

Synthesis of Antiviral Nucleosides from Crotonaldehyde. Part 3.1,2 Total Synthesis of Didehydrodideoxythymidine (d4T)

Michael E. Jung* and John M. Gardiner*§

*Department of Chemistry & Biochemistry, University of California Los Angeles,
Los Angeles, California 90024*

Abstract: The total synthesis of the antiviral agent d4T **3** from the epoxyalcohol **2**, itself derived from crotonaldehyde **1**, in 6 steps and 18% overall yield is described.

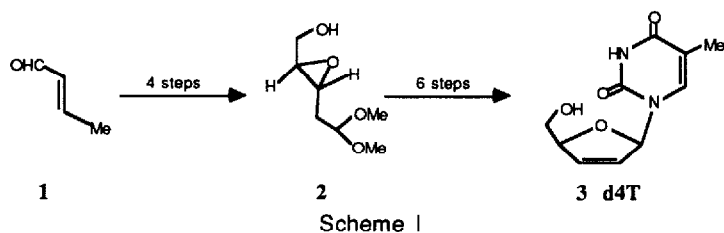
Inhibition of viral reverse transcriptase is currently the most established effective point of intervention for the treatment of retroviral diseases such as AIDS. Modified 2'-deoxynucleosides lacking a 3'-hydroxyl group are often good inhibitors of HIV reverse transcriptase, and thus exhibit anti-HIV activity. These include the currently approved therapies for AIDS or ARC, 3'-azido-3'-deoxythymidine (AZT),³ and dideoxyinosine, ddI^{4,5}, and several other drugs currently in clinical trials as anti-AIDS drugs, including ddC.⁶

The modified nucleoside didehydrodideoxythymidine, d4T, **3**, is also attracting current interest as another potentially clinically useful anti-HIV agent.⁷ AZT insensitive HIV strains do not show cross resistance to d4T,⁸ and d4T readily crosses the blood brain barrier.⁹ Furthermore, its lower toxicity than, and comparable potency to, AZT suggest considerable potential for d4T as an anti-AIDS drug.¹⁰ A number of syntheses from nucleoside starting materials,¹¹ or from carbohydrate derived materials such as ribonolactone,¹² have been reported, but no synthesis to date has commenced from non-chiral pool materials.

As part of our program to develop novel and versatile synthetic routes to modified nucleosides,¹³ we have recently reported the syntheses of the anti-AIDS drug AZT,¹ and of the anti-HIV agent ddC,² each in nine steps from the inexpensive achiral starting material, crotonaldehyde, **1**. Chirality was introduced by a Sharpless-Katsuki asymmetric epoxidation to give the common chiral epoxy alcohol, **2**.

We now report that the epoxy alcohol, **2**, can also be elaborated in six steps to the anti-HIV agent, d4T (**3**), (Scheme I), and also to the 5'-acetyl-3'-thiophenylthymidine, **8a**, and 5'-acetyl-3'-selenophenylthymidine, **8b**, nucleoside analogues in four steps from **2**.

§ Current address: *Department of Pharmaceutical Sciences, Aston University, Birmingham B4 7ET, United Kingdom.*



