Concerted Conjugate Addition of Nucleophiles to Alkenoates. 2. Synthesis of 2′,3′-Dideoxy-2′-*β*-fluoro-3′-(*N*-hydroxy-*N*-methylamino)-D-arabinofuranosyl Nucleosides

Shifeng Pan, Jianwu Wang, and Kang Zhao*

29 Washington Place, Department of Chemistry, New York University, New York 10003

Received August 5, 1998

Structurally modified nucleosides have proven to be a valuable source of antiviral agents (Figure 1).[1] Structure **1** represents an example of such agents that display high antiviral activity. This class of 2′,3′-dideoxynucleosides is made by the replacement of the 2′,3′-hydroxyl groups on the ribose ring with hydrogen or/and fluorine atoms. The substitution of a fluorine atom at the 2′-position has resulted in several classes of compounds with effective antiviral activity.[2] Analysis of structure−activity relationships shows that many active 2′-fluorinated nucleosides (including F-ddA **1b**; B = adenine) adopt a 2′-*β*-configuration while the corresponding 2′-α-isomers tend to be inactive.[3] Compounds **2**−**4** feature several of the other related biologically active dideoxynucleosides that possess a variety of 2′,3′-substituents. It appears that the increase of the 3′-substituent size does not always diminish the antiviral activity of nucleoside analogues. The 3′-substituents of biologically active compounds include a hydroxymethyl group (such as **2**)[4] or nitrogen-containing moieties (**3** and **4**).[5,6] Compounds **3a**, which contain nucleophilic nitrogen substituents (R = H, or alkyl) at the 3′-position, have been shown to possess anti-HIV activity.[5] The synthesis of the corresponding fluoride derivatives **3b** has not been reported, probably due to the difficulty in preparing *trans*-2-fluoroethylamine-type structures. We now report a procedure that allows introduction of a 3′-hydroxylamine group into nucleoside structure **4b**, which contains a 2′-*β*-fluorine atom. The trans relationship

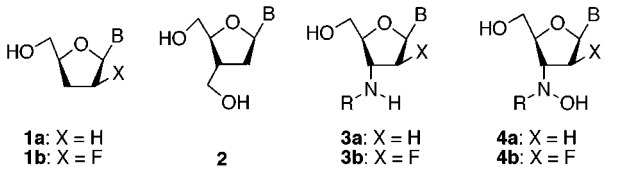
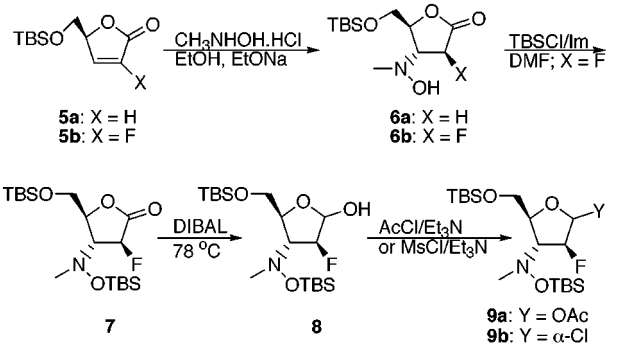


Figure 1.

Scheme 1



of the fluoride and amine moieties can be effectively controlled by the conjugate addition of *N*-alkylhydroxylamine to a 2-fluorolactone.[7]

Our synthetic route involves a key conjugate addition of *N*-methylhydroxylamine to butenolides **5** (Scheme 1), which can be prepared in high yield from D-glyceraldehyde.[8] It has been reported that nucleophiles generally attack butenolide **5a** (X = H) from the less hindered α-face due to the bulky O-protected hydroxymethyl group.[9,10] We have also carried out the reaction of butenolide **5a** with *N*-methylhydroxylamine hydrochloride, after neutralization in situ by triethylamine in THF. The corresponding adduct **6a** was exclusively formed in high yield.[10a] Unfortunately, the use of the 2-fluoro material **5b** failed to give the desired product **6b** under this triethylamine-neutralization condition. Alternatively, sodium ethoxide was used to generate a free *N*-methylhydroxylamine nucleophile, and *N*-methylhydroxylamine was added to the trisubstituted butenolide **5b** in refluxing ethanol to furnish compound **6b** as a single isomer. The ^{1}H NMR spectrum of compound **6b** showed a doublet of doublets at 5.5 ppm, which was assigned to H-2. The trans relationship of the two protons at the 2,3-positions was assigned on

