with tetrahydrofuran (15 mL) and chilled to −78 °C, and s-BuLi (1.08 mL of a 0.75 M solution in hexane, 0.816 mmol) was added, resulting in a deep red solution which was stirred for an additional 30 min. The temperature was then lowered to −98 °C, and 1-iodo-3-pentyne 17 (0.16 g, 0.82 mmol) was slowly added (4 min), followed by stirring till the solution was a persistent faint yellow (7 h). The reaction was quenched with 20% NH_4Cl (1 mL) and warmed to room temperature, and the solvent was removed under reduced pressure. General workup procedure gave an oily residue which was immediately subjected to standard hydrazinolysis conditions[12] for removal of the auxiliary. The resulting material was purified by chromatography (SiO_2) [deactivated with (5%) triethylamine, eluent: hexane (50%)–ethyl acetate (45%)] to give the title compound (82 mg, 78%): hydrochloride, mp 194.5–196 °C; $[\alpha]^{22}_D$ +7.0° (c 0.56, CH_2Cl_2); IR (film) 3332, 2917, 2832, 1735, 1609, 1514, 1463, 1354, 1324, 1258, 1223, 1112, 1032, 1002, 856, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1 H), 6.55 (s, 1 H), 3.99 (dd, J = 3.3, 6.3 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 1 H), 3.15 (m, 1 H), 2.95 (m, 1 H), 2.68 (q, J = 5.2, 10.5 Hz, 2 H), 2.31 (m, 2 H), 1.8–2.0 (m, 2 H), 1.79 (s, 3 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.2, 147.1, 131.1, 127.2, 111.7, 109.1, 78.7, 76.1, 55.9, 55.8, 54.2, 40.5, 35.5, 29.4, 15.7 ppm. Anal. Calcd for $C_{16}H_{22}NO_2Cl$: C, 64.96; H, 7.49; N, 4.73. Found: C, 64.74; H, 7.72; N, 4.73.

(S)-3-[(Z)-Propylidene]-9,10-dimethoxy-1,2,4,6,7,11b-hexahydrobenzo[a]quinolizidine (20). Following the procedure of Overman and Sharp,[21] an aqueous solution (3 mL) of the alkynylisoquinoline 18 (82 mg, 0.316 mmol) was heated (95 °C, 4 h) in the presence of NaI (10 equiv), camphorsulfonic acid (1.2 equiv), and formaldehyde (35% by wt, 10 equiv). The reaction mixture was filtered through a small pad of Celite, washing repeatedly with CH_2Cl_2. Following normal aqueous workup the solution was dried over K_2CO_3 (0.5 g) and evaporated to dryness giving 80 mg (64% yield) of a yellow solid. This solid corresponds to the [(E)-iodoethylidene]benzoquinolizidine 19. Anal. Calcd for $C_{17}H_{25}NO_3ClI$: C, 45.00; H, 5.27; N, 3.08. Found: C, 44.93; H, 4.87; N, 2.73. 19: ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (s, 1 H), 6.55 (s, 1 H), 3.93 (dd, J = 2.2, 10.6 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.2 (d, J = 9.9 Hz, 1 H), 2.95 (m, 4 H), 2.59 (s, 3 H), 2.3 (m, 1 H), 1.6 (m, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.5, 147.1, 137.8, 129.6, 126.3, 111.3, 108.4, 102.6, 95.6, 61.9, 55.9, 55.8, 50.8, 39.9, 31.8, 29.9, 29.1 ppm. To a chilled (−78 °C) tetrahydrofuran (4 mL) solution of the benzoquinolizidine (24 mg, 0.06 mmol) was added s-BuLi (0.632 mL of a 0.75 M solution in hexane, 0.632 mmol). After 30 min the orange solution was quenched with methanol, followed by a typical aqueous workup for metalation/alkylation. The 16 mg (97.5% yield) of crude solid product was very pure by ^1H NMR. The benzoquinolizidine could be purified by crysallization of its hydrochloride salt (ether/acetone), mp 234–236 °C. Due to the hygroscopic nature of this salt, it failed to give correct combustion analysis. However, the free base could be suitably dried (KOH, 24 h, 0.1 Torr) for further analyses: $[\alpha]^{22}_D$ −86° (c 0.36, CH_2Cl_2); IR (film) 2933, 2831, 2740, 1611, 1518, 1463, 1367, 1331, 1260, 1230, 1212, 1171, 1135, 1099, 1040, 1016, 906, 855, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (s, 1 H), 6.56 (s, 1 H), 5.3 (q, J = 6.6, 13.5 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.76 (dd, J = 1.3, 12.4 Hz, 1 H), 3.27 (d, J = 10.7 Hz, 1 H), 3.1 (m, 2 H), 2.2–2.7 (m, 6 H), 1.66 (d, J = 6.8 Hz, 3 H), 1.5 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 147.3, 146.9, 134.1, 130.1, 126.6, 118.0, 111.3, 111.2, 108.3, 108.2, 62.9, 55.9, 55.7, 52.0, 34.7, 32.6, 29.1, 12.8 ppm. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.97; H, 8.66; N, 4.86.

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Registry No. (-)-1, 483-18-1; **2**, 136657-36-8; *cis*-**3**, 2609-32-7; *trans*-**3**, 136657-35-7; (±)-**4**, 19778-10-0; (−)-**4**, 136657-33-5; **9**, 128778-92-7; **10**, 136657-32-4; **11**, 136587-48-9; **12** (isomer 1), 136587-49-0; **12** (isomer 2), 136587-50-3; **13** (isomer 1), 136587-51-4; **13** (isomer 2), 136657-34-6; **14**, 136587-58-1; **15a**, 136587-56-9; (*E*)-**15b**, 136587-54-7; (*Z*)-**15b**, 136587-55-8; **15c**, 136587-57-0; **16a**, 105104-40-3; (*E*)-**16b**, 136587-52-5; (*Z*)-**16b**, 136587-53-6; **16c**, 18388-03-9; **17**, 18719-28-3; **18**, 136587-59-2; **19**, 136587-61-6; **20**, 136587-60-5; **20**·HCl, 136587-62-7; 3-MeOBnCl, 824-98-6.

Nucleic Acid Related Compounds. 68. Fluorination at C5′ of Nucleoside 5′-Thioethers with DAST/Antimony(III) Chloride or Xenon Difluoride To Give 5′-*S*-Aryl-5′-fluoro-5′-thiouridines[1]

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Oxidation of 2′,3′-di-*O*-acetyl-5′-*S*-(4-methoxyphenyl)-5′-thiouridine (**2a**) with 3-chloroperoxybenzoic acid (MCPBA) gave the diastereomeric sulfoxides **4a**. Treatment of **2a** with xenon difluoride or **4a** with (diethylamino)sulfur trifluoride/antimony(III) chloride gave efficient conversions to the 2′,3′-di-*O*-acetyl-5′-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thiouridine diastereomers **6a**. The stereochemistry and conformation of **6a**(5′*R*) were established by X-ray crystallography. The α-fluoro thioethers were oxidized to their sulfoxide and sulfone derivatives with MCPBA, deprotected, and characterized.

