MeO) 2.18, 2.05 (Ac's)
9a(2′*S*)[n,r]	6.36 (15.4[q])		5.39[d] (7.6, 14.2[s])	4.15–4.45	4.15–4.45	5.82[d] (8.0, 2.2[t])	7.34	8.70	7.36, 6.82 (8.8)	3.78 (MeO) 2.12, 1.95 (Ac's)
9b(2′*R*)[n]	6.24 (14.0[q])		5.48[d] (5.0, 16.0[s])	4.25–4.35	4.25–4.35	5.72 (8.0)	7.65[d] (3.0[u])	11.58		2.18 (MeS) 2.09, 2.04 (Ac's)
9b(2′*S*)[n]	6.32[p] (17.0[q])		5.75[d] (3.0, 15.0[s])	4.25–4.35	4.25–4.35	5.74 (8.0)	7.72[p]	11.58		2.16 (MeS) 2.09, 2.02 (Ac's)
10b(2′*S*)[v]	6.42[p] (17.0[q])		6.0[h]	4.62–4.71	4.62–4.71	5.71 (8.0)	7.85	11.62	7.98, 7.90 7.63, 7.53 (8.8)	2.12 (1.2,[w] MeS)
11a(2′*S*)[x]	6.52 (22.0[q])		5.87[d] (9.0, 20.0[s])	4.20–4.28	4.28–4.39	5.76 (8.0)	7.73	11.50	7.68, 7.20 (9.0)	3.88 (MeO) 2.08, 1.70 (Ac's)
11b(2′*S*)[y]	6.53 (21.0[q])		5.85[d] (7.0, 20.0[s])	4.35–4.42	4.35–4.42	5.72 (8.0)	7.62	11.56		3.15[c] (2.0,[w] $MeSO_2$) 2.17, 2.08 (Ac's)
12a(2′*S*)	6.35 (21.5[q])		4.70 (9.0, 22.0[s])	3.80[e] (2.0, 3.0)	3.75,[e] 3.58[e] (13.0)	5.72 (8.0)	7.68	11.40	7.75, 7.14 (9.0)	5.95[c] (8.5,[j] OH3′) 5.30[k] (5.0,[l] OH5′) 3.88 (MeO)
12b(2′*S*)	6.40 (22.4[q])		4.70 (9.0, 23.6[s])	3.82–3.90 (2.0, 5.0)	3.71,[e] 3.65[e] (14.0)	5.68 (8.0)	7.65	11.50		6.60[c] (7.8,[j] OH3′) 5.35[k] (4.8,[l] OH5′) 3.12[c] (2.0,[w] $MeSO_2$)
13a(2′*S*)	6.78 (21.0[q])		5.87[d] (7.8, 18.5[s])	4.35–4.45	4.35–4.45	7.12 (8.0)	8.53		7.68, 7.22 (8.8)	9.50, 8.48 (triazole); 3.88 (MeO), 2.08, 1.72 (Ac's)
13b(2′*S*)	6.75 (20.0[q])		5.90[d] (7.7, 18.5[s])	4.42–4.54	4.42–4.54	7.12 (8.0)	8.45			9.50, 8.47 (triazole); 3.19[c] (2.0,[w] $MeSO_2$) 2.14, 2.08 (Ac's)

Table I (Continued)

compd	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[e] ($J_{3'-4'}$)	H4′[f] ($J_{4'-5',5''}$)	H5′,5″[f,g] ($J_{5'-5''}$)	H5[c] (J_{5-6})	H6[c]	NH[h]	aromatic[c] (J_{A-B})	others[i]
14a(2′*S*)	6.46 (22.5[q])		4.65 (9.0, 21.5[s])	3.58[e] (2.0, 2.5)	3.78,[e] 3.72[e] (13.0)	5.73 (7.5)	7.60		7.70, 7.12 (8.8)	7.35,[h] 7.28[h] (NH's) 5.85,[c] (8.5,[j] OH3′) 5.20,[k] (5.5,[l] OH5′) 3.88 (MeO)
14b(2′*S*)	6.53 (22.3[q])		4.65 (8.5, 23.0[s])	3.65[e] (5.5, 3.5)	3.80–3.88	5.74 (7.8)	7.54			7.32,[h] 7.28[h] (NH's) 6.45[c] (8.0,[l] OH3′) 5.27[k] (5.5,[l] OH5′) 3.08[c] (2.0,[w] $MeSO_2$)

[a] Chemical shifts (δ) in Me_2SO-d_6 at 400 MHz unless noted otherwise. [b] "Apparent" first-order coupling constants (hertz, in parentheses). [c] Doublet unless noted otherwise. [d] Doublet of doublets unless noted otherwise. [e] Doublet of doublets of doublets unless noted otherwise. [f] Multiplet unless noted otherwise. [g] Upfield resonance assigned to H5″(*pro-R*). [h] Broad singlet. [i] Singlet unless noted otherwise. [j] ($^3J_{HO-CH}$). [k] Triplet. [l] ($^3J_{HO-CH_2}$). [m] Signals assigned from spectrum of the mixture (correlated with integrated intensities). Signals in upper row refer to major diastereomer (tentatively *R*-S). [n] Signals for the 2′*R* and 2′*S* diastereomers assigned from a spectrum of the mixture by correlation of integrated intensities with the ^{19}F NMR spectrum. [o] Proton shifts for the minor 2′*R* isomer were identical except δ 7.42[c] (J_{HA-HB} = 8.8 Hz, aromatic), 3.75[i] (MeO), 2.15,[i] 2.04[i] (Ac's). [p] Broad doublet. [q] ($^3J_{1'-F}$). [r] In $CDCl_3$. [s] ($^3J_{3'-F}$). [t] ($^4J_{5-NH}$). [u] ($^5J_{6-F}$). [v] Proton shifts for the minor 2′*R* isomer were identical. In $CDCl_3$ the 2′*R* isomer had δ 6.42[c] (16.8,[q] H1′) and the 2′*S* δ 6.56[c] (14.6,[q] H1′). [w] ($^4J_{CH_3-F}$). [x] Proton shifts for the minor 2′*R* isomer were identical except δ 6.20[c] (21.0,[q] H1′), 5.70[c] (J_{5-6} = 8.0 Hz, H5), 1.97,[i] 1.62[i] (Ac's). [y] Proton shifts for the minor 2′*R* isomer were identical except δ 7.65[d] (J_{5-6} = 8.0 Hz, 2.0,[u] H6), 5.70[c] (H5), 3.18[c] (1.5,[w] $MeSO_2$), 2.20,[i] 2.10[i] (Ac's).

