

The Stereochemical Outcome of the DAST Fluorination of 4'-Thiopyrimidine Nucleosides with "Up" Hydroxyl Groups is Controlled by the Oxidation State of the Sulfur Atom

Lak S. Jeong and Victor E. Marquez*

Laboratory of Medicinal Chemistry, Developmental Therapeutics Program, Division of Cancer Treatment,
National Cancer Institute, NIH, Bethesda, Maryland 20892, U.S.A.

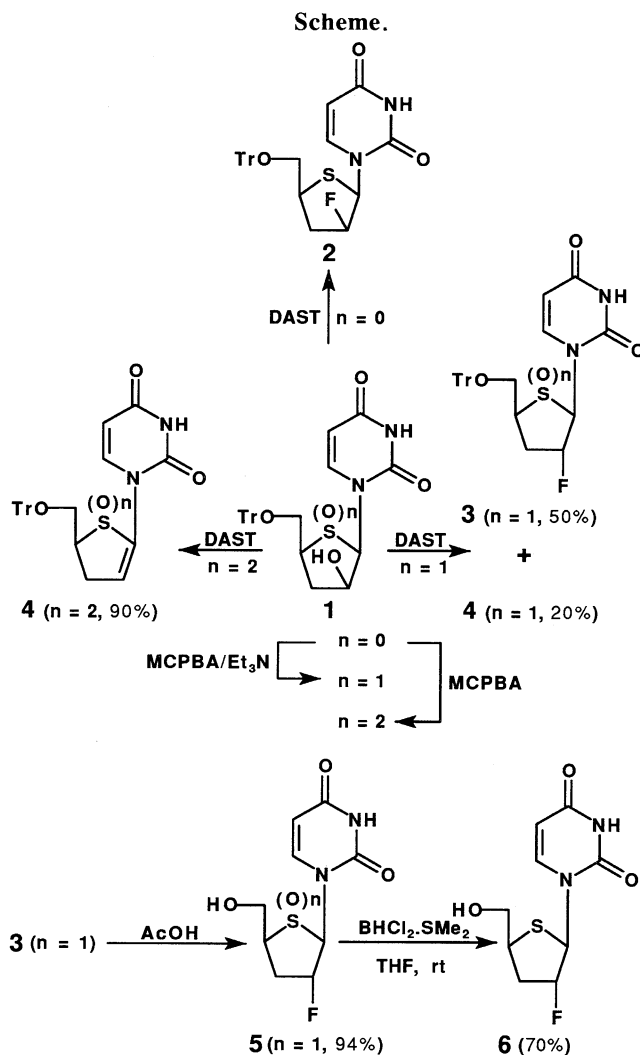
(Received January 9, 1995)

DAST fluorination of 1-(5-*O*-trityl-3-deoxy-4-thio- β -D-*threo*-pentofuranosyl)uracil proceeds with retention of configuration, while the corresponding sulfoxide gives mainly the inverted product. The sulfone proceeds with elimination.

Fluorine substitution of the sugar ring of dideoxynucleosides has been studied extensively for the development of new anti-HIV agents.¹ The presence of fluorine in these molecules generally enhances biological potency and chemical stability relative to the parent, unfluorinated nucleoside.² Since 2',3'-dideoxy-4'-thiocytidine was reported to be a moderately active anti-HIV agent,³ we investigated the effect of sugar fluorine substitution on 4'-thio-2',3'-dideoxypyrimidine nucleosides.^{4,5} During these investigations, we discovered that deoxy-4'-thiopyrimidine nucleosides having a hydroxyl group with an "up" configuration at 2' or 3', gave fluorinated nucleosides with overall retention of configuration [e.g., the conversion of **1** ($n = 0$) to **2**, Scheme] after reaction with diethylaminosulfur trifluoride (DAST).⁴ This result is contrary to what is normally observed with conventional nucleosides where DAST reactions proceed with inversion of configuration.¹ Although our results with the 4'-thiopyrimidine nucleosides were confirmed by X-ray analysis of the final products,⁴ we could only surmise the involvement of sulfur in these reactions via an intermediate episulfonium ion. In this communication, we would like to present chemical evidence in support of sulfur's involvement in these reactions by abrogating this participation via conversion to the corresponding sulfoxide or sulfone. Furthermore, these findings provide for a simple methodology to govern the stereochemical outcome of the reaction according to the oxidation state of the sulfur atom. For example, the reaction proceeds with retention of configuration when $n = 0$, with inversion of configuration when $n = 1$, and with the exclusive formation of elimination products when $n = 2$ (Scheme).