S-Adenosylmethionine (AdoMet, SAM) is the methyl donor for most enzyme-mediated methylations and produces *S*-adenosylhomocysteine (AdoHcy, SAH) as the byproduct. Since AdoHcy is a feedback inhibitor of methylation enzymes, its degradation is crucial for the continuation of biosynthesis and cell division.[2] Enzymatic decarboxylation of AdoMet gives the 5′-aminopropylsulfonium compound that serves as an aminopropyl donor for the biosynthesis of polyamines. The nucleosidic byproduct of that pathway is 5′-*S*-methyl-5′-thioadenosine (MTA).[3] Methylthioadenosine phosphorylase (MTA-Pase)[4] effects glycosyl cleavage of MTA and the resulting 5-*S*-methyl-5-thioribose 1-phosphate is converted to methionine by a salvage pathway.[5] It has been found that

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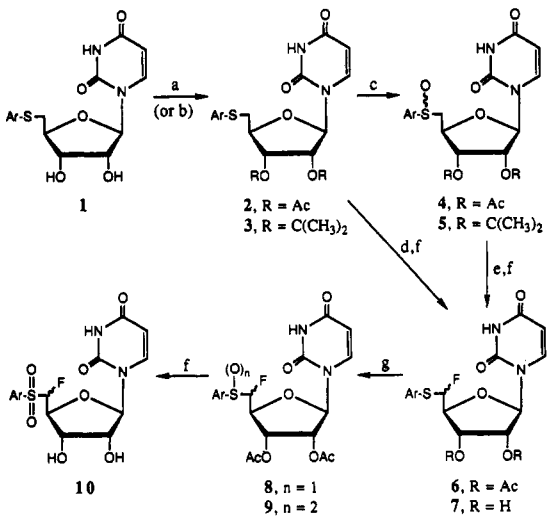
5′-deoxy-5′-haloadenosine derivatives exert biological effects by phosphorolysis (MTAPase) to give the active 5-deoxy-5-haloribose 1-phosphate analogues.[6a] The corresponding 5′-deoxy-5′-haloinosine derivatives produce parallel effects in cell lines that are deficient in MTAPase but have normal levels of purine nucleoside phosphorylase (PNPase), an enzyme that catalyzes phosphorolysis of hypoxanthine but not adenine nucleosides.[6b] SIBA (5′-*S*-isobutyl-5′-thioadenosine) causes potent cellular effects[7a] and 5′-*S*-phenyl-5′-thioadenosine has antiviral activity.[7b] We considered that 5′-*S*-aryl-5′-fluoro-5′-thiouridines **7**, which are nucleoside α-fluoro 5′-thioethers, might be alternative substrates of uridine phosphorylase (UrdPase, E.C. 2.4.2.3).[8] If so, the resulting 5-*S*-aryl-5-fluoro-5-thioribose 1-phosphates would be (fluoro)thioacetal analogues that might inhibit the noted salvage pathway enzymes.[5,6,8]

We recently noted applications of McCarthy's reaction of sulfoxides with (diethylamino)sulfur trifluoride (DAST)[9] to give the first examples of nucleoside α-fluoro thioethers[10] with our sulfoxide/DAST/antimony(III) chloride modification.[11] McCarthy and co-workers have reported parallel studies on the preparation of isopropylidene derivatives of 5′-*S*-aryl-5′-fluoro-5′-thioadenosine and their conversion into diastereomeric 5′-deoxy-5′-fluoro-4′,5′-didehydroadenosines that function as mechanism-based inhibitors of SAHase with antiviral[12a,b] and antimalarial[12c] activity. The analogous synthesis, competitive inhibition of MTAPase, and antiproliferative properties of 5′-fluorinated analogues of MTA have been reported,[13] and 5′-*S*-(difluoromethyl)-5′-thioadenosine has been found to be an inhibitor, but not substrate, of MTAPase.[14] Treatment of the sodium salt of methyl 2,3-*O*-isopropylidene-5-thioribofuranoside with FCH_2Cl, F_2CHCl, or CF_3I followed by deprotection gave 5-deoxy-5-*S*-(mono, di, or trifluoro)methyl-5-thioribose,[15,16] respectively. The mono and difluoro analogues have antitumor activity,[15] and the trifluoromethyl compound is an inhibitor of a 5-*S*-methyl-5-thioribose kinase.[16]

Alkyl aryl sulfides with α-hydrogen atoms have been converted directly to α-fluoro thioethers with xenon difluoride[17] or *N*-fluoropyridinium triflates.[18] A recent review[19] of applications of DAST for the synthesis of fluorinated-sugar nucleosides, excluding the α-fluoro thioether nucleosides,[10,12,13] is available. We now report two efficient methods for the synthesis of α-fluoro 5′-thioether derivatives of uridine. One utilized the transformation of sulfoxides to α-fluoro thioethers with DAST.[9,11] The other represents the first application of the conversion of sulfides to α-fluoro sulfides with xenon difluoride.[17]

Scheme I[a]



Series: a, Ar = $C_6H_4OCH_3(4)$; b, Ar = $C_6H_4OH(4)$; c, Ar = $C_6H_4OCOCH_3(4)$

[a] (a) DMAP/Ac_2O; (b) $CuSO_4/H_2SO_4/Me_2CO$; (c) MCPBA/CH_2Cl_2/−40 °C; (d) XeF_2/MeCN/−20 °C to ambient; (e) DAST/$SbCl_3/CH_2Cl_2$/ambient; (f) NH_3/MeOH; (g) MCPBA/CH_2Cl_2.

Efficient transformations of nucleosides to 5′-*S*-aryl-5′-thionucleosides via 5′-chloro-5′-deoxynucleosides (prepared by thionyl chloride/pyridine/acetonitrile modification of the usual $SOCl_2$/HMPA procedure[20]) have been developed.[21] Replacement of 5′-chloro with arenethiolate (ArSH/NaH/DMF) gave 5′-*S*-(4-methoxyphenyl)-5′-thiouridine (**1a**, 94%) or **1b** (92%).[21] Catalytic 4-(dimethylamino)pyridine in acetic anhydride (DMAP/Ac_2O)[22] effected quantitative acetylation of **1a** to **2a**, which was oxidized quantitatively [MCPBA(1.02 equiv)/CH_2Cl_2/−40 °C] to give the diasteromeric sulfoxides **4a** (~1:1, ^1H NMR). Treatment of **4a** with DAST(2 equiv/ZnI_2(cat.)/$CHCl_3/N_2$ for 12 h at ambient temperature gave the fluoro diastereoisomers **6a** (~1:1, 71% after column chromatography) with ^{19}F NMR δ −157.50 (dd, $^2J_{F\text{-}5'}$ = 52.5 Hz, $^3J_{F\text{-}4'}$ = 11.7 Hz, F5′*R*) and −159.27 (dd, $^2J_{F\text{-}5'}$ = 52.5 Hz, $^3J_{F\text{-}4'}$ = 17 Hz, F5′*S*) (upfield from CCl_3F).

As noted in our work with adenosine,[10] treatment of protected 5′-*S*-phenyl-5′-thionucleosides with ZnI_2/DAST[9] gave deoxygenated starting material as the major product.

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Deoxygenation of sulfoxides to sulfides by sodium iodide/boron trifluoride etherate[23] and sodium iodide/titanium(IV) chloride[24] have been reported. Recently, it was noted[25] that conversions of methyl phenyl sulfoxide into the α-fluoro sulfide with ZnI_2/DAST were not reproducible and gave mixtures of the fluorination product and deoxygenated starting material. Similar problems with nucleosides have been reported.[13] We found that $SbCl_3$ was the most convenient and efficient catalyst of a number of Lewis acids tested, and this modification resulted in improvements in rates and yields of the fluorination process.[10,11] $SbCl_3$(0.1 equiv)/DAST(2 equiv) minimized deoxygenation and provided more rapid fluorination with less color and byproduct formation.

Treatment of **4a** with DAST/$SbCl_3$/CH_2Cl_2 for 3 h at ambient temperature gave **6a** (~1:1, 85% after column chromatography). No deoxygenated (unfluorinated) starting sulfide **2a** was detected. Reaction progress was monitored conveniently by TLC and confirmed by ^1H NMR spectroscopy. The polar sulfoxides **4a** migrate much more slowly on TLC than products **6a**, and the ^1H NMR multiplet for sulfoxides **4a** centered at δ ~3.3 (H5′,H5″) disappeared with concomitant appearance of two doublets of doublets shifted downfield by about 2.9 ppm for **6a**.