Table II. ^{13}C NMR Spectal Data[a,b]

compd	C2	C4	C5	C6	C1′	C2′	C3′	C4′	C5′	aromatic C1″	aromatic C2″	aromatic C3″	aromatic C4″	others
1a	150.88	162.96	102.42	140.07	88.04	55.78[c]	72.55	86.73	61.61	123.35	135.04	114.91	159.53	55.26[c] (MeO)
1b	151.02	163.30	102.59	140.71	87.43	53.06	71.98	86.67	61.41					13.68 (MeS)
2a[d]	150.39	162.40	102.64	139.63	88.10	51.20	73.80	80.31	63.21	121.59	135.00	114.80	159.56	55.24 (MeO)
2b[d]	149.76	161.90	102.09	139.32	86.41	48.58	72.54	79.46	62.47					13.37 (MeS)
3b	150.49	162.72	102.81	140.56	88.28	49.70	74.07	79.93	64.10	128.06	131.25	129.05	138.75	164.63, 163.92 (Bz's)
										127.79	131.12	128.96	138.48	14.24 (MeS)
4a(*R*-S)[d]	149.57	162.56	101.97	141.94	82.72	64.70	72.29	79.55	62.78	130.84	130.84	114.87	161.50	55.51 (MeO)
4a(*S*-S)[d]	149.68	162.61[c]	102.63	139.86	82.26	65.85	72.93	80.17	62.67	131.40	127.86	114.86	162.11[c]	55.57 (MeO)
6a(*R*-S)	149.73	162.70	101.95	141.44	85.52	69.13[c]	70.72[c]	81.89	60.72	125.86	132.71	114.62	161.19	55.46 (MeO)
6a(*S*-S)	149.91	162.25[c]	102.42	139.63	86.57	71.13[c]	71.83[c]	80.97	61.41	127.44	132.20	114.67	162.20[c]	55.48 (MeO)
11a(2′*S*)[d]	150.08	163.14	101.97	141.71	86.90[e] (40.0[f])	106.59[e] (234.0[g])	68.11[e] (13.6[h])	75.90	61.71	125.65	132.25	115.48	165.51	56.30 (MeO)
11b(2′*S*)[d]	150.38	163.05	102.13	141.09	86.45[e] (37.3[f])	105.70[e] (232.8[g])	67.83[e] (13.2[h])	75.99	61.64					38.54[i] ($MeSO_2$)
12a(2′*S*)	149.68	162.77	101.23	141.34	86.18[e] (39.0[f])	107.88[e] (229.0[g])	68.61[e] (15.8[h])	80.84	58.04	126.41	132.16	114.59	164.48	55.89 (MeO)
12b(2′*S*)	150.13	163.24	101.48	141.44	85.75[e] (38.4[f])	107.67[e] (227.4[g])	68.62[e] (15.7[h])	80.77	57.95					38.31 ($MeSO_2$)
13a(2′*S*)[d]	153.14	159.59	95.51	144.40	88.21[e] (38.5[f])	106.29[e] (238.6[g])	68.27[e] (13.3[h])	79.27	61.78	125.30	132.26	115.42	165.45	154.73, 150.48, (triazole) 56.20 (MeO)
13b(2′*S*)[d]	153.71	159.67	94.90	144.45	87.95[e] (40.2[f])	105.56[e] (238.7[g])	67.63[e] (14.6[h])	79.28	61.75					154.76, 149.88, (triazole) 38.64 ($MeSO_2$)
14a(2′*S*)	154.45	165.78	93.92	142.82	87.08[e] (38.8[f])	108.28[e] (229.0[g])	68.99[e] (16.2[h])	80.54	58.40	127.09	132.44	114.70	164.64	55.93 (MeO)
14b(2′*S*)	154.62	165.77	94.05	142.53	86.49[e] (38.0[f])	107.78[e] (227.9[g])	68.40[e] (15.7[h])	80.21	58.10					38.62 ($MeSO_2$)

[a] Chemical shifts (δ) in Me_2SO-d_6 at 75.5 MHz. [b] Proton-decoupled singlets unless noted otherwise. [c] Assignments may be reversed. [d] Signals for acetyl groups at δ 168.64–170.37 (CO) and 19.72–20.53 (CH_3). [e] Doublet. [f] ($^2J_{C1'-F}$). [g] ($^1J_{C2'-F}$). [h] ($^2J_{C3'-F}$). [i] Signal close to Me_2SO-d_6 signals, but resolved clearly in $CDCl_3$.

schemes are included in the supplementary material. The glycosyl torsion angles C6–N1–C1′–O4′ are 58.5 (5)°, 38.6 (2)°, and 27.1 (4)° in **6a**(*S*-S), **11a**(2′*S*), and **11b**(2′*S*), respectively, and the furanose pseudorotation angles are 179.4° ($^2T_3$ conformation), 55.1° ($_4T^\circ$), and 72.4 ($^\circ T_4$). The C3′–C4′–C5′–O5′ torsion angle in **6a**(*S*-S) is 50.5 (6)° in the normal g^+ (gg) range. In contrast, this angle in **11a**(2*S*) is −62.9 (2)° [g^- (tg)], and 174.8 (3)° [t (gt)] in **11b**(2′*S*). All hydrogen atoms bonded to nitrogen and oxygen are involved in intermolecular hydrogen bonds. Nearly parallel uracil and benzene ring orientations (dihedral angles between the ring planes are 13.3° and 11.7°, respectively) would allow favorable π–π interactions in both **6a**(*S*-S) (Figure 1) and **11a**(2′*S*) (Figure 2).

Thus, both the DAST/$SbCl_3$ treatment of protected nucleoside 2′-sulfoxides and direct treatment of their precursor thioethers with XeF_2 give good yields of 2′-fluoro thioethers that can be oxidized to stable 2′-fluoro sulfones. The latter compounds with geminal electronegative fluoro and sulfone substituents at C2′ represent analogues of the exciting 2′,2′-difluoro nucleosides which exhibit potent antitumor activity. Biological and enzyme inhibitory studies with these new analogues are in progress.

