Pergamon

Tetrahedron Letters 39 (1998) 729–732

TETRAHEDRON LETTERS

A New Thymine Free Synthesis of the Anti-AIDS Drug d4T via Regio/stereo Controlled β-Elimination of Bromoacetates

Bang-Chi Chen,*† Sandra L. Quinlan, J. Gregory Reid and Richard H. Spector

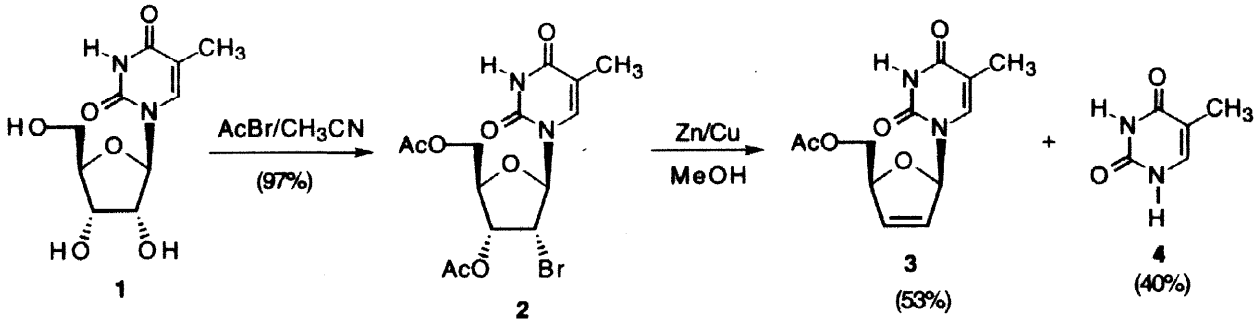
Process Exploration Labs I, Technical Operations
Bristol-Myers Squibb Company, Syracuse, NY 13221

Received 14 April 1997; revised 12 May 1997; accepted 14 May 1997

Summary: *The anti-AIDS drug d4T was prepared without contamination of the nucleoside bond cleaved by-product thymine from the readily available ribonucleoside 5-methyluridine (**1**). This was accomplished by using a new strategy which involved a regio/stereo controlled β-elimination of trans-bromoacetates **6**.*

2',3'-Didehydro-3'-deoxythymidine (d4T) is an important new antiviral agent for the treatment of AIDS.[1,2] Many methods have been developed for its preparation,[3-6] including the approach from 5-methyluridine (**1**) via bromoacetate **2** (Scheme 1).[7] This synthesis was attractive due to its simplicity as well as the ready availability of the starting material.[7,8] A major limitation for its use on large scale, however, was the formation of large amounts of thymine by-product during the reductive elimination of bromoacetate **2**, which was difficult to remove without chromatographic separation.[7]

Scheme 1:

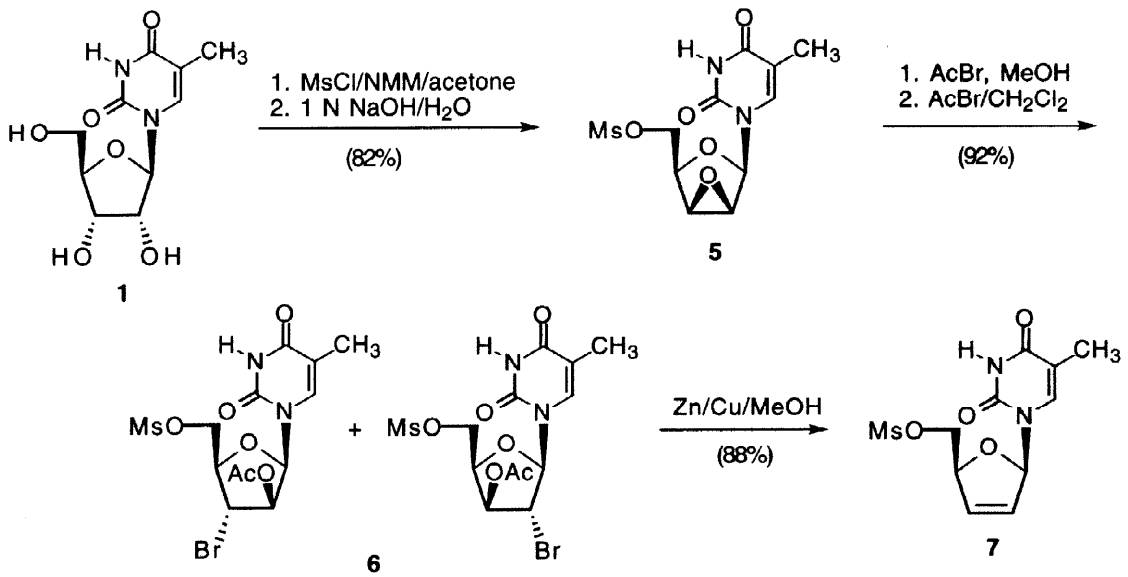


Competitive nucleoside bond cleavage is a common drawback in the zinc mediated reductive elimination of cis-2'α-bromo-3'α-acyloxynucleosides such as compound **2**.[3,7] Similar results were also obtained in the uridine system.[7] While nucleoside bond cleavage could be a consequence of the instability of the nucleoside bond towards the reaction conditions, we envisioned that the formation of the thymine by-product in the zinc reduction of **2** was the result of the trans-β-elimination of the nucleoside base being competitive with the desired cis-β-elimination of the bromoacetate. This