Crystallization and recrystallization of the **6a** mixture from methanol afforded one diastereomer (42%, 36% from **4a**) whose *R* configuration at C5′ was established by X-ray crystallography. The ^{19}F NMR spectrum of this compound had the lower field doublet of doublets at δ −157.50. The spectrum of the mother liquor indicated a mixture of **6a** (5′*R*/*S*, ~1:5.7). Attempts to crystallize this material were unsuccessful. Deprotection (NH_3/MeOH) and crystallization (MeOH) afforded **7a**(5′*S*) (30% based on **4a**). The ^{13}C NMR signals for C5′ and C4′ appeared as doublets at δ 101.20 ($^1J_{C5'\text{-}F}$ = 223.4 Hz) and 84.71 ($^2J_{C4'\text{-}F}$ = 20.1 Hz) with 63.7 and 2.1 ppm downfield shifts, respectively, relative to these peaks for the unfluorinated sulfide **1a**.[21] Deprotection of **6a**(5′*R*) afforded **7a**(5′*R*) (83%). Characteristic NMR spectral differences between diastereomer pairs include (i) ^{19}F chemical shifts (5′*R* diastereomers downfield from 5′*S*), (ii) ^{19}F and ^1H coupling constants (5′*S* diastereomer has 5–12 Hz larger $^3J_{F\text{-}H4'}$ than 5′*R*), and (iii) ^{13}C coupling constants (5′*R* diastereomer has larger $^2J_{C4'\text{-}F}$ than 5′*S*).

Direct fluorination with XeF_2[17] proceeded smoothly. Treatment of **2a** with XeF_2 (1.05 equiv) in anhydrous CH_2Cl_2 or CH_3CN under N_2 in Teflon or glass at −25 °C for 1 h gave **6a** (5′*R*/*S*, ~1:1.3; 91% after column chromatography). Although XeF_2 is less readily available than DAST, the rapid and clean fluorination of **2a** to **6a** with 1.05 equiv of XeF_2 that permits deletion of the oxidation step required in the DAST/sulfoxide sequence[9-13] are advantages of this direct conversion of thioethers to α-fluoro thioethers.

Treatment of α-fluoro thioether sulfoxides with DAST[9] or further reaction of α-fluoro thioethers with XeF_2[17a] have been reported to give α,α-difluoro thioethers. However, our nucleoside analogues did not undergo this second conversion. Oxidation of **6a** (5′*R*/*S*, ~1:1) with MCPBA (1.05 equiv) afforded **8a** (98%) as a mixture of four diastereomers (^{19}F NMR) plus minor peaks from the "overoxidized" sulfones **9a**. Treatment of **8a** with DAST/$SbCl_3$ resulted in deoxygenation to give **6a** in moderate to high yields. The ratio of 5′-fluoro diastereomers formed was essentially unchanged from the original **6a** (before oxidation) in harmony with deoxygenation chemistry only, at sulfur.

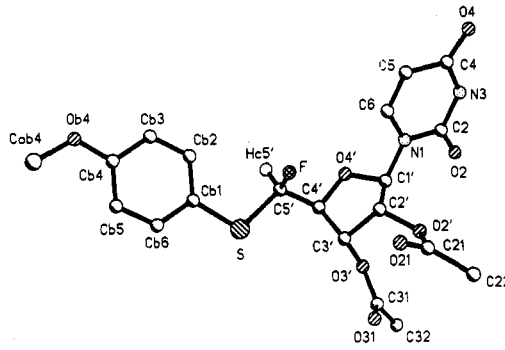

Figure 1. X-ray crystal structure of **6a**(5′*R*) drawn with SHELXTL PLUS.[30] Hydrogen atoms with the exception of Hc5′ were omitted for clarity.

Treatment of **6a** with XeF_2 gave recovered **6a** plus minor amounts of a more polar product that was identified as sulfoxides **8a**. This is compatible with partial reaction of XeF_2 with **6a** to give sulfur(IV) difluoride derivatives that do not proceed to the desired 5′,5″-difluoro sulfide derivatives but undergo hydrolysis to sulfoxides. Formation of sulfur(IV) difluoride derivatives by treatment of sulfides with XeF_2 and their hydrolysis to sulfoxides has been observed previously.[17b,d]

McCarthy and co-workers[9] found that introduction of a 4-methoxy group on the phenyl ring of alkyl aryl thioethers dramatically increased the rates of DAST/sulfoxide reactions and yields of α-fluoro thioether products. Since we observed parallel differences with nucleoside counterparts,[10] we prepared 5′-*S*-(4-hydroxyphenyl)-5′-thiouridine[21] (**1b**) to probe whether a more powerfully activating phenol group would promote further reactivity. However, treatment of the 2′,3′-*O*-isopropylidene derivative **3b** with XeF_2 (or the corresponding sulfoxides **5b** with DAST/$SbCl_3$) gave <5% of the desired α-fluoro thioethers (^{19}F NMR analysis of the complex reaction mixtures), which suggested that side reactions and/or reagent/catalyst complexing with the phenolic function occurred.

Acetylation of **1b** (DMAP/Ac_2O[22]) followed by oxidation of the resulting triacetate **2c** with MCPBA gave **4c** (5′*R*/*S*, ~1:1) quantitatively. Treatment of **4c** with DAST/$SbCl_3$ afforded the 5′-fluoro diastereomers **6c** (5′*R*/*S*, ~1:1.2; 89%). A higher diastereomer ratio (5′*R*/*S*, ~1:1.4) of **6c** (83%) was obtained when the protected sulfide **4c** was treated with XeF_2. However, difluorination was not achieved to a significant extent with either procedure. No significant differences in reactivity between nucleoside thioethers protected with isopropylidene or acetyl groups were observed in contrast to claims made by Sufrin et al.[13] Deprotection of **6c** (NH_3/MeOH) gave **7b** in high yield.

MCPBA oxidation of **6a**(5′*R*) gave **9a**(5′*R*), and deprotection gave the 5′-fluoro sulfone **10a** (90%). Oxidation of the **6a** diastereomers from the crystallization mother liquor (5′*R*/*S*, ~1:5.7) and "diffusion crystallization"[26] of the product gave **9a**(5′*S*). Deprotection afforded **10a**(5′*S*) (60% from **6a**). It also was prepared from **7a**(5′*S*) by acetylation, oxidation, and deacetylation. NMR spectral data are given in Tables I and II and the Experimental Section.

Figure 1 contains a computer drawing of **6a**(5′*R*). Positional and thermal parameters of the atoms (Tables