Experimental Section

Uncorrected melting points were determined on a microstage block. ^1H (400 MHz), ^{13}C (75.5 MHz), and ^{19}F NMR (376.5 MHz) NMR spectra were determined in Me_2SO-d_6 solutions unless otherwise noted with Me_4Si internal (^1H and ^{13}C) and CCl_3F external (^{19}F) standards (negative ^{19}F chemical shifts upfield from CCl_3F). High-resolution EI mass spectra were determined at 70 eV and low resolution spectra at 20 eV. (Diethylamino)sulfur trifluoride (DAST) was used as received from Aldrich Chemical Co. Equivalent yields of oxidation products were obtained with

3-chloroperoxybenzoic acid (MCPBA, 85%; Aldrich) with or without extraction to remove 3-chlorobenzoic acid. Xenon difluoride was obtained from PCR, Inc. Reagent-grade chemicals were used, and solvents were purified, dried, and distilled. TLC (silica) sheets were developed in $MeOH/CHCl_3$ (1:19) and/or $Me_2CO/CHCl_3$ (1:3) with visualization under UV (254-nm) light. Sulfur-containing compounds were detected by spraying TLC plates with a solution of $PdCl_2$ (0.4 g) in concentrated hydrochloric acid/H_2O (1:9, 100 mL). Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. Gradient flash chromatography [$CHCl_3$ to $Me_2CO/CHCl_3$ (1:3)] was performed with a 2% increasing gradient of Me_2CO. Solvents were flash evaporated at <25 °C under water aspirator or mechanical oil pump (in vacuo) vacuum. Solids were dried at elevated temperatures in vacuo over P_4O_{10} before weighing. $MgSO_4$ was used to dry all organic phase extractions.

2′-*S*-(4-Methoxyphenyl)-2′-thiouridine (1a). Method A. Sodium hydride (374 mg, 7.79 mmol; 50% dispersion in mineral oil) in a flame-dried three-neck flask was flushed with N_2 and washed with anhydrous Et_2O (2 × 30 mL). DMF (20 mL) was added, the flask was placed in an ice bath, and a solution of 4-methoxybenzenethiol (1.03 g, 7.35 mmol) in DMF (5 mL) was added dropwise. The mixture was allowed to warm to ambient temperature with continued stirring for 1 h and 2,2′-anhydro-1-β-D-arabinofuranosyluracil[23] (1.52 g, 6.72 mmol) in DMF (60 mL) was added. The mixture was heated at 65–70 °C for 24 h and evaporated, and H_2O (70 mL) was added. The milky suspension was neutralized (pH 7, HCl/H_2O) and extracted ($CHCl_3$, 2 × 50 mL) to remove excess 4-methoxybenzenethiol. The aqueous layer was evaporated, and the white residue was dried, dissolved (MeOH), and applied to a short column. Elution ($MeOH/CHCl_3$, 3:97) and crystallization (EtOH) gave needles of **1a** (1.99 g, 81%): mp 199–200 °C (lit.[21a] mp 200–201 °C); UV (MeOH) max 227, 253 nm (ε 10 900, 13 000), min 220, 238 nm (ε 10 500, 8900); MS *m/z* 366.0894 (6.3, M^+ [$C_{16}H_{18}N_2O_6S$] = 366.0885). Anal. Calcd for $C_{16}H_{18}N_2O_6S$ (366.4): C, 52.45; H, 4.95; N, 7.65; S, 8.75. Found: C, 52.44; H, 4.98; N, 7.76; S, 8.85.

Method B. 4-Methoxybenzenethiol (3.34 g, 23.89 mmol) was added to a stirred suspension of 2,2′-anhydro-1-β-D-arabinofuranosyluracil[23] (3.0 g, 13.3 mmol) in DMF (35 mL), and the mixture was heated at reflux for 18 h, cooled, and evaporated. The oil was triturated (Et_2O), and the colorless solid was crystallized (EtOH) to give needles of **1a** (3.89 g, 80%) identical to the product of method A.

3′,5′-Di-*O*-acetyl-2′-*S*-(4-methoxyphenyl)-2′-thiouridine (2a). DMAP (33 mg, 0.27 mmol) was added to a suspension of **1a** (2.0 g, 5.46 mmol) in Ac_2O (6 mL), and the mixture was stirred at ambient temperature overnight. MeOH (50 mL) was added, and the mixture was stirred for 1 h and evaporated. The residue was dissolved in $CHCl_3$ (70 mL); washed with H_2O (50 mL), $NaHCO_3/H_2O$ (30 mL), H_2O (50 mL), 1 N HCl/H_2O (30 mL), H_2O (50 mL), and brine (50 mL); and evaporated to give **2a** (2.44 g, quant) as a colorless foam of sufficient purity for use in subsequent reactions: UV (MeOH max 228, 252 nm (ε 11 300, 13 800), min 220, 237 nm (ε 10 400, 10 100); MS *m/z* 450.1096 (16, M^+ [$C_{20}H_{22}N_2O_8S$] = 450.1096).

3′,5′-Di-*O*-acetyl-2′-deoxy-2′-[(4-methoxyphenyl)sulfinyl]uridine [4a(*R*/*S*-S)]. MCPBA (630 mg of 85% reagent, 3.12 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a stirred solution of **2a** (1.35 g, 3.0 mmol) in CH_2Cl_2 (30 mL) at −50 °C, and the temperature was allowed to rise to −30 °C. The solution was poured into $NaHCO_3/H_2O$ (20 mL), the organic layer was separated, and the aqueous layer was extracted ($CHCl_3$, 2 × 30 mL). The combined organic phase was washed with H_2O (2 × 40 mL) and brine (2 × 40 mL), dried, and evaporated to give a colorless solid foam. Gradient flash chromatography gave the more rapidly migrating **4a**(2′*R*-S) (643 mg, 46%) [UV (MeOH) max 247 nm (ε 18 600), min 222 nm (ε 7200); MS *m/z* 311.0882 (49, M − $C_7H_7O_2S$ [$C_{13}H_{15}N_2O_7$] = 311.0879); MS CI(NH_3) *m/z* 467 (7, MH^+)] and the more slowly migrating **4a**(2′*S*-S) (645 mg, 46%): UV (MeOH) max 251 nm (ε 15 600), min 222 nm (ε 7500); MS *m/z* 311.0879 (42, M − $C_7H_7O_2S$ [$C_{13}H_{15}N_2O_7$] = 311.0879); MS CI(NH_3) *m/z* 467 (7, MH^+).