0040-4039/98/$19.00 © 1998 Bristol-Myers Squibb Company. Published by Elsevier Science Ltd.
PII: S0040-4039(97)01084-8

problem was expected to be minimized by either inverting the stereochemistry of the acetoxy group at the 3'-position so that it would be trans to the 2'-bromo substituent, or by changing the positions of the 2'-bromo and 3'-acetoxy groups so that the bromo substituent would no longer be vicinal to the thymine base. Herein, we describe the preparation of such compounds **6** and their zinc reductive eliminations to 5'-mesyl-d4T **7** (Scheme 2). Subsequent transformation of **7** to the anti-AIDS drug d4T will also be disclosed (Scheme 3).

Scheme 2:



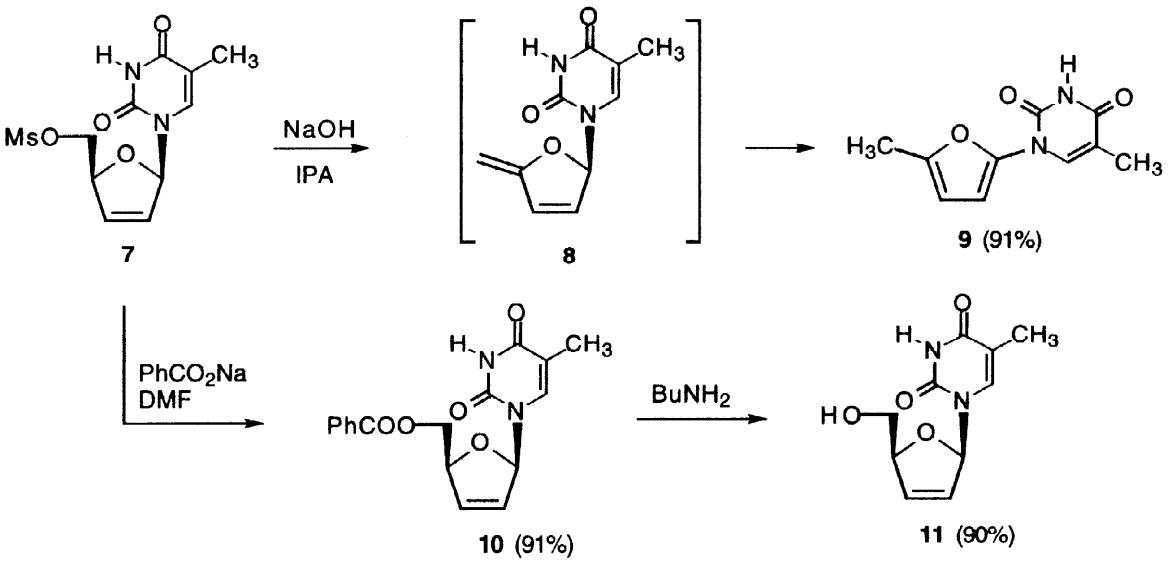
Reaction of 5-methyluridine (**1**) with mesyl chloride and N-methylmorpholine in acetone afforded 2',3',5'-trismesyl-5-methyluridine[5b] which upon treatment with 1N sodium hydroxide resulted in the formation of 5'-mesyl-2',3'-anhydro-5-methyluridine (**5**) in 82% isolated yield.[9,10] The epoxide **5** was then opened with hydrogen bromide (generated in situ from acetyl bromide and methanol) to afford a mixture of bromo alcohols which, without isolation, was treated with acetyl bromide to give a 92% yield of trans-bromoacetates **6** as a mixture of regioisomers.[11] Subsequent zinc reduction afforded 5'-mesyl-d4T **7** in 88% isolated yield.[12] In sharp contrast to the previous reduction with cis-bromoacetate **2** where about 40% thymine was formed,[7] the zinc reduction of the trans-bromoacetates **6** afforded 5'-mesyl-d4T **7** without significant nucleoside bond cleavage as detected by HPLC and NMR analyses of the reaction mixture.

The hydrolysis of 5'-mesyl-d4T **7** was initially attempted using sodium hydroxide (Scheme 3). Interestingly, the desired d4T product was not observed, instead, furan **9** was obtained in 91% yield.[12] This product presumably resulted from the attack of the hydroxide anion at the C-5' hydrogen of **7**, giving rise to the β-elimination product **8**. Aromatization of **8** yielded 2-methyl-5-thyminylfuran (**9**).