(1) For selected recent reviews, see: (a) De Clercq, E. *Ann. New York Acad. Sci.* **1994**, 438. (b) Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother*. **1995**, *39*, 1017. (c) Wilson, L. J.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis* **1995**, 1465. (d) Pan, S.; Amankulor, N. M.; Zhao, K. *Tetrahedron* **1998**, *54*, 6587. (e) Chu, C. K. *Nucleic Acids Symp. Ser.* **1996**, *35*, 1. (f) Mitsuya, H. *Anti-HIV Nucleosides: Past, Present and Future*; Texas: Landes, 1997.

(2) For selected reviews and recent examples of fluorinated nucleosides, see: (a) Herdewijn, P.; Aerschot, A. V.; Kerremans, L. *Nucleosides Nucleotides* **1989**, *8*, 65. (b) Bergstrom, D. E.; Swartling, D. J. *Fluorine Substituted Analogs of Nucleic Acid Components*. In *Fluorine-Containing Molecules: Structure, Reactivity, Synthesis and Applications*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH: New York, 1988; pp 259−308. (c) Ford, H., Jr.; Siddiqui, M. A.; Driscoll, J. S.; Marquez, V. E.; Kelley, J. A.; Mitsuya, H.; Shirasaka, T. *J. Med. Chem*. **1995**, *38*, 1189. (d) Krawczyk, S. H.; Nassiri, M. R.; Kucera, L. S.; Kern, E. R.; Ptak, R. G.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem*. **1995**, *38*, 4106. (e) Ma, T.; Lin, J.-S.; Newton, M. G.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem*. **1997**, *40*, 2750. (f) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. *J. Org. Chem*. **1998**, *63*, 2161.

(3) Marquez, V. E.; Lim. B. B.; Barchi, J. J., Jr.; Nicklaus, M. C. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum: New York, 1993; pp 265−284 and references therein.

(4) For selected recent examples, see: (a) Lin, T.-S.; Zhu, J.-L.; Dutschman, G. E.; Cheng, Y.-C.; Prusoff, W. H. *J. Med. Chem*. **1993**, *36*, 353. (b) Faul, M. M.; Huff, B. E.; Dunlap, S. E.; Frank, S. A.; Fritz, J. E.; Kaldor, S. W.; Le Tourneau, M. E.; Staszak, M. A.; Ward, J. A.; Werner, J. A.; Winneroski, L. L. *Tetrahedron* **1997**, *53*, 8085. (c) Lee-Ruff, E.; Ostrowski, M.; Ladha, A.; Stynes, D. V.; Vernik, I.; Jiang, J.-L.; Wan, W.-Q.; Ding, S.-F.; Joshi, S. *J. Med. Chem*. **1996**, *39*, 5276. (d) Gould, J. H. M.; Mann, J. *J. Chem. Soc., Chem. Commun*. **1997**, 243. (e) Tseng, C. K−H.; Marquez, V. E.; Milne, G. W. A.; Wysocki, Jr., R. J.; Mitsuya, H.; Shirasaki, T.; Driscoll, J. S. *J. Med. Chem*. **1991**, *34*, 343. (f) Boettiger, D.; Johansson, N.-G.; Samuelsson, B.; Zhang, H.; Putkonen, P.; Vrang, L.; Oeberg, B. *AIDS* **1997**, *11*, 157.