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

compd	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[d] ($J_{3'-4'}$)	H4′[e] ($J_{4'-5',5''}$)	H5′,5″[d,f] ($J_{5'-5''}$)	H5[c] (J_{5-6})	H6[c]	NH[g]	aromatic[c] (J_{A-B})	other[h]
2a[i]	5.84 (5.5)	5.49 (6.5)	5.28 (4.6)	4.04 (5.5, 6.5)	3.29, 3.20 (13.0)	5.66 (8.0)	7.66	11.44	7.32, 6.88 (8.5)	2.00, 2.04 (Ac's), 3.72 (CH_3O)
2c[i]	5.89 (5.5)	5.53 (6.5)	5.34 (4.5)	4.15 (5.5, 6.5)	3.46, 3.36 (13.0)	5.70 (8.0)	7.72	11.49	7.42, 7.10 (8.5)	2.06, 2.10, 2.28 (Ac's)
3b[i]	5.73[h]	5.06[e] (6.0)	4.78 (3.5)	4.00[j]	3.09[j]	5.63 (8.0)	7.71	11.41	6.73, 7.27 (8.5)	1.28, 1.45 (CMe_2), 9.62[g] (OH)
4a[k]	5.92, 5.87 (5.0, 6.0)	5.59, 5.58 (5.0, 6.0)	5.44, 5.30 (4.5, 5.5)	4.20, 4.40 (6.0, 7.0)	3.43, 3.38, 3.30, 3.18 (13.0)	5.70, 5.72 (8.0)	7.71, 7.84	11.48, 11.51	7.63, 7.65, 7.14, 7.16 (8.5)	2.02, 2.05, 2.07, 2.08 (Ac's), 3.82, 3.83 (CH_3O)
4c[i,k]	5.96, 5.88 (5.0, 5.5)	5.61, 5.58 (5.5, 5.5)	5.47, 5.34 (5.5, 5.5)	4.42,[j] 4.29[j]	3.16–3.60[j]	5.71, 5.74 (8.0)	7.70, 7.87	11.50, 11.53	7.37, 7.40, 7.76, 7.78 (8.5)	2.04, 2.07, 2.09, 2.10, 2.31, 2.32 (Ac's)
5b[i,k]	5.76, 5.82 (1.5, 2.0)	5.09, 5.12 (6.0, 6.0)	4.82, 4.92 (4.5, 3.5)	4.08,[j] 4.32[j]	3.10–3.40[j]	5.65, 5.66 (8.0)	7.74	11.41	6.94, 7.52; 6.94, 7.54 (8.5)	1.28, 1.44 (CMe_2), 1.28, 1.51 (CMe_2), 10.24[g] (OH)
6a(5′*R*)	6.00 (5.0)	5.55 (5.0)	5.53 (4.0)	4.30 (5.0,[l] 11.7[m])	6.19 (52.5[n])	5.77 (8.0)	7.70	11.50	7.48, 7.00 (8.5)	2.12, 2.07 (Ac's), 3.80 (CH_3O)
6a(5′*S*)[o]	6.00 (5.5)	5.54 (6.5)	5.48 (5.0)	4.36 (5.0,[l] 17.0[m])	6.16 (52.5[n])	5.78 (8.0)	7.71	11.48	7.46, 7.01 (8.5)	2.12, 2.04 (Ac's), 3.78 (CH_3O)
6c(5′*R*)[p]	6.00 (5.5)	5.52–5.58[j]	5.52–5.58[j]	4.38 (4.8,[l] 12.4[m])	6.41 (53.5[n])	5.75 (8.0)	7.69	11.50	7.19, 7.58 (8.5)	2.06, 2.10, 2.28 (Ac's)
6c(5′*S*)[p]	6.02 (5.5)	5.52–5.58[j]	5.48 (4.5)	4.43 (5.0,[l] 18.5[m])	6.38 (53.5[n])	5.77 (8.0)	7.69	11.50	7.20, 7.56 (8.5)	2.05, 2.11, 2.28 (Ac's)
7a(5′*R*)	5.86 (6.5)	4.17[e] (5.0)	4.11[e] (3.0)	4.00 5.0,[l] 14.4[m])	6.07 (53.5[n])	5.73 (8.0)	7.60	11.42	7.00, 7.47 (9.0)	5.56[c] (6.0,[q] OH2′), 5.53[c] (5.0,[q] OH3′), 3.78 (CH_3O)
7a(5′*S*)	5.86 (5.5)	4.10[j]	4.10[j]	4.05 (4.5,[l] 20.0[m])	6.10 (53.5[n])	5.74 (8.0)	7.60	11.40	6.98, 7.49 (9.0)	5.57[c] (5.0,[q] OH2′), 5.49[c] (4.0,[q] OH3′), 3.78 (CH_3O)
7b(5′*R*)[p]	5.82 (6.3)	3.92–4.16[j]	3.92–4.16[j]	3.92–4.16[j] (5.0,[l] 15.0[m])	5.98 (53.5[n])	5.70 (8.0)	7.59	11.40	6.78, 7.32 (9.0)	5.42–5.60[g] (OH2′, OH3′), 9.85[g] (OH)
7b(5′*S*)[p]	5.83 (5.7)	3.92–4.16[j]	3.92–4.16[j]	3.92–4.16[j] (4.5,[l] 20.0[m])	6.01 (53.5[n])	5.72 (8.0)	7.61	11.40	6.78, 7.34 (9.0)	5.42–5.60[g] (OH2′, OH3′), 9.85[g] (OH)
9a(5′*R*)	5.98 (5.7)	5.62 (5.5)	5.40 (5.5)	4.56 (5.5,[l] 14.5[m])	6.14 (45.0[n])	5.64 (8.0)	7.38	11.49	7.20, 7.85 (9.0)	2.03, 2.09 (Ac's), 3.87 (CH_3O)
9a(5′*S*)	5.92 (5.2)	5.62 (6.0)	5.56 (6.0)	4.62 (2.8,[l] 25.0[m])	6.10 (45.0[n])	5.64 (8.0)	7.40	11.45	7.20, 7.84 (9.0)	2.04, 2.10 (Ac's), 3.85 (CH_3O)
10a(5′*R*)	5.87 (6.5)	4.12–4.20[j]	4.12–4.20[j]	4.12–4.20[j] (6.0,[l] 15.0[m])	5.98 (45.0[n])	5.63 (8.0)	7.45	11.40	7.20, 7.82 (9.0)	5.68[c] (4.0,[q] OH2′), 5.58[c] (6.0,[q] OH3′), 3.88 (CH_3O)
10a(5′*S*)	5.80 (6.5)	4.00[e] (5.0)	4.22[e] (3.0)	4.33 (3.0,[l] 27.0[m])	6.03 (45.0[n])	5.55 (8.0)	7.13	11.38	7.15, 7.81 (9.0)	5.68[c] (5.0,[q] OH2′), 5.62[c] (6.0,[q] OH3′), 3.85 (CH_3O)

[a] Chemical shifts (δ) in Me_2SO-d_6 at 400 MHz unless otherwise noted. [b] "Apparent" first-order coupling constants (Hz, in parentheses). [c] Doublet. [d] Doublet of doublets. [e] Doublet of doublets of doublets. [f] Upfield signal is assigned to 5″(*R*)-H. [g] Broad singlet. [h] Singlet. [i] 200 MHz. [j] Multiplet. [k] Mixture of diastereomers. [l] ($^3J_{4'-5'}$). [m] ($^3J_{4'-F}$). [n] ($^2J_{5'-F}$). [o] Assigned from a spectrum of both diastereomers by comparison with that of the 5′*R* isomer. [p] Signals for 5′*R* and 5′*S* assigned from the spectrum of a mixture on the basis of ^{19}F NMR integration. [q] ($^3J_{OH-CH}$).

2S and 4S), bond lengths and angles (Table 3S), and important torsion angles (Table 5S) are included in the supplementary material. The C6–N1–C1′-O4′ glycosyl torsion angle is staggered at 60.1 (4)°. The C3′–C4′–C5′–F torsion angle is 49.6 (4)° with the carbon–fluorine bond in the stereoelectronically expected gauche orientation. The pseudorotation angle of the sugar ring is 158°, indicating an envelope conformation (^{2}E). H3 is involved in an intermolecular hydrogen bond.

Experimental Section

Uncorrected melting points were determined on a microstage block. NMR spectra were determined in Me_2SO-d_6 unless otherwise noted with Me_4Si as internal [^{1}H (400 MHz); ^{13}C (75.5 MHz)] and CCl_3F as external [^{19}F (376.5 MHz)] standards. ^{19}F NMR chemical shifts upfield from the standard have negative values. High resolution EI mass spectra were determined at 70 eV and low resolution spectra at 20 eV. DAST was used as received from Aldrich Chemical Co. Aldrich 85% MCPBA gave equivalent yields before or after extraction to remove 3-chlorobenzoic acid. Xenon difluoride was obtained from PCR, Inc. Reagent grade chemicals were used as obtained and solvents were purified, dried, and distilled before use. TLC was performed on silica sheets [upper phase of EtOAc/PrOH/H_2O (4:1:2) unless otherwise noted] with visualization under UV (2537 Å) 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. 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.

2′,3′-Di-*O*-acetyl-5′-*S*-(4-methoxyphenyl)-5′-thiouridine (2a). DMAP (24 mg, 0.2 mmol) was added to a suspension of 5′-*S*-(4-methoxyphenyl)-5′-thiouridine[21] (**1a**, 1.47 g, 4.0 mmol) in Ac_2O (3 mL), and the mixture was stirred at ambient temperature for 10 h. MeOH (15 mL) was added, and the solution stirred for 1 h and concentrated in vacuo. The residue was partitioned (2% HOAc/H_2O//$CHCl_3$) and the organic phase washed with $NaHCO_3$/H_2O (2×), NaCl/H_2O, H_2O, dried (Na_2SO_4), and evaporated to afford **2a** (1.78 g, 99%) as a white foam with MS *m*/*z* 450.1103 (34, $M^+[C_{20}H_{22}N_2O_8S]$ = 450.1097), 139.0240 (87, $CH_3OC_6H_4S$) of sufficient purity for use in subsequent reactions.