Subsequently, the less basic sodium benzoate was used. Reaction of **8** with 1.2 equivalent of sodium benzoate in DMF at 100°C for 6 hours afforded 5'-benzoyl-d4T **10** in 91% isolated yield.

Aminolysis of **10** with butylamine followed by crystallization from isopropanol gave d4T product in 90% yield.[5b]

Scheme 3:



In summary, a synthesis of the anti-AIDS drug d4T not complicated by competitive thymine formation has been developed which involves zinc reductive elimination of a mixture of trans-bromoacetates **6**. This new strategy successfully stops the extensive nucleoside bond cleavage encountered previously[7] and is expected to work in other related nucleoside systems such as uridine. In addition, the newly prepared highly functionalized nucleosides **6** are potentially useful intermediates for the preparation of other modified nucleosides in the quest for more effective antiviral and anti-AIDS drugs.

References and Notes

† Current address: Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, Princeton, NJ 08543-4000.

1. Lin, T.-S.; Schinazi, R. F.; Prusoff, W. H. *Biochem. Pharmacol.* **1987**, *36*, 2713; Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162; Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. *Antimicrob. Agents Chemother.* **1987**, *31*, 907; and references cited therein.
2. Compared to AZT, d4T displayed reduced toxicity toward bone marrow, see: Mansuri, M. M.; Starrett, J. E., Jr.; Ghazzouli, I.; Hitchcock, M. J. M.; Sterzycki, R. Z.; Brankovan, V.; Lin, T.-S.; August, E. M.; Prusoff, W. H.; Sommadossi, J.-P.; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 461.
3. For reviews see (a) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745; Dueholm, K. L.; Pedersen, E. B. *Synthesis*, **1992**, 1; (b) Herdewijin, P.; Balzarini, J.; De Clercq, E., in *Advances in Antiviral Drug Design, Vol. 1*, De Clercq, E., Ed., JAI Press Inc., Middlesex, England, **1993**, p233;

4. For leading reference on the preparation of d4T from thymidine see: Joshi, B. V.; Rao, T.; Sudhakar, R.; Reese, C. B. *J. Chem. Soc. Perkin Trans. I*, **1992**, 2537.
5. For leading references on the preparation of d4T from 5-mu see: (a) Luzzio, F. A.; Menes, M. E. *J. Org. Chem.* **1994**, *59*, 7267; (b) Chen, B.-C.; Quinlan, S. L.; Stark, D. R.; Reid, J. G.; Audia, V. H.; George, J. G.; Eisenreich, E.; Brundidge, S. P.; Racha, S.; Spector, R. H. *Tetrahedron Lett.* **1995**, *36*, 7957 and references cited therein.
6. For leading references on the preparation of d4T from non-nucleoside starting materials see: Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampall, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887; Kim, C. U.; Misco, P. F. *Tetrahedron Lett.* **1992**, *33*, 5733.
7. Mansuri, M. M.; Starrett, J. E. Jr.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780.
8. 5-Methyluridine (**1**) can be prepared efficiently by an enzymatic ribosyl transfer reaction see: Hori, N.; Uehara, K.; Mikami, Y. *Biosci., Biotechnol., Biochem.*, **1992**, *56*, 580; Hennen, W. J.; Wong, C.-H. *J. Org. Chem.* **1989**, *54*, 4692.
9. A similar procedure has been previously reported for the preparation of 5'-mesyl-2',3'-anhydrouridine, see: Codington, J. F.; Fecher, R.; Fox, J. J. *J. Org. Chem.* **1962**, *27*, 163.
10. ^{1}H NMR data for compound **5**: (DMSO-d_6) δ 1.79 (s, 3H), 3.22 (s, 3H), 4.10 (m, 2H), 4.38 (m, 2H), 4.55 (m, 1H), 6.15 (s, 1H), 7.49 (s, 1H), 11.48 (s, 1H).
11. Ratio of the diastereomers **6** was 2.6:1. ^{1}H NMR data for the major isomer (DMSO-d_6) δ 1.79 (s, 3H), 1.94 (s, 3H), 3.25 (s, 3H), 4.40-4.70 (m, 4H), 5.62 (t, J=6.8 Hz, 1H), 6.35 (d, J=6.7 Hz, 1H), 7.40 (s, 1H), 11.42 (s, 1H); ^{1}H NMR data for the minor isomer (DMSO-d_6) δ 1.79 (s, 3H), 1.96 (s, 3H), 3.24 (s, 3H), 4.40-4.70 (m, 4H), 5.57 (t, J=3.7 Hz, 1H), 6.35 (d, J=3.8 Hz, 1H), 7.49 (s, 1H), 11.48 (s, 1H).
12. Compounds **7** and **9** showed spectroscopic data identical to those reported in the literature, see: Joshi, B. V.; Reese, C. B. *J. Chem. Soc. Perkin Trans. I*, **1992**, 441.