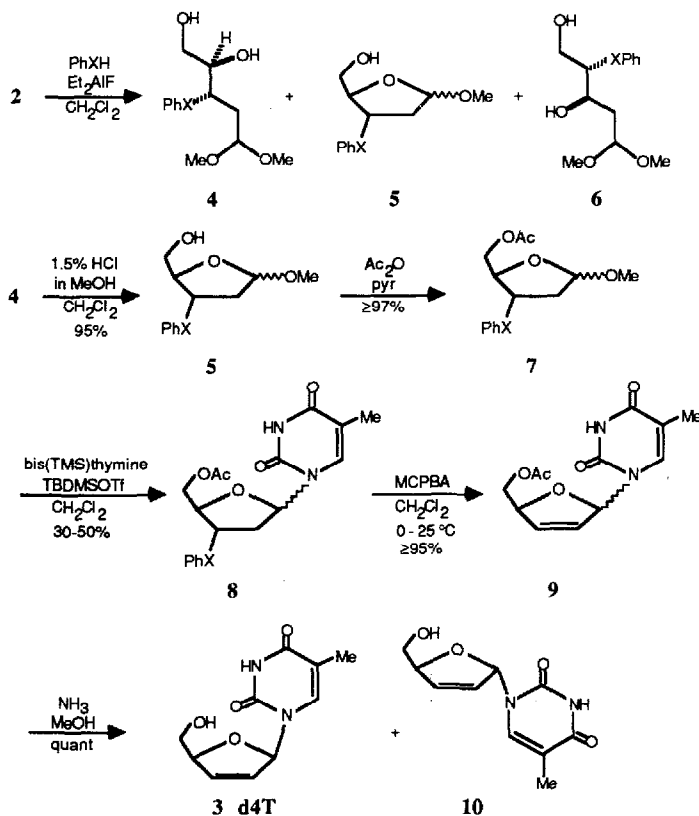
Ring opening of the epoxy alcohol **2** with either thiophenol or selenophenol (1 equiv), was catalysed by diethylaluminum fluoride (other Lewis acids were ineffective), affording mixtures of the anticipated 1,2-diol products, **4**, (major product; 50% X = S; 30% X = Se), together with 8-10% of the undesired 1,3-diols, **6**, and 9-11% of the methyl glycosides, **5**. The minor products were separated from the major diol by either flash chromatography or preparative tlc. Cyclization of the diols **4** to the glycosides **5** proceeded in near quantitative yield, by employment of the conditions utilized previously in our syntheses of AZT¹ and ddC.² Combination of the glycosides (**5**) obtained from this reaction and from concomitant cyclization during the ring opening reaction, therefore affords **5a** and **5b** from epoxyalcohol **2** in overall yields of 48% and 29% respectively.

Acetylation of these alcohols to give the acetates **7** proceeded in $\geq 97\%$ yield, after chromatography. Vorbrüggen coupling¹⁴ of these acetates with 2-3 equivalents of bis(trimethylsilyl)thymine catalysed by 2-3 equivalents of *t*-butyldimethylsilyl triflate (TBDMSOTf) in acetonitrile, yielded the 5'-acetyl-3'-thiophenylthymidine, (**8a**) and 5'-acetyl-3'-selenophenylthymidine, (**8b**), in 30% and 50% yields respectively, as anomeric mixtures.^{12c,d}

Treatment of the seleno compound, **8b**, with 1 equivalent of *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane at -5°C , and warming to room temperature over 2 hours, resulted in elimination of PhSeOH to give 5'-acetyl-d4T (**9**), in $\geq 95\%$ yield.¹⁵ Deacetylation was effected in quantitative yields by treatment with methanolic ammonia to provide d4T, **3**, and the α anomer, **10**, as a 1:1.5 mixture.¹⁶ The ¹H NMR spectra of **9** and **3** matched those reported in the literature.^{11a}

This route thus provides an anomeric mixture of d4T and its α anomer, **10**, in six steps and 18% overall yield from epoxyalcohol **2**, and in 10 steps and 5% overall yield from crotonaldehyde. We are currently attempting to separate the α and β anomers, d4T and **10**, and also the anomeric mixtures of d4T precursors **8** and **9**. The 5'-acetyl-3'-thiophenyl-thymidine (**8a**) and 5'-acetyl-3'-selenophenylthymidine (**8b**), are obtained in overall yields of 16% and 19% respectively from epoxy alcohol **2**.

The completion of this total synthesis, together with those of AZT¹ and ddC,² clearly establishes this methodology as a general and versatile strategy towards the efficient synthesis of a range of important antiviral modified nucleosides from cheap achiral starting materials. Further work on the extension of this methodology to other important types of modified nucleosides is underway.¹⁷



Scheme II. (a) X = S; (b) X = Se

Acknowledgment. We thank the National Institutes of Health (AI26692 and GM47228) and Burroughs-Wellcome for generous financial assistance, and the Royal Society (UK), Wellcome Trust, and SERC (UK) for travel grant assistance (to JMG).