2′-Deoxy-2′(*R*-S)-[(4-methoxyphenyl)sulfinyl]uridine [6a(2′*R*-S)]. Saturated NH_3/MeOH (5 mL) was added to a solution of **4a**(2′*R*-S) (200 mg, 0.43 mmol) in MeOH (10 mL), stirring was continued at ambient temperature for 6 h, and the solution was evaporated. The residue was recrystallized ($MeOH/CHCl_3$) to give white crystals of **6a**(2′*R*-S) (130 mg, 80%): mp 246–248 °C; UV (MeOH) max 247 nm (ε 17 900), min 222 nm (ε 7600); MS CI(NH_3) *m/z* 383 (7, MH^+). Anal. Calcd for $C_{16}H_{18}N_2O_7S$ (382.4): C, 50.26; H, 4.74; N, 7.33; S, 8.39. Found: C, 50.21; H, 4.70; N, 7.34; S, 8.48.

2′-Deoxy-2′(*S*-S)-[(4-methoxyphenyl)sulfinyl]uridine [6a(2′*S*-S)]. Deprotection (NH_3/MeOH, 5 mL) of **4a**(2′*S*-S) (200 mg, 0.43 mmol) and crystallization ($MeOH/CHCl_3$) [as described for **6a**(2′*R*-S)] gave needles of **6a**(2′*S*-S) (127 mg, 78%): mp 238–239 °C; UV (MeOH) max 252 nm (ε 14 900), min 223 nm (ε 6700); MS CI(NH_3) *m/z* 383 (10, MH^+). Anal. Calcd for $C_{16}H_{18}N_2O_7S$ (382.4): C, 50.26; H, 4.74; N, 7.33; S, 8.39. Found: C, 49.88; H, 4.60; N, 7.35; S, 8.15.

3′,5′-Di-*O*-acetyl-2′-deoxy-2′-[(4-methoxyphenyl)sulfonyl]uridine (7a). A solution of **2a** (450 mg, 1.0 mmol) and MCPBA (487 mg of 85% reagent, 2.4 mmol) in CH_2Cl_2 (40 mL) was stirred at ambient temperature overnight. Saturated $NaHCO_3/H_2O$ (10 mL) was added, stirring was continued for 10 min, and the organic layer was separated. The aqueous layer was extracted ($CHCl_3$, 2 × 10 mL), and the combined organic phase was washed with H_2O (20 mL) and brine (2 × 20 mL) and dried. Evaporation gave **7a** (477 mg, 99%) as a colorless amorphous solid: UV (MeOH) max 246 nm (ε 17 400), min 224 nm (ε 7000); MS CI(NH_3) *m/z* 483 (17, MH^+).

Sulfoxides **4a**(2′*R*-S) (100 mg, 0.21 mmol) and **4a**(2′*S*-S) (100 mg, 0.21 mmol) were oxidized separately with MCPBA (58 mg of 85% reagent, 0.29 mmol) in CH_2Cl_2 at ambient temperature for 3 h to give 102 mg (99%) and 100 mg (97%) of **7a**, respectively, after the same workup.

2′-Deoxy-2′-[(4-methoxyphenyl)sulfonyl]uridine (8a). A solution of **7a** (200 mg, 0.41 mmol) in MeOH (10 mL) and 10 M HCl/H_2O (1 mL) was refluxed for 24 h and evaporated. The residue was crystallized (EtOH) to give **8a** (135 mg, 82%): mp 208–210 °C; UV (MeOH) max 244 nm (ε 20 200), min 222 nm (ε 5000); MS *m/z* 398 (1, M^+). Anal. Calcd for $C_{16}H_{18}N_2O_8S$ (398.4): C, 48.24; H, 4.55; N, 7.05; S, 8.05. Found: C, 48.41; H, 4.41; N, 6.98; S, 8.00.

3′,5′-Di-*O*-acetyl-2′-fluoro-2′-*S*-(4-methoxyphenyl)-2′-thiouridine [9a(2′*R*/*S*)]. Method A (DAST). DAST (0.65 mL, 794 mg, 4.93 mmol) was added to a mixture of **4a** (2′*R*/*S*, ~1:1) (1.0 g, 2.14 mmol) and $SbCl_3$ (97 mg, 0.42 mmol) in CH_2Cl_2 (30 mL) under N_2, and stirring was continued at ambient temperature overnight. Cold saturated $NaHCO_3/H_2O$ (10 mL) was added carefully, stirring was continued for 30 min, the organic layer was separated, and the aqueous layer was extracted ($CHCl_3$, 2 × 20 mL). The combined organic phase was washed with H_2O (2 × 30 mL) and brine (2 × 30 mL), dried, and evaporated to give a light yellow solid foam. Gradient flash chromatography gave **9a** (2′*R*/*S*, ~1:6.5; 562 mg, 56%) [UV (MeOH) max 246 nm (ε 17 700), min 223 nm (ε 7600); ^{19}F NMR δ −128.27 (bt, $^3J_{F-1'} \cong {}^3J_{F-3'} \cong 16.5$ Hz, 0.87, F2′*S*), −139.26 (bs, 0.13, F2′*R*); ^{19}F NMR ($CDCl_3$) δ −131.49, (bs, 0.87, F2′*S*), −141.11 (bs, 0.13, F2′*R*); MS *m/z* 468.0989 (8, M^+ [$C_{20}H_{21}FN_2O_8S$] = 468.1002)] and **2a** (195 mg, 20%) as colorless amorphous solids.

Analogous treatment of **4a**(2′*R*-S) (200 mg, 0.43 mmol) with DAST (0.13 mL, 158 mg, 0.98 mmol) and $SbCl_3$ (19 mg, 0.08 mmol) in CH_2Cl_2 (10 mL) gave **9a** (2′*R*/*S*, ~ 1:6.5; 109 mg, 54%) and **2a** (46 mg, 24%).