2′,3′-Di-*O*-acetyl-5′-deoxy-5′-[(4-methoxyphenyl)sulfinyl]uridine (4a; 5′*R*/*S*, ~1:1). MCPBA (621 mg, 3.06 mmol as 85% reagent) in CH_2Cl_2 (30 mL) was added dropwise to a stirred solution of **2a** (1.35 g, 3 mmol) in CH_2Cl_2 (30 mL) at −40 °C. TLC (MeOH/$CHCl_3$, 1:9) indicated that oxidation was complete when the MCPBA had been added. The reaction

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

compd	C2	C4	C5	C6	C1′	C2′	C3′	C4′[c]	C5′[d]	aromatic C1″	aromatic C2″	aromatic C3″	aromatic C4″	other
6a(5′*R*)	150.64	163.16	102.99	141.46	87.30	71.27	69.73	80.56 (26.6)	100.81 (218.7)	120.51	135.56	115.28	160.43	169.71, 169.54 (C=O) 55.37 (CH_3O) 20.25, 20.14 (Ac's)
6a(5′*S*)[e]	150.42	163.22	103.01	141.46	87.80	71.65	69.99	81.84 (20.7)	100.65 (224.3)	121.15	135.19	115.34	160.42	169.72, 169.63 (C=O) 55.45 (CH_3O) 20.33, 20.19 (Ac's)
7a(5′*R*)	151.19	163.32	102.72	140.85	87.50	72.06	70.32	83.45 (24.7)	101.49 (219.0)	121.05	135.48	115.25	160.34	55.42 (CH_3O)
7a(5′*S*)	151.11	163.36	102.63	140.53	88.00	72.56	70.64	84.71 (20.1)	101.20 (223.4)	121.86	135.07	115.24	160.24	55.42 (CH_3O)
7b(5′*R*)[f]	150.95	162.96	102.48	104.48	87.32	71.97	70.19	83.33 (24.1)	101.48 (222.0)	118.56	135.43	116.10	158.34	
7b(5′*S*)[f]	150.82	162.96	102.37	140.19	87.87	72.44	70.49	84.54 (20.4)	101.12 (222.0)	119.32	135.15	116.32	158.44	
9a(5′*R*)[g]	150.30	162.42	103.91	139.27	87.72	72.05	69.41	79.20 (20.4)	100.00 (223.4)	126.56	131.81	114.96	165.22	169.46, 169.25 (C=O) 55.93 (CH_3O) 20.46, 20.36 (Ac's)
9a(5′*S*)[g]	150.18	162.54	103.58	138.44	86.52	71.86	70.73	79.25 (18.0)	100.64 (224.0)	126.91	132.41	114.46	165.13	169.78, 169.55 (C=O) 55.89 (CH_3O) 20.53, 20.35 (Ac's)
10a(5′*R*)	150.82	162.74	102.41	140.29	86.63	71.60	70.18	80.60 (23.8)	99.39 (216.5)	126.48	131.67	114.77	164.34	55.88 (CH_3O)
10a(5′*S*)	150.60	162.72	102.21	139.45	87.34	71.88	70.45	79.89 (16.6)	100.50 (219.9)	126.87	131.83	114.55	164.29	55.81 (CH_3O)

[a] Chemical shifts (δ) in Me_2SO-d_6 unless otherwise noted were recorded at 75.5 MHz with off resonance or attached proton test techniques. [b] Singlets unless otherwise noted. [c] Doublet ($^2J_{C4'-F}$). [d] Doublet ($^1J_{C5'-F}$). [e] Assignments made from the spectrum of a 5′*R*/*S* mixture by comparison with that of **6a**(5′*R*). [f] Signals for 5′*R* and 5′*S* assigned from the spectrum of a mixture on the basis of ^{19}F NMR integration. [g] Spectrum in $CDCl_3$.

mixture was poured into ice-cold saturated $NaHCO_3/H_2O$ (70 mL) and extracted ($CHCl_3$, 2 × 50 mL). The combined organic phase was washed with $NaCl/H_2O$ and H_2O, dried (Na_2SO_4), and concentrated to give **4a** (1.39 g, 99%; 5′*R*/*S*, ~1:1) as a white foam with MS *m*/*z* 466.1048 (0.1, $M^+[C_{20}H_{22}N_2O_9S]$ = 466.1046), 311.0880 (8, M − $CH_3OC_6H_4SO$ = 311.0870), 155.0173 (34, $CH_3OC_6H_4SO$), 139.0217 (35, $CH_3OC_6H_4S$) of sufficient purity for use in the next step.

2′,3′-Di-*O*-acetyl-5′-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thiouridine (6a). Method A (DAST). DAST (0.53 mL, 0.645 g, 4 mmol) was added by syringe to a stirred solution of **4a** (932 mg, 2 mmol) and $SbCl_3$ (45 mg, 0.2 mmol) in CH_2Cl_2 (20 mL) under N_2 at ambient temperature. TLC ($MeOH/CHCl_3$ 1:9 or $Me_2CO/CHCl_3$ 1:3) indicated complete reaction after 3 h. Ice-cold saturated $NaHCO_3/H_2O$ was added and stirring was continued for 30 min to destroy excess DAST. The layers were separated and the H_2O layer was extracted with $CHCl_3$ (2 × 25 mL). The combined organic phase was washed with $NaHCO_3/H_2O$, $NaCl/H_2O$, and H_2O, dried (Na_2SO_4), concentrated, and chromatographed on a silica column ($MeOH/CHCl_3$, 1.5:98.5) to give **6a** (795 mg, 85%; 5′*R*/*S*, ~1:1) as a white foam: ^{19}F NMR δ −157.50 (dd, $^2J_{F-5'}$ = 52.5 Hz, $^3J_{F-4'}$ = 11.7 Hz, 0.5, F5′*R*), −159.27 (dd, $^2J_{F-5'}$ = 52.5 Hz, $^3J_{F-4'}$ = 17 Hz, 0.5, F5′*S*); MS *m*/*z* 468.1004 (17, $M^+[C_{20}H_{21}FN_2O_8S]$ = 468.1003), 139.0218 (100, $CH_3OC_6H_4S$).

Method B (XeF_2). A solution of **2a** (450 mg, 1 mmol) in anhydrous CH_3CN (7 mL) was injected by syringe into a suspension of XeF_2 (178 mg, 1.05 mmol) in anhydrous CH_3CN (2 mL) in a glass flask with a rubber septum at −25 °C. Xenon gas was evolved and further gas evolution caused reversal of the syringe plunger as warming to ambient temperature occurred. HF was consumed after 1 h by *careful* addition of $(Me_3Si)_2NH$ (0.225 mL, 0.16 g, 1.1 mmol). Evaporation in vacuo gave a slightly yellow foam that was dissolved in $CHCl_3$ and washed with $NaHCO_3/H_2O$, $NaCl/H_2O$, and H_2O, dried (Na_2SO_4), and evaporated to give **6a** (449 mg, 96%; 5′*R*/*S*, ~1:1.3). Column chromatography ($MeOH/CHCl_3$, 1.5:98.5) gave **6a** (426 mg, 91%): ^{19}F NMR δ −157.50 (dd, $^2J_{F-5'}$ = 52.5 Hz, $^3J_{F-4'}$ = 11.7 Hz, 0.43, F5′*R*), −159.27 (dd, $^2J_{F-5'}$ = 52.5 Hz, $^3J_{F-4'}$ = 17 Hz, 0.57, F5′*S*); MS *m*/*z* 468.1012 (26, $M^+[C_{20}H_{21}FN_2O_8S]$ = 468.1003), 139.0222 (100, $CH_3OC_6H_4S$).