(5) For selected examples of 3′-nitrogen-containing substituents, see: (a) Lin, T. S.; Fisher, P. H.; Prusoff, W. H. *Biochem. Pharmacol*. **1982**, *31*, 125. (b) Motawia, M. S.; Wengel, J.; Abdel-Megid, A. E.-S.; Pedersen, E. B. *Synthesis* **1989**, 384. (c) Kocács, T.; Párkányi, L.; Pelczer, I.; Cervantes-Lee, F.; Pannell, K. H.; Torrence, P. F. *J. Med. Chem*. **1991**, *34*, 2595. (d) Hossain, N.; Papchikhin, A.; Garg, N.; Fedorov, I.; Chattopadhyaya, J. *Nucleosides Nucleotides* **1993**, *12*, 499. (e) Huang, J. J.; Ragouzeos, A.; Rideout, J. L. *J. Heterocycl. Chem*. **1995**, *32*, 691. (f) García-Alles, L. F.; Magdalena, J.; Gotor, V. *J. Org. Chem*. **1996**, *61*, 6980. (g) Fedorov, I. I.; Kazmina, E. M.; Gurskaya, G. V.; Jasko, M. V.; Zavodnic, V. E.; Balzarini, J.; De Clercq, E.; Faraj, A.; Sommadossi, J.-P.; Imbach, J.-L.; Gosselin, G. *J. Med. Chem*. **1997**, *40*, 486.

(6) (a) Tronchet, J. M. J.; Criton, M.; Zsely, M.; Besomi, P.; Barbalat-Rey, F. *Carbohydr. Lett*. **1996**, *2*, 205. (b) Gi, H.-J. Dissertation, New York Universtiy, 1998.

(7) Niu, D.; Zhao, K. *J. Am. Chem. Soc*., submitted.

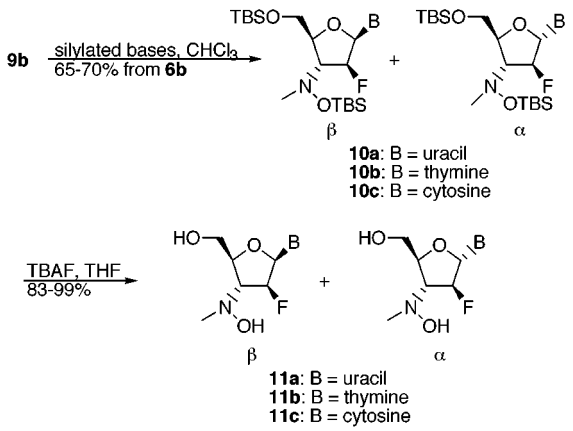
(8) (a) Patrick, T. B.; Lanahan, M. V.; Yang, C.; Walker, J. K.; Hutchinson, C. L.; Neal, B. E. *J. Org. Chem*. **1994**, *59*, 1210. (b) Häfele, B.; Jäger, V. *Liebigs Ann. Chem*. **1987**, 85.

(9) For the related examples, see: (a) Chu, C. K.; Beach, J. W.; Ullas, G. V.; Kosugi, Y. *Tetrahedron Lett*. **1988**, *29*, 5349. (b) Caine, D.; Venkataramu, S. D.; Kois, A. *J. Org. Chem*. **1992**, *57*, 2960. (c) Collis, M. P.; Hockless, D. C. R.; Perlmutter, P. *Tetrahedron Lett*. **1995**, *36*, 7133.

(10) (a) Xiang, Y.; Gong, Y.; Zhao, K. *Tetrahedron Lett*. **1996**, *37*, 4877. (b) Xiang, Y.; Gi, H.-J.; Niu, D.; Schinazi, R. F.; Zhao, K. *J. Org. Chem*. **1997**, *62*, 7430.

10.1021/jo9815507 CCC: $18.00
Published on Web 12/10/1998

Scheme 2



the basis of their coupling constant (7.7 Hz), which is consistent with the literature data of a related system.[11] The ^{1}H NMR spectroscopic data of **6b** were compared with that of the well-studied compound **6a**, and the expected 2,3,4-trans,trans configuration of **6b** was determined.[7,10] It can be assumed that both electronic and steric effects control the resulting trans,trans stereochemistry.