Analogous treatment of **4a**(2′*S*-S) (200 mg, 0.43 mmol) with DAST (0.13 mL, 158 mg, 0.98 mmol) and $SbCl_3$ (19 mg, 0.08 mmol) in CH_2Cl_2 (10 mL) (7 h) gave **9a** (2′*R*/*S*, ~1:6.5; 117 mg, 58%) and **2a** (39 mg, 20%).

Method B (XeF_2). A solution of **2a** (1.0 g, 2.22 mmol) in CH_2Cl_2 (10 mL) was added quickly to a suspension of XeF_2 (413 mg, 2.44 mmol) in CH_2Cl_2 (5 mL) under N_2 at −35 °C, and stirring was continued at ambient temperature for 2.5 h. The mixture was poured into $NaHCO_3/H_2O$ (20 mL) and stirred for 30 min. The organic layer was separated, washed with H_2O (30 mL) and brine (2 × 30 mL), dried, and evaporated. Gradient flash chromatography gave **9a** (2′*R*/*S*, ~1:4.5; 520 mg, 50%) with data identical to that from method A except for the diastereomer ratios, **4a**(2′*R*-S) (155 mg, 15%), and **4a**(2′*S*-S) (93 mg, 9%).

3′,5′-Di-*O*-acetyl-2′-deoxy-2′-fluoro-2′-[(4-methoxyphenyl)sulfonyl]uridine [11a(2′*R*/*S*)]. MCPBA (1.49 g of 85%

reagent, 7.37 mmol) in CH_2Cl_2 (30 mL) was added to **9a** (2′*R*/*S*, ~1:4.5; 1.5 g, 3.20 mmol) in CH_2Cl_2 (20 mL), the solution was stirred overnight at ambient temperature, and $NaHCO_3/H_2O$ (20 mL) was added. After the mixture was stirred for 10 min, the organic layer was separated and the aqueous layer was extracted ($CHCl_3$, 2 × 15 mL). The combined organic phase was washed with H_2O (50 mL) and brine (2 × 50 mL), dried, and evaporated. The residue was chromatographed (MeOH/$CHCl_3$, 1:99), and the resulting solid foam (1.53 g, 96%) crystallized ($EtOAc/Et_2O$) to give **11a** (2′*R*/*S*, ~1:4.4; 1.27 g, 80%). The major isomer **11a**(2′*S*) was obtained by preparative HPLC (silica cartridge; Me_2CO/hexane, 9:11), but the minor isomer **11a**(2′*R*) [^{19}F NMR δ −156.17 (bt, $^3J_{F-1'} \cong {}^3J_{F-3'} \cong 20.7$ Hz, 0.18, F2′*R*)] was not obtained pure. Compound **11a**(2′*S*): mp 154–155 °C ($EtOAc/Et_2O$, "diffusion crystallized"[27]); UV (MeOH) max 249 nm (ϵ 25 100), min 222 nm (ϵ 3800); ^{19}F NMR δ −156.85 (dd, $^3J_{F-1'}$ = 22.0 Hz, $^3J_{F-3'}$ = 20.0 Hz, F2′*S*); MS *m*/*z* 500.0906 (2, M^+ [$C_{20}H_{21}FN_2O_{10}S$] = 500.0901). Anal. Calcd for $C_{20}H_{21}FN_2O_{10}S$ (500.5): C, 48.00; H, 4.23; N, 5.60; S, 6.41. Found: C, 48.17; H, 4.17; N, 5.59; S, 6.38.

2′-Deoxy-2′(*S*)-fluoro-2′-[(4-methoxyphenyl)sulfonyl]uridine [12a(2′*S*)]. A solution of **11a**(2′*S*) (500 mg, 1.0 mmol) in MeOH (20 mL) and saturated NH_3/MeOH (10 mL) was stirred at ambient temperature for 6 h and evaporated, and the residue was diffusion crystallized[27] (EtOH/hexane) to give **12a**(2′*S*) (369 mg, 80%): mp 117–119 °C (followed by dec); UV (MeOH) max 248 nm (ϵ 25 400), min 223 nm (ϵ 3900); ^{19}F NMR δ −160.11 (dd, $^3J_{F-1'} \cong 21.5$ Hz, $^3J_{F-3'} \cong 22.0$ Hz, F2′*S*); MS *m*/*z* 416.0701 (3.1, M^+ [$C_{16}H_{17}FN_2O_8S$] = 416.0689). Anal. Calcd for $C_{16}H_{17}FN_2O_8S \cdot C_2H_6O$ (462.4): C, 46.75; H, 5.01; N, 6.06; S, 6.93. Found: C, 46.72; H, 4.74; N, 6.07; S, 7.37. EtOH was confirmed by ^1H NMR.

2′-*S*-Methyl-2′-thiouridine (1b). Sodium hydride (508 mg, 10.6 mmol, 50% in mineral oil) in a flame-dried flask under N_2 was washed (2 × dry hexane), and DMF (20 mL) was added. The flask was cooled (−40 °C bath), and methanethiol (468 mg, 9.72 mmol) was added slowly to the stirred suspension. After 20 min, the mixture was stirred at ambient temperature for 1 h and then cooled (ice bath). A solution of 2,2′-anhydro-1-β-D-arabinofuranosyluracil[23] (2.0 g, 8.84 mmol) in DMF (70 mL) was added dropwise, the mixture was heated at 70 °C for 16 h, and the solvent was evaporated. H_2O (20 mL) was added, the mixture was neutralized (1 N HCl/H_2O), and the solvent was evaporated. The residue was dissolved (MeOH, 10 mL) and chromatographed (MeOH/$CHCl_3$, 1:49) to give **1b** (1.89 g, 78%) as a colorless solid foam that did not crystallize (lit.[21c] mp 124–126 °C): UV (MeOH) max 260 nm (ϵ 9400), min 229 (ϵ 2800); MS *m*/*z* 274.0630 (1, M^+ [$C_{10}H_{14}N_2O_5S$] = 274.0623). In subsequent preparations, crude **1b** was acylated directly.