Compound **1** ($n = 0$) was oxidized to the sulfoxide derivative **1** ($n = 1$, single diastereoisomer) after treatment with *m*-chloroperbenzoic acid (MCPBA) in the presence of triethylamine (CH_2Cl_2 , 15 h, 5 °C). Even when this reaction was performed at room temperature for 35 h, further oxidation to the sulfone **1** ($n = 2$) was only 10%. In the absence of triethylamine, however, the sulfone was the sole product. Treatment of **1** ($n = 1$) with DAST/ CH_2Cl_2 (-78 °C to -10 °C) afforded the fluorinated product **3** ($n = 1$) plus the elimination product **4** ($n = 1$) in 50% and 20% yields, respectively. An increase in reaction temperature led to a more rapid reaction and a substantially increased amount of elimination product.

The anomeric proton ($\text{H}-1'$) of **2** appears in the ^1H NMR spectrum as a doublet of doublets ($J_{1',\text{F}} = 19.4$ Hz, and $J_{1',2'} = 4.2$ Hz) which corresponds to an 2'-*endo* conformation. For compound **3** ($n = 1$), however, the same signal appears just as a doublet ($J_{1',\text{F}} = 26.5$ Hz, and $J_{1',2'} \approx 0$ Hz) congruous with the opposite 3'-*endo* conformation. Although these data are consistent with a difference in the stereochemistry for the



fluorine, conclusive proof for the inversion of configuration in the case of sulfoxide **3** ($n = 1$) was obtained after the removal of the trityl group and reduction of the sulfoxide **5** ($n = 1$)⁶ to give compound **6**. The physical and spectral (^1H NMR, ^{13}C NMR and FAB MS) properties of this compound matched those obtained from an authentic sample of **6**, whose structure we had previously solved by X-ray analysis.⁵ Use of DAST with the sulfone gave exclusively the elimination product **4** ($n = 2$). In summary, our finding substantiates the participation of sulfur during the DAST fluorination of 4'-thionucleosides and provides for a simple methodology to control the stereochemistry of the reaction as a function of the oxidation state of the sulfur.

References and Notes

- 1 P. Herdewijn, A. Van Aerschot, and L. Kerremans, *Nucleosides Nucleotides*, **8**, 65 (1989).
- 2 V. E. Marquez, B. B. Lim, J. J. Barchi, Jr., and M. C. Nicklaus in *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K. and Baker, D. C. (Eds.); Plenum Press, New York, **1993**, pp 265-284.
- 3 J. A. Secrist, III, R. M. Riggs, K. N. Tiwari, and J. A. Montgomery, *J. Med. Chem.*, **35**, 533 (1992).
- 4 L. S. Jeong, M. C. Nicklaus, C. George, and V. E. Marquez, *Tetrahedron Lett.*, **35**, 7569 (1994).
- 5 L. S. Jeong, M. C. Nicklaus, C. George, and V. E. Marquez, *Tetrahedron Lett.* **35**, 7573 (1994).
- 6 Compound **5**: white solid; mp 180 °C (dec.); $[\alpha]_{D}^{25} = 8.83^{\circ}$ (c 0.12, MeOH); UV (H₂O) λ_{max} 262.8 nm (ϵ 14,520, pH 7), 261.8 nm (ϵ 15,350, pH 2), 265.8 nm (ϵ 12,640, pH 11); ¹H NMR (CD₃OD) δ 2.52-2.80 (m, 2 H, H-3'), 3.51-3.61 (m, 1 H, H-4'), 3.93-4.05 (m, 2 H, H-5'), 5.25 (dd, $J = 24.1, 3.1$ Hz, 1 H, H-1'), 5.49 (dm, $J = 50.6$ Hz, 1 H, H-2'), 5.76 (d, $J = 8.0$ Hz, 1 H, H-5), 7.75 (d, $J = 8.0$ Hz, 1 H, H-6); ¹³C NMR (CD₃OD) δ 34.1 ($J = 23.5$ Hz, C-3'), 60.5 (C-5'), 70.5 (C-4'), 93.5 ($J = 16.8$ Hz, C-1'), 95.2 ($J = 171.2$ Hz, C-2'), 103.8 (C-5), 146.2 (C-6), 152.6 (C-4), 165.9 (C-2); FAB MS m/z (relative intensity) 263 (MH⁺, 100). *Anal.* Calcd for C₉H₁₁FN₂O₄S: C, 41.22; H, 4.23; N, 10.68. Found: C, 40.93; H, 4.36; N, 10.31.