2′,3′-Di-*O*-acetyl-5′(*R*)-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thiouridine [6a(5′*R*)]. A solution of **6a** (200 mg, method A; 5′*R*/*S*, ~1:1) in MeOH (30 mL) was allowed to stand overnight at ~0 °C. The resulting crystals (92 mg, 46%; 5′*R*/*S*, ~9:1) were dissolved in hot MeOH (35 mL) and slowly cooled to give needles of **6a**(5′*R*) (78 mg, 39%): mp 210–212 °C; UV (MeOH) max 244 nm (ϵ 18100), min 220 nm (ϵ 10100); ^{19}F NMR δ −157.50 (dd, $^2J_{F-5'}$ = 52.5 Hz, $^3J_{F-4'}$ = 11.7 Hz, F5′*R*); MS *m*/*z* 468.1005 (21, $M^+[C_{20}H_{21}FN_2O_8S]$ = 468.1003), 139.0222 (100, $CH_3OC_6H_4S$). Anal. Calcd for $C_{20}H_{21}FN_2O_8S$ (468.5): C, 51.28; H, 4.52; N, 5.98; S, 6.84. Found: C, 51.32; H, 4.55; N, 5.91; S, 6.95.

The latter mother liquor was concentrated and the residue crystallized (MeOH, 5 mL) to give additional **6a**(5′*R*) (6 mg, 3%) with mp 210–212 °C and identical NMR spectral data. Repeated attempts to crystallize the second diastereoisomer were unsuccessful.

5′(*R*)-Fluoro-5′-*S*-(4-methoxyphenyl)-5′-thiouridine [7a(5′*R*)]. Saturated NH_3/MeOH (15 mL) was added to a stirred solution of **6a**(5′*R*) (200 mg, 0.43 mmol) in MeOH (60 mL). After 2 h at ambient temperature, the solution was evaporated to give a crystalline solid that was recrystallized (MeOH) to give **7a**(5′*R*) (134 mg, 82%): mp 230–232 °C; UV (MeOH) max 244 nm (ϵ 18200), min 223 nm (ϵ 10800); ^{19}F NMR δ −156.86 (dd, $^2J_{F-5'}$ = 53.5 Hz, $^3J_{F-4'}$ = 14.4 Hz, F5′*R*); MS *m*/*z* 384.0785 (27, $M^+[C_{16}H_{17}FN_2O_6S]$ = 384.0791). Anal. Calcd for $C_{16}H_{17}FN_2O_6S$ (384.4): C, 50.00; H, 4.46; N, 7.29; S, 8.34. Found: C, 49.88; H, 4.41; N, 7.27; S, 8.67.

5′(*S*)-Fluoro-5′-*S*-(4-methoxyphenyl)-5′-thiouridine [7a(5′*S*)]. A solution of **6a** (400 mg, 0.85 mmol) [residue from the first evaporated mother liquor (from method A) with 5′*R*/*S*, ~1:5.7] in MeOH (40 mL) was treated by the above [**6a**(5′*R*) → **7a**(5′*R*)] procedure to give **7a**(5′*S*) (200 mg, 61%): mp 248–250 °C; UV (MeOH) max 246 nm (ϵ 18500); min 224 nm (ϵ 10300); ^{19}F NMR δ −160.82 (dd, $^2J_{F-5'}$ = 53.5 Hz, $^3J_{F-4'}$ = 20 Hz, F5′*S*); MS *m*/*z* 384.0787 (3, $M^+[C_{16}H_{17}FN_2O_6S]$ = 384.0791). Anal. Calcd for $C_{16}H_{17}FN_2O_6S$: C, 50.00; H, 4.46; N, 7.29; S, 8.34. Found: C, 50.24; H, 4.47; N, 7.24; S, 8.54.

2′,3′-Di-*O*-acetyl-5′-*S*-[4-(acetyloxy)phenyl]-5′-thiouridine (2c). DMAP (11 mg, 0.09 mmol) was added to a suspension of 5′-*S*-(4-hydroxyphenyl)-5′-thiouridine[21] (**1b**, 0.5 g, 1.42 mmol) in Ac_2O (3.5 mL), and the mixture was stirred at ambient temperature overnight. The resulting solution was treated with MeOH and evaporated in vacuo after 30 min. The residue was partitioned (2% $HOAc/H_2O//CHCl_3$) and the $CHCl_3$ layer washed with $NaHCO_3/H_2O$ (2×), $NaCl/H_2O$, and H_2O, dried (Na_2SO_4), and evaporated to give **2c** (0.67 g, 99%) as a white foam with MS *m*/*z* 478.1049 (7, $M^+[C_{21}H_{22}N_2O_9S]$ = 478.1046).

2′,3′-Di-*O*-acetyl-5′-[[4-(acetyloxy)phenyl]sulfinyl]-5′-deoxyuridine (4c). Oxidation of **2c** (125 mg, 0.26 mmol) with

MCPBA (53 mg, 0.26 mmol as 85% reagent) [as described above for **2a** → **4a**] gave **4c** (128 mg, quant; R/S, ~1:1) with MS (FAB) m/z 495 (22, M + 1).

2′,3′-Di-*O*-acetyl-5′-*S*-[4-(acetyloxy)phenyl]-5′-fluoro-5′-thiouridine (6c). Method A. Treatment of **4c** (123 mg, 0.25 mmol) with DAST [as described above for **4a** → **6a** (reaction time 5 h)] gave **6c** (110 mg, 89%; 5′R/S, ~1:1.2): ^{19}F NMR δ −157.29 (dd, $^2J_{F\text{-}5'}$ = 53.5 Hz, $^3J_{F\text{-}4'}$ = 12.4 Hz, 0.46, F5′R), −159.76 (dd, $^2J_{F\text{-}5'}$ = 53.5 Hz, $^3J_{F\text{-}4'}$ = 18.5 Hz, 0.54, F5′S).

Method B. A solution of **2c** (0.42 g, 0.88 mmol) in anhydrous CH_3CN (2 mL) was injected by syringe into a suspension of XeF_2 (158 mg, 0.93 mmol) in anhydrous CH_3CN (1 mL) at −20 °C in a Teflon bottle with a rubber septum. Xenon gas was evolved immediately and continued upon warming to ambient temperature. The mixture was stirred for 2 h and treated *carefully* with $(Me_3Si)_2NH$ (0.21 mL, 1 mmol) to consume HF and excess XeF_2. Evaporation gave a slightly yellow foam that was partitioned ($NaHCO_3/H_2O//CHCl_3$), and the $CHCl_3$ layer washed with $NaCl/H_2O$ and H_2O, dried (Na_2SO_4), and evaporated. Column chromatography (MeOH/$CHCl_3$, 1:49) of the residue gave **6c** (363 mg, 83%; 5′R/S, ~1:1.4): ^{19}F NMR δ −157.29 (dd, $^2J_{F\text{-}5'}$ = 53.5 Hz, $^3J_{F\text{-}4'}$ = 12.4 Hz, 0.42, F5′R), −159.76 (dd, $^2J_{F\text{-}5'}$ = 53.5 Hz, $^3J_{F\text{-}4'}$ = 18.5 Hz, 0.58, F5′S); MS m/z 496.0965 (7, $M^+[C_{21}H_{21}FN_2O_9S]$ = 496.0952), 454.0860 (74, M − C_2H_2O).

5′-Fluoro-5′-*S*-(4-hydroxyphenyl)-5′-thiouridine (7b). A solution of **6c** (99 mg, 0.2 mmol; 5′R/S, ~1:1.4) in MeOH (10 mL) was treated with saturated NH_3/MeOH (10 mL) at 0 °C, stirred at ambient temperature for 4 h, and evaporated. The residue was diffusion crystallized[26] (MeOH/$CHCl_3$) to give **7b** (45 mg, 61%; 5′R/S, ~1:1.4): mp 168–171 °C dec; UV (MeOH) max 246 nm (ε 18 500), min 227 nm (ε 12 600); ^{19}F NMR δ −156.46 (dd, $^2J_{F\text{-}5'}$ = 53.5 Hz, $^3J_{F\text{-}4'}$ = 15 Hz, 0.41, F5′R), −160.42 (dd, $^2J_{F\text{-}5'}$ = 53.5 Hz, $^3J_{F\text{-}4'}$ = 20 Hz, 0.59, F5′S); MS (FAB) m/z 371 (1, M + 1); MS (EI) m/z 126.0140 (75, HOC_6H_4SH), 112.0277 (100, B + 1). Anal. Calcd for $C_{15}H_{15}FN_2O_6S$ (370.4): C, 48.64; H, 4.08; N, 7.56. Found: C, 48.34; H, 4.18; N, 7.56.