3′,5′-Di-*O*-acetyl-2′-*S*-methyl-2′-thiouridine (2b). DMAP (28 mg, 0.23 mmol) was added to a suspension of **1b** (1.24 g, 4.52 mmol) in Ac_2O (10 mL), and the mixture was stirred overnight at ambient temperature. The flask was placed in an ice bath, MeOH (50 mL) was added, and the mixture was stirred for 1 h and evaporated. The light yellow gum was dissolved ($CHCl_3$, 100 mL), and the solution was washed with 1 N HCl/H_2O (30 mL), H_2O (2 × 50 mL), and brine (2 × 50 mL), dried, and evaporated to give colorless amorphous **2b** (1.6 g, 99%) of sufficient purity for use in the next step. Diffusion crystallization[27] ($CHCl_3$/hexane) afforded fine needles of **2b** (1.26 g, 78%): mp 143–144 °C; UV (MeOH) max 258 nm (ϵ 10 100), min 228 nm (ϵ 3700); MS *m*/*z* 358.0833 (1, M^+ [$C_{14}H_{18}N_2O_7S$] = 358.0834). Anal. Calcd for $C_{14}H_{18}N_2O_7S$ (358.3): C, 46.92; H, 5.06; N, 7.82; S, 8.95. Found: C, 46.62; H, 4.99; N, 7.70; S, 8.85.

3′,5′-Di-*O*-acetyl-2′-deoxy-2′-(methylsulfinyl)uridine [4b(*R*/*S*-S)]. Oxidation (MCPBA; 211 mg of 85% reagent, 1.04 mmol) of **2b** (358 mg, 1.0 mmol) (as described for **4a**) gave **4b** (*R*/*S*-S, ~2:1; 82 mg, 22%): MS *m*/*z* 311 (11, M − $SOCH_3$). A subsequent experiment with direct purification of the reaction mixture by column chromatography (without aqueous workup) gave **4b** (*R*/*S*-S, ~2:1; 325 mg, 87%).

3′,5′-Di-*O*-acetyl-2′-deoxy-2′-(methylsulfonyl)uridine (7b). MCPBA (271 mg of 85% reagent, 1.34 mmol) in CH_2Cl_2 (10 mL) was added to **2b** (200 mg, 0.56 mmol) in CH_2Cl_2 (10 mL), and stirring was continued at ambient temperature for 24 h. The solution was concentrated and chromatographed (MeOH/$CHCl_3$, 1.5:98.5) to give colorless amorphous **7b** (167 mg, 77%): UV (MeOH) max 256 nm (ϵ 8900), min 230 nm (ϵ 5100); MS *m*/*z* 331 (0.5, M − OAc).

2′-Deoxy-2′-(methylsulfonyl)uridine (8b). A solution of **7b** (120 mg, 0.30 mmol) in MeOH (10 mL) and HCl/H_2O (10 M, 1 mL) was heated at reflux for 24 h and evaporated. The white solid was crystallized (MeOH) to give **8b** (70 mg, 74%): mp 226–227 °C; UV (MeOH) max 258 nm (ϵ 9200), min 228 nm (ϵ 2600); MS *m*/*z* 195 (1, M − B). Anal. Calcd for $C_{10}H_{14}N_2O_7S$ (306.3): C, 39.21; H, 4.61; N, 9.15; S, 10.47. Found: C, 39.15; H, 4.49; N, 9.18; S, 10.30.

3′,5′-Di-*O*-acetyl-2′-fluoro-2′-*S*-methyl-2′-thiouridine [9b(2′*R*/*S*)]. Method B. A solution of **2b** (1.0 g, 2.79 mmol) in CH_2Cl_2 (10 mL) was added quickly to a suspension of XeF_2 (509 mg, 3.01 mmol) in CH_2Cl_2 (5 mL) at −40 °C, and the mixture was stirred at ambient temperature for 1.5 h. Starting **2b** (~20%, TLC) remained, and a second portion of XeF_2 (54 mg, 0.32 mmol) was added at −30 °C. Stirring was continued at ambient temperature for an additional 30 min, and the mixture was poured into saturated $NaHCO_3/H_2O$ (20 mL) and stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted ($CHCl_3$, 2 × 20 mL). The combined organic phase was washed with H_2O (30 mL) and brine (2 × 20 mL), dried, and evaporated to give a solid foam (800 mg) that contained **9b**, **2b**, and **4b**. Since **9b** decomposed on a Merck silica column at ambient temperature within 5 min, gradient chromatography was performed on Mallinckrodt Silica R, 200–425 mesh, type 60A to give colorless amorphous **9b** (2′*R*/*S*), ~1.5:1; 230 mg, 22%): UV (MeOH) max 258 nm (ϵ 9200), min 228 nm (ϵ 2600); ^{19}F NMR δ −140.16 (m, 0.4, F2′*S*), −145.07 (m, 0.6, F2′*R*); MS *m*/*z* 376 (80, M^+). This purified sample underwent decomposition upon standing at ambient temperature.

3′,5′-Di-*O*-acetyl-2′-deoxy-2′-fluoro-2′-(methylsulfonyl)uridine [11b(2′*R*/*S*)]. Crude **9b** (800 mg) from **2b** (1.0 g, 2.79 mmol) and XeF_2 (563 mg, 3.33 mmol) (as described for **9b**) was dissolved in CH_2Cl_2 (30 mL), treated dropwise with MCPBA (1.17 g of 85% reagent, 5.81 mmol) in CH_2Cl_2 (20 mL), and stirred at ambient temperature for 8 h. Saturated $NaHCO_3/H_2O$ (20 mL) was added, stirring was continued for 10 min, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL), and the combined organic phase was washed with H_2O (30 mL) and brine (2 × 30 mL), dried, and evaporated. Gradient chromatography gave **11b** (2′*R*/*S*, ~ 1:4.6; 523 mg, 46%) and **7b** (130 mg, 12%) as colorless solid foams. Recrystallizations ($CHCl_3$) of the **11b** mixture gave needles of **11b**(2′*S*) (342 mg, 30%): mp 182–183 °C; UV (MeOH) max 255 nm (ϵ 10 200), min 226 nm (ϵ 2700); ^{19}F NMR δ −160.51 (m, $^3J_{F-1'} \cong {}^3J_{F-3'} \cong 21$ Hz, $^4J_{F-CH_3} = 2.0$ Hz, F2′*S*); MS *m*/*z* 408.0657 (6, M^+ [$C_{14}H_{17}FN_2O_9S$] = 408.0638). Anal. Calcd for $C_{14}H_{17}FN_2O_9S$ (408.4): C, 41.18; H, 4.20; N, 6.86; S, 7.85. Found: C, 41.14; H, 4.13; N, 6.67; S, 7.97. Isolation of the pure minor isomer **11b**(2′*R*) [^{19}F NMR δ −158.48 (m, 0.18, F2′*R*)] was not achieved.

