New Approach to the Synthesis of β-2'-Deoxyribonucleosides: Intramolecular Vorbrüggen Coupling[1]