5′-*S*-(4-Hydroxyphenyl)-2′,3′-*O*-isopropylidene-5′-thiouridine (3b). Anhydrous $CuSO_4$ (4 g) and concentrated H_2SO_4 (0.05 mL) were added to a suspension of 5′-*S*-(4-hydroxyphenyl)-5′-thiouridine[21] (**1b**, 2.12 g, 6 mmol) in anhydrous Me_2CO (50 mL) and stirring was continued at ambient temperature for 8 h (TLC indicated complete reaction). The mixture was filtered, the filter cake washed with Me_2CO, and the combined filtrate stirred with anhydrous CaO (1 g) for 90 min. The mixture was filtered, the filter cake washed with Me_2CO, the combined filtrate evaporated, and the residue was recrystallized from $CHCl_3$ to give **3b** (2.12 g, 90%): mp 192–193 °C; UV (MeOH) max 229 nm (ε 9800), 256 nm (ε 17 100); min 221 nm (ε 9100), 235 nm (ε 9200); MS m/z 392.1044 (18, $M^+[C_{18}H_{20}N_2O_6S]$ = 392.1042). Anal. Calcd for $C_{18}H_{20}N_2O_6S$ (392.4): C, 55.09; H, 5.14; N, 7.14; S, 8.17. Found: C, 54.95; H, 5.01; N, 7.01; S, 8.04.

5′-Deoxy-5′-[(4-hydroxyphenyl)sulfinyl]-2′,3′-*O*-isopropylideneuridine (5b). MCPBA (615 mg, 3.03 mmol as 85% reagent) in CH_2Cl_2 (40 mL) was added dropwise to a stirred solution of **3b** (1.17 g, 3 mmol) in CH_2Cl_2/MeOH (100 mL, 9:1) at −40 °C (oxidation complete by TLC within 10 min). The reaction mixture was washed with saturated $NaHCO_3/H_2O$ and the aqueous layer extracted (EtOAc, 5 × 80 mL). The combined organic phase was washed with $NaCl/H_2O$ (20 mL) and H_2O (20 mL), dried (Na_2SO_4), and evaporated to give **5b** (1.08 g, 88%) as a white amorphous glass. A sample of this material was diffusion crystallized[26] (EtOH/EtOAc) to give white needles of **5b** (~1.9:1): mp 227–229 °C; UV max 248 nm (ε 15 800), min 220 nm (ε 5700); MS m/z 393.0757 (2, M − CH_3 = 393.0757), 267.0985 (4, M − HOC_6H_4SO), 112.0260 (100, B + 1). Anal. Calcd for $C_{18}H_{20}N_2O_7S$ (408.4): C, 52.93; H, 4.94; N, 6.86; S, 7.85. Found: C, 52.61; H, 4.81; N, 6.63; S, 7.66.

2′,3′-Di-*O*-acetyl-5′-deoxy-5′-fluoro-5′-[(4-methoxyphenyl)sulfinyl]uridine (8a). MCPBA (75 mg, 0.37 mmol as 85% reagent) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **6a** [180 mg, 0.385 mmol; 5′R/S, ~1:1.3] in CH_2Cl_2 (20 mL) at −30 °C and stirring continued at −20 to −10 °C for 3 h. Additional MCPBA (10 mg, 0.05 mmol) was added to complete the oxidation. After being stirred at −15 °C for 30 min, the solution was poured into $NaHCO_3/H_2O$. The organic layer was washed with $NaHCO_3/H_2O$, $NaCl/H_2O$, and H_2O, dried (Na_2SO_4), and evaporated to give **8a** (182 mg, 99%) as a white foam: ^{19}F NMR δ −188.09 (dd, $^2J_{F\text{-}5'}$ = 46 Hz, $^3J_{F\text{-}4'}$ = 14 Hz, 0.32, 5′F), −195.73 (dd, $^2J_{F\text{-}5'}$ = 46 Hz, $^3J_{F\text{-}4'}$ = 28 Hz, 0.38, 5′F), −198.83 (dd, $^2J_{F\text{-}5'}$ = 47 Hz, $^3J_{F\text{-}4'}$ = 21.5 Hz, 0.17, 5′F), −201.35 (dd, $^2J_{F\text{-}5'}$ = 46.5 Hz, $^3J_{F\text{-}4'}$ = 10 Hz, 0.09, 5′F); MS m/z 329.0787 (27, M − $CH_3OC_6H_4SO$ = 329.0785), 155.0180 (100, $CH_3OC_6H_4SO$); MS CI(NH_3) 485 (72, M + H), 502 (20, M + NH_4). This product contained ~4% (^{19}F NMR) of the **9a** (sulfone) diastereomers.

2′,3′-Di-*O*-acetyl-5′-deoxy-5′(*R*)-fluoro-5′-[(4-methoxyphenyl)sulfonyl]uridine [9a(5′*R*)]. MCPBA (375 mg, 1.85 mmol as 85% reagent) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **6a**(5′R) (347 mg, 0.74 mmol) in CH_2Cl_2 (25 mL) and stirring was continued for 18 h at ambient temperature. The solution was poured into $NaHCO_3/H_2O$ (20 mL) and stirred for 15 min. The layers were separated and the H_2O layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic phase was washed with H_2O (2 × 30 mL) and $NaCl/H_2O$ (30 mL), dried ($MgSO_4$), and evaporated to give a colorless foam (370 mg, 100%) of sufficient purity for deprotection. This material was diffusion crystallized[26] (EtOAc/hexane) to afford **9a**(5′R) (300 mg, 81%) as fine needles: mp 191–193 °C dec; UV (MeOH) max 245 nm (ε 24 500), min 224 nm (ε 6100); ^{19}F NMR δ −188.65 (dd, $^2J_{F\text{-}5'}$ = 45.0 Hz, $^3J_{F\text{-}4'}$ = 14.5 Hz, F5′R); MS m/z 500 (0.5, M^+). 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, 47.95; H, 4.05; N, 5.43; S, 6.67.

5′-Deoxy-5′(*R*)-fluoro-5′-[(4-methoxyphenyl)sulfonyl]uridine [10a(5′*R*)]. Deprotection (NH_3/MeOH) of **9a**(5′R) (325 mg, 0.65 mmol) gave a colorless solid that was crystallized (EtOH/H_2O, 4:1) to give **10a**(5′R) (245 mg, 90%) as needles: mp 235 °C; UV (MeOH) max 246 nm (ε 24 200), min 225 nm (ε 7500); ^{19}F NMR δ −187.11 (dd, $^2J_{F\text{-}5'}$ = 45 Hz, $^3J_{F\text{-}4'}$ = 15 Hz, F5′R); MS m/z 416 (10, M^+). Anal. Calcd for $C_{16}H_{17}FN_2O_8S$ (416.4): C, 46.15; H, 4.12; N, 6.73; S, 7.70. Found: C, 46.12; H, 4.18; N, 6.62; S, 7.90.

2′,3′-Di-*O*-acetyl-5′-deoxy-5′(*S*)-fluoro-5′-[(4-methoxyphenyl)sulfonyl]uridine [9a(5′*S*)]. A stirred solution of **6a** (450 mg, 0.96 mmol; 5′R/S, ~1:5.7) in CH_2Cl_2 (25 mL) was treated with MCPBA (505 mg, 2.5 mmol as 85% reagent) in CH_2Cl_2 (30 mL) [as described above for **6a**(5′R) → **9a**(5′R)] and a colorless foam (480 mg, quant) was diffusion crystallized[26] (EtOAc/hexane) to give **9a**(5′S) (336 mg, 70%) as needles: mp 138 °C; UV (MeOH) max 246 nm (ε 24 900), min 223 nm (ε 7600); ^{19}F NMR δ −193.32 (dd, $^2J_{F\text{-}5'}$ = 45.0 Hz, $^3J_{F\text{-}4'}$ = 25.0 Hz, F5′S); MS m/z 500 (0.4, M^+). 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, 48.31; H, 4.09; N, 5.52; S, 6.56.