2′-Deoxy-2′(*S*)-fluoro-2′-(methylsulfonyl)uridine [12b(2′*S*)]. Saturated NH_3/MeOH (8 mL) was added to **11b**(2′*S*) (200 mg, 0.49 mmol) in MeOH (15 mL), stirring was continued at ambient temperature for 6 h, the solution was evaporated, and the colorless solid was crystallized (*t*-BuOH/hexane) to give **12b**(2′*S*) (130 mg, 82%): mp 204–206 °C; UV (MeOH) max 256 nm (ϵ 9500), min 226 nm (ϵ 2700); ^{19}F NMR δ −163.94 (m, $^3J_{F-1'}$ = 22.4 Hz, $^3J_{F-3'}$ = 23.6 Hz, $^4J_{F-CH_3} = 2.0$ Hz, F2′*S*); MS *m*/*z* 324 (20, M^+). Anal. Calcd for $C_{10}H_{13}FN_2O_7S$ (324.3): C, 37.04; H, 4.04; N, 8.64; S, 9.89. Found: C, 37.17; H, 4.00; N, 8.66; S, 9.93.

3′,5′-Bis-*O*-(4-chlorobenzoyl)-2′-*S*-methyl-2′-thiouridine (3b). A solution of **1b** (1.69 g, 5.83 mmol) in pyridine (20 mL) was treated dropwise with 4-chlorobenzoyl chloride (1.55 mL, 2.13 g, 12.17 mmol) at ambient temperature, and stirring was continued overnight. The solution was evaporated, the residue was dissolved in $CHCl_3$ (100 mL), and the solution was washed with H_2O (2 × 30 mL), 1 N HCl/H_2O (30 mL), H_2O (2 × 30 mL), and brine (2 × 30 mL), dried, and evaporated. Chromatography (MeOH/$CHCl_3$, 1:99) gave **3b** (2.75 g, 85%) that crystallized (toluene) as fine needles: mp 175–176 °C; UV (MeOH) max 244 nm (ϵ 39 800),

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min 218 nm (ε 6900); MS *m/z* 438 (42, M - BH). Anal. Calcd for $C_{24}H_{20}Cl_2N_2O_7S$ (551.4): C, 52.28; H, 3.65; N, 5.08; S, 5.82. Found: C, 52.18; H, 3.53; N, 4.97; S, 5.54.

3′,5′-Bis-*O*-(4-chlorobenzoyl)-2′-deoxy-2′-(methylsulfinyl)uridine [5b(*R*/*S*-S)]. MCPBA (449 mg of 85% reagent, 2.22 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of **3b** (1.2 g, 2.17 mmol) in CH_2Cl_2 (40 mL) at −60 °C, and the temperature was allowed to rise to −30 °C during the addition. $NaHCO_3/H_2O$ (20 mL) was added, the organic layer was separated, and the aqueous layer was extracted ($CHCl_3$, 2 × 20 mL). The combined organic phase was washed with H_2O (2 × 50 mL) and brine (50 mL), dried, and evaporated to give colorless solid **5b** (*R*/*S*-S, ~3:1; 1.23 g, quant). Diffusion crystallization[27] ($CHCl_3$/hexane) gave **5b** (*R*/*S*-S, ~5:1; 750 mg, 61%): mp 183–184 °C; UV (MeOH) max 244 nm (ε 39300), min 218 nm (ε 7200); MS *m/z* 503 (6, M - SOMe). Anal. Calcd for $C_{24}H_{20}Cl_2N_2O_8S$ (567.4): C, 50.80; H, 3.55; N, 4.94. Found: C, 50.62; H, 3.42; N, 5.11.

2′-Deoxy-2′(*R*-S)-(methylsulfinyl)uridine [6b(2′*R*-S)]. A suspension of **5b** (*R*/*S*-S, ~5:1; 200 mg, 0.35 mmol) in MeOH (15 mL) and HCl/H_2O (10 M, 1 mL) was heated at reflux for 24 h and evaporated. The white solid was washed (Et_2O and $CHCl_3$) and crystallized (MeOH) to give **6b**(*R*-S) (57 mg, 50%): mp 204–206 °C; UV (MeOH) max 260 nm (ε 9100), min 228 nm (ε 3200); MS *m/z* 272 (0.5, M - 18). Anal. Calcd for $C_{10}H_{14}N_2O_6S$ (290.3): C, 41.38; H, 4.86; N, 9.65. Found: C, 41.52; H, 5.01; N, 9.63.

3′,5′-Bis-*O*-(4-chlorobenzoyl)-2′(*S*)-fluoro-2′-*S*-methyl-2′-thiouridine [10b(2′*S*)]. Method A. DAST (0.69 mL, 851 mg, 5.29 mmol) was added to **5b** (1.0 g, 1.76 mmol; *R*/*S*-S, ~3:1) and $SbCl_3$ (44 mg, 0.19 mmol) in CH_2Cl_2 (50 mL) under N_2, and stirring was continued at ambient temperature for 48 h. Cold saturated $NaHCO_3/H_2O$ (20 mL) was added carefully, the mixture was stirred for 20 min, the organic layer was separated, and the aqueous layer was extracted ($CHCl_3$, 2 × 20 mL). The combined organic phase was washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried, and evaporated. Chromatography (MeOH/$CHCl_3$, 0.5:99.5) gave **10b** (2′*R*/*S*, ~1:7; 612 mg, 61%). Crystallization (MeCN) of this material gave **10b** (2′*R*/*S*, ~1:10; 500 mg, 50%). Recrystallization (2 × MeCN) gave **10b**(2′*S*): mp 159–162 °C dec; UV (MeOH) max 244 nm (ε 39900), min 218 nm (ε 10800); ^{19}F NMR δ −140.05 (m, F2′*S*); MS *m/z* 568 (2, M^+). Anal. Calcd for $C_{24}H_{19}Cl_2FN_2O_7S$ (569.5): C, 50.63; H, 3.36; N, 4.92; S, 5.63. Found: C, 50.82; H, 3.30; N, 5.04; S, 5.74.