Protection of the hydroxyl group of **6b** with TBSCl in dry DMF gave compound **7** (93% yield), which was converted to the corresponding lactol **8** by DIBAL reduction in CH_2Cl_2. Glycosyl acetate and glycosyl chloride are two intermediates that are often used for coupling with nucleoside bases. Hence, acetate **9a** was prepared by acetylation of **8**; chloride **9b**[12] was prepared by employing mesyl chloride in the presence of triethylamine and a catalytic amount of tributylamine.[13]

Initially, the glycosylation of acetate **9a** with TMS-protected heterocyclic base in the presence of trimethylsilyl triflate was attempted, but the desired coupling product was not isolated due to the silyl transformation reaction between the silylated nucleoside bases and **9a**. Similar observations have been reported in the literature.[11] Glycoside chloride **9b** was reacted with silylated heterocyclic bases, including uracil, thymine, and cytosine. Glycosylation reactions proceeded smoothly to afford the TBS-protected nucleosides **10**, and overall yields for three steps from the corresponding lactone **6b** were in the range of 65−70% (Scheme 2). Protected nucleosides **10** were generally obtained as an anomeric mixture (α and *β*) in a ratio of about 1:1. No attempt was made to improve the ratio of α/*β* anomers since the final nucleoside analogues of both isomers were needed for biological evaluations. Deprotection of the TBS groups was easily achieved by treatment of TBAF in dry THF, resulting in 83−99% yields. Finally, uridine **11a** and cytidine **11c** were separated by silica gel column chromatography. The initial antiviral studies of cytidine **11c** displayed very encouraging anti-HIV-1 results.[14] The anomeric configuration of nucleoside analogues **11** can be determined by a well-established rule;[15] the shielding/deshielding effects of nucleoside bases make the chemical shift of H-4′ appear at a lower field for α-isomers than for that of the corresponding *β*-isomers.

This synthesis offers an efficient method for preparation of 2′,3′-dideoxy-2′-fluoro-3′-(*N*-hydroxyl-*N*-methylamino)-D-arabinofuranosyl nucleosides **11** via the conjugate addition of *N*-methylhydroxylamine to a lactone. *N*-Methylhydroxylamine proved to be an excellent nucleophile toward sp^2 centers in that it added to 2-fluorobutenolide **5b** in a regio- and diastereoselective fashion to afford compound **6b** with the desired *β*-configuration of the 2-fluorine atom. Additional advantages for using conjugate addition reactions exist, namely: (a) the difficult step of fluorination in the presence of *N*-alkoxyamine moieties is avoided and (b) the synthesis of the key intermediates **9** can be achieved in four high-yield steps from the readily available starting material **5b**. The title compounds **11**, which contain 2′-*N*-alkyl-*N*-hydroxylamine groups, are useful for investigating the electronic and steric properties of a *N*-hydroxylamine structure in terms of replacing the 2′-hydroxymethyl group of nucleoside analogues **2**.

Acknowledgment. We acknowledge Drs. Neville Kallenbach and Gregory Linn for their suggestions in the preparation of this manuscript. Also, we are grateful to the NSF Faculty Early Career Development Program, the New York University Technology Transfer Fund, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their financial support. S.P. acknowledges the New York University MacCracken Fellowship.

Supporting Information Available: Experimental details and copies of ^{1}H and ^{13}C NMR spectra for compounds **6b** and **11a**−**c** (26 pages).

JO9815507

(11) Araki, K.; Yun, W. Q.; O′Toole, J.; Toscano, P. J.; Welch, J. T. *Carbohydr. Res.* **1993**, *249*, 139.

(12) Glycoside chloride **9b** was too unstable to be purified by silica gel chromatography, and thus, it was directly used in the next step without purification.

(13) Okabe, M.; Sun, R.-C.; Zenchoff, G. B. *J. Org. Chem*. **1991**, *56*, 4392.

(14) Preliminary results indicated that both the α- and *β*-isomers of cytidine analogues **11c** exhibit excellent anti-HIV-1 activity in vitro. The toxicity of the *β*-isomer is high against CEM cell lines while α-isomer is not toxic. The confirmed biological results will be published shortly.

(15) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem*. **1988**, *53*, 4780.