5′-Deoxy-5′(*S*)-fluoro-5′-[(4-methoxyphenyl)sulfonyl]uridine [10a(5′*S*)]. Deprotection (NH_3/MeOH) of **9a**(5′S) (200 mg, 0.4 mmol) gave a colorless solid that was crystallized (EtOH/H_2O, 4:1) to give **10a**(5′S) (141 mg, 85%): mp 264–265 °C; UV (MeOH) max 246 nm (ε 24 100), min 222 nm (ε 5400); ^{19}F NMR δ −193.23 (dd, $^2J_{F\text{-}5'}$ = 45.0 Hz, $^3J_{F\text{-}4'}$ = 27 Hz, F5′S); MS m/z 416 (14, M^+). Anal. Calcd for $C_{16}H_{17}FN_2O_8S$ (416.4): C, 46.15; H, 4.12; N, 6.73; S, 7.70. Found: C, 46.06; H, 4.26; N, 6.62; S, 7.92.

X-ray Structure Determination of 2′,3′-Di-*O*-acetyl-5′-(*R*)-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thiouridine [6a(5′*R*)]. A crystal of **6a**(5′R) (from MeOH) was mounted on a Nicolet R3 diffractometer that utilized Mo Kα (λ = 0.71073 Å) radiation. Lattice parameters and the orientation matrix were determined by a least-squares procedure with 25 carefully centered reflections (12.9° < 2θ < 25.7°). Data were collected with a variable scanning rate 2θ–θ collection mode. X-ray methods were used to confirm the absolute configuration by the method of Rogers.[27] Thus, Friedel pairs were measured during data collection and these data were not merged.

Direct methods gave the crystal structure. Positions of all non-hydrogen atoms were located in the resulting E map. The phenyl group was refined as a rigid body and non-hydrogen atoms of the molecule were refined anisotropically. The methyl groups were refined as rigid bodies with tetrahedral angles and C–H bond lengths of 0.96 Å. Positions of other hydrogen atoms were obtained from difference maps. Hydrogens except those bonded to phenyl carbons were allowed to ride on the attached heavy atoms.

(27) Rogers, D. *Acta Crystallogr., Sect. A* **1981**, *37*, 734.

Positions of the phenyl hydrogens were held fixed during refinement. Isotropic thermal parameters for the methyl hydrogens were set at 1.2 times the initial equivalent isotropic thermal parameter of the methyl carbon and were not refined. Remaining hydrogen isotropic thermal parameters were refined. An extinction correction was applied. The absolute configuration was confirmed in the refinement. The value of η was 1.3 (3) with $\eta = +1$ indicating the proper absolute configuration and $\eta = -1$ the wrong choice. Structure solution details are included in the supplementary material. Standard atomic scattering factors were used.[28] Computer programs used are contained in the program package SHELXTL.[29]

(28) *International Tables for X-Ray Crystallography*; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974; Vol. 4, p 99.
(29) Sheldrick, G. M. *SHELXTL. An Integrated System for Solving, Refining, and Displaying Crystal Structures from Diffraction Data*; University of Göttingen: Federal Republic of Germany, 1983; 4th revision.
(30) Sheldrick, G. M. *SHELXTL PLUS*. Siemens Analytical X-ray Instruments, Inc., Madison, WI, 1990.

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Registry No. **1a**, 136721-70-5; **1b**, 136721-71-6; **2a**, 136721-72-7; **2c**, 136721-73-8; **3b**, 136721-74-9; **4a**(5′*R*), 136721-75-0; **4a**(5′*S*), 136721-76-1; **4c**(5′*R*), 136721-77-2; **4c**(5′*S*), 136721-78-3; **5b**(5′*R*), 136721-79-4; **5b**(5′*S*), 136721-80-7; **6a**(5′*R*), 136721-81-8; **6a**(5′*S*), 136721-82-9; **6c**(5′*R*), 136721-83-0; **6c**(5′*S*), 136721-84-1; **7a**(5′*R*), 136721-85-2; **7a**(5′*S*), 136721-86-3; **7b**(5′*R*), 136721-87-4; **7b**(5′*S*), 136721-88-5; (*R*,*R*)-**8a**, 136721-89-6; (*R*,*S*)-**8a**, 136779-77-6; (*S*,*R*)-**8a**, 136779-78-7; (*S*,*S*)-**8a**, 136779-79-8; **9a**(5′*R*), 136721-90-9; **9a**(5′*S*), 136721-91-0; **10a**(5′*R*), 136721-92-1; **10a**(5′*S*), 136721-93-2.

Supplementary Material Available: Tables 1S-5S containing a summary of the crystal data, structure determination details, atom positional and thermal parameters, bond lengths and angles, and important sugar torsion angles of **6a**(5′*R*) (6 pages). Ordering information is given on any current masthead page.

Comparative Structural Studies of [3.1.0]-Fused 2′,3′-Modified β-D-Nucleosides by X-ray Crystallography, NMR Spectroscopy, and Molecular Mechanics Calculations

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A structural study is reported on the [3.1.0]-fused nucleosides 2′,3′-dideoxy-2′,3′-α-methyleneuridine (**1**), 1-(2′,3′-dideoxy-2′,3′-epimino-β-D-ribofuranosyl)uracil (**2**), 1-(2′,3′-dideoxy-2′,3′-epithio-β-D-ribofuranosyl)uracil (**3**), 2′,3′-*O*-anhydroadenosine (**4**), 1-(2′,3′-dideoxy-2′,3′-epithio-β-D-lyxofuranosyl)uracil (**5**), 1-(2′,3′-*O*-anhydro-β-D-lyxofuranosyl)uracil (**6**), 9-(2′,3′-*O*-anhydro-β-D-lyxofuranosyl)adenine (**7**), and 1-(2′,3′-*O*-anhydro-β-D-lyxofuranosyl)thymine (**8**). Note that compounds **1**-**4** have the three-membered fused ring in the exo orientation (α-face) and compounds **5**-**8** have the three-membered fused ring in the endo orientation (β-face). The X-ray crystal structure of compounds **1** and **4** show that both systems have an almost planar furanoid ring. Comparisons are made with the crystal structures of the native nucleosides (i.e., uridine and adenosine, respectively). This shows that the cyclopropane unit in **1** and the epoxide ring in **4** have virtually the same impact on the furanoid conformation, i.e., flattening of the furanoid ring is in both cases accompanied by shortening of the bonds C1′-C2′ and C2′-C3′ by ca. 0.03 Å, and expansion of the bond angles C1′-C2′-C3′ and C2′-C3′-C4′ by 5-6°. Comparison of the crystal structures of [3.1.0]-fused nucleosides **1** and **4** with three [3.3.0]-fused nucleosides from the literature with a flattened sugar ring showed that C2′-C3′ [3.1.0]-fused nucleosides display subtle structural differences, despite the fact that rotation around C2′-C3′ is blocked. Secondly, a ^{1}H NMR conformational study on compounds **1**-**8** is reported. Thirdly, we have investigated whether molecular mechanics calculations (using Allinger's MM2-87 method as provided in the CHEM3D package) can be used to study the conformational properties of systems **1**-**8**. In this respect, the structural data on **1**, **4**, and **8** were used to evaluate the performance of the MM2-87 method. It turns out that the molecular mechanics calculations lead to a fairly accurate picture of the structure of the modified sugar ring, while the calculated values for the torsion angles γ and χ frequently show disparities with respect to the experimental data. It is put forward that this will be partly due to the fact that intermolecular interactions in the crystal (hydrogen bonding and base stacking) have an impact on the molecular conformation; this effect is not mimicked in our calculations.

Introduction

The search for potential agents against the human immunodeficiency virus type I (HIV I) has greatly stimulated studies on structurally modified nucleosides in the last years.[1] Most of this work has been devoted to nucleoside analogues lacking the 3′-hydroxyl group. Several members of this family of compounds have shown antiretroviral

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(1) For an excellent review, see: Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533.

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