References and Notes

- (1) Part 1. Jung, M. E.; Gardiner, J. M. *J. Org. Chem.* **1991**, *56*, 2614.
- (2) Part 2. Jung, M. E.; Castro, C.; Gardiner, J. M. *Tetrahedron Lett.* **1991**, *32*, 5717.
- (3) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 7096.
- (4) Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Broder, S. *Science* **1989**, *245*, 412.
- (5) For recent reviews on the use of dideoxynucleosides for treatment of AIDS see: (a) Norbeck, D. W. *Ann. Rep. Med. Chem.* **1990**, *25*, 149; (b) Yarchoan, R.; Mitsuya, H.; Broder, S. *Ann. Rep. Med. Chem.* **1988**, *23*, 253; (c) Mansuri, M. M.; Martin, J. C. *Ann. Rep. Med. Chem.* **1988**, *23*, 161.
- (6) (a) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1911; (b) Broder, S. *Am. J. Med.* **1990**, *88* (5B), 2S-7S; (c) Jeffries, D. J. *J. Antimicrob. Chemother.* **1989**, *23* (Suppl. A), 29.

- (7) (a) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533; (b) Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. *Antimicrob. Agents Chemother.* **1987**, *31*, 907; (c) Ho, H. T.; Hitchcock, M. J. M. *ibid.* **1989**, *33*, 844.
- (8) (a) Larder, B. A.; Chesebro, D.; Richman, D. D. *Antimicrob. Agents Chemother.* **1990**, *34*, 436; (b) Richman, D. D.; Grimes, J. M.; Lagakos, S. W. *J. Acquired Immune Defic. Synd.* **1990**, *3*, 743.
- (9) Russell, J. W.; Whiterock, V. J.; Marrero, D.; Klunk, L. J. *Nucleosides & Nucleotides* **1989**, *8*, 845.
- (10) Mansuri, M. M.; Hitchcock, M. J. M.; Buroker, R. A.; Bregman, C. L.; Ghazzouli, I.; Desiderio, J. V.; Starrett, J. E.; Sterzycki, R. Z.; Martin, J. C. *Antimicrob. Agents Chemother.* **1990**, *34*, 637.
- (11) (a) Mansuri, M. M.; Starrett, J. E.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780; (b) Martin, J. C.; Mansuri, M. M.; Starrett, J. E.; Ghazzouli, I.; Ho, H. T.; Hitchcock, M. J. M. *Nucleosides & Nucleotides* **1989**, *8*, 841.
- (12) (a) Chu, C. K.; Babu, J. R.; Beach, J. W.; Ahn, S. K.; Huang, H.; Jeong, L. S.; Lee, S. J. *J. Org. Chem.* **1990**, *55*, 1418; (b) Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T. *J. Org. Chem.* **1991**, *56*, 5402; (c) Wilson, L. J.; Liotta, D. *Tet. Lett.* **1990**, *31*, 1815; (d) Chu, C. K.; Raghavachari, R.; Beach, J. W.; Kosugi, Y.; Ullas, G. V. *Nucleosides & Nucleotides* **1989**, *8*, 903. Chu et al have reported similarly that 3-phenylselenenyl-2,3-deoxyribose shows no selectivity on Vorbruggen coupling, while the 2 α -phenylselenenyl analogue shows high β -selectivity on Vorbruggen coupling due to neighbouring group assistance from interaction of the selenium with the oxonium intermediate^{12a}. (The analogous 2 α -phenylsulfenyl ribosides similarly show good β -stereoselectivity on Vorbruggen coupling, for which sulfur neighbouring group participation (via an episulfonium intermediate) can be invoked^{12c}.)
- (13) For other strategies towards both C- and N-modified nucleosides from D-glucosamine, see: (a) Jung, M. E.; Trifunovich, I. D.; Gardiner, J. M.; Clevenger, G. L. *J. Chem. Soc. Chem. Commun.* **1990**, 84; (b) Jung, M. E.; Trifunovich, I. D. *Tetrahedron Lett.* **1992**, *33*, in press.
- (14) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654ff; Vorbrüggen, H.; Krollkiewicz, K.; Benna, B. *Chem. Ber.* **1981**, *114*, 1234ff and references therein.
- (15) The appearance of the intermediate selenoxide while the reaction was cold, and its disappearance as elimination proceeded on warming, could be followed easily by tlc. A similar elimination on the 5'-TBDMS analogue of **8b** has recently been reported: see ref 12b.
- (16) The anomers were not distinguishable by tlc.
- (17) The diethyl analogue of our epoxy alcohol intermediate **4** has recently been shown by other workers to be a convenient intermediate towards the rapid synthesis of 4'-thio nucleosides: Uenishi, J.; Motoyama, M.; Nishiyama, Y.; Wakabayashi, S. *J. Chem. Soc. Chem. Commun.* **1991**, 1421.