^{19}F NMR spectra of the crude mixture and mother liquors had peaks at δ −145.10 (m, F2′*R*), but not in the region of δ −180 to −185 (FCH_2S).

Method B. A solution of **3b** (138 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added quickly to a suspension of XeF_2 (45 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) under N_2 at −40 °C, and stirring was continued at ambient temperature for 4 h. TLC showed mainly starting **3b** plus minor amounts of **10b** and **5b**. After 7 and 18 h, greater quantities of the sulfoxides **5b** were present, but no increase in **10b** was observed. Additional byproducts were formed with longer reaction times, and no improvements were observed with $CHCl_3$ or CH_3CN as solvent.

1-[3,5-Di-*O*-acetyl-2-deoxy-2(*S*)-fluoro-2-[(4-methoxyphenyl)sulfonyl]-β-D-*erythro*-pentofuranosyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2-one [13a(2′*S*)]. A solution of **11a**(2′*S*) (200 mg, 0.40 mmol) in CH_3CN (5 mL) was added to a cooled (ice bath) mixture of Et_3N (0.47 mL, 347 mg, 3.44 mmol), 1,2,4-triazole (253 mg, 3.6 mmol), and $POCl_3$ (0.07 mL, 117 mg, 0.76 mmol) in CH_3CN (10 mL), and stirring was continued at ambient temperature for 24 h. Et_3N (0.36 mL, 261 mg, 2.58 mmol) and H_2O (0.2 mL, 200 mg, 11 mmol) were added, and the mixture was stirred for 10 min and evaporated. The residue was dissolved in $CHCl_3$ (30 mL), and the solution washed with saturated $NaHCO_3/H_2O$ (15 mL), H_2O (20 mL), and brine (2 × 20 mL), dried, and concentrated. Chromatography (MeOH/$CHCl_3$, 1.5:98.5) gave colorless amorphous **13a**(2′*S*) (215 mg, 97%): UV (MeOH) max 252, 314 nm (ε 28900, 6100), min 223, 282 nm (ε 9000, 4300); ^{19}F NMR δ −168.64 (dd, $^3J_{F-1'}$ = 21.0 Hz, $^3J_{F-3'}$ = 18.5 Hz, F2′*S*); MS *m/z* 551 (3, M^+).

1-[3,5-Di-*O*-acetyl-2-deoxy-2(*S*)-fluoro-2-(methylsulfonyl)-β-D-*erythro*-pentofuranosyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2-one [13b(2′*S*)]. Treatment of a solution of **11b**(2′*S*) (180 mg, 0.44 mmol) in CH_3CN (5 mL) with cold Et_3N (0.52 mL, 383 mg, 3.79 mmol), 1,2,4-triazole (279 mg, 3.97 mmol), and $POCl_3$ (0.08 mL, 129 mg, 0.85 mmol) in CH_3CN (13 mL) followed by workup and purification [as described for **13a**(2′*S*)] gave colorless amorphous **13b**(2′*S*) (170 mg, 84%): UV (MeOH) max 252, 314 nm (ε 12000, 6100), min 228, 280 nm (ε 5700, 3900); ^{19}F NMR δ −172.22 (m, $^3J_{F-1'}$ = 20.0 Hz, $^3J_{F-3'}$ = 18.5 Hz, $^4J_{F-CH_3}$ = 2.0 Hz, F2′*S*; MS *m/z* 459 (0.5, M^+).

2′-Deoxy-2′(*S*)-fluoro-2′-[(4-methoxyphenyl)sulfonyl]cytidine [14a(2′*S*)]. NH_3/H_2O (*d* = 0.88, 0.6 mL) was added to a solution of **13a**(2′*S*) (140 mg, 0.25 mmol) in dioxane (8 mL), stirring was continued at ambient temperature for 6 h, and the solution was evaporated. The residue was dissolved in saturated NH_3/MeOH (4 mL), stirred for 16 h, and evaporated to give a white solid that was crystallized (MeOH/H_2O) to give needles of **14a**(2′*S*) (86 mg, 78%): mp 254–256 °C dec; UV (MeOH) max 248 nm (ε 24400), min 220 nm (ε 3500); ^{19}F NMR δ −171.03 (dd, $^3J_{F-1'}$ = 22.5 Hz, $^3J_{F-3'}$ = 21.5 Hz, F2′*S*); MS *m/z* 304 (16, M - BH). Anal. Calcd for $C_{16}H_{18}FN_3O_7S \cdot H_2O$ (433.4): C, 44.34; H, 4.65; N, 9.70; S, 7.40. Found: C, 44.45; H, 4.45; N, 9.64; S, 7.94.

2′-Deoxy-2′(*S*)-fluoro-2′-(methylsulfonyl)cytidine [14b(2′*S*)]. A solution of **13b**(2′*S*) (160 mg, 0.35 mmol) in dioxane (10 mL) was treated with NH_3/H_2O (*d* = 0.88; 1 mL) and then saturated MeOH/NH_3 (7 mL) [as described for **14a**(2′*S*)] to give a white solid that was crystallized (MeOH) to give needles of **14b**(2′*S*) (81 mg, 72%): mp 242–245 °C dec; UV (MeOH) max 244, 269 nm (ε 9700, 8800), min 222, 257 nm (ε 6700, 7200); ^{19}F NMR δ −174.69 (m, $^3J_{F-1'}$ = 22.3 Hz, $^3J_{F-3'}$ = 23.0 Hz, $^4J_{F-CH_3}$ = 2.0 Hz, F2′*S*); MS *m/z* 323 (1, M^+). Anal. Calcd for $C_{10}H_{14}FN_3O_6S$ (323.3): C, 37.15; H, 4.36; N, 13.00; S, 9.92. Found: C, 37.06; H, 4.28; N, 12.86; S, 10.20.

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Supplementary Material Available: The X-ray crystallography Experimental Section, references, and Tables 1S–19S containing a summary of the crystal data, structure determination details, atom positional and thermal parameters, bond lengths and angles, important sugar torsion angles, and hydrogen bond data for **6a**(*S*-S), **11a**(2′*S*), and **11b**(2′*S*) (25 pages). This material is contained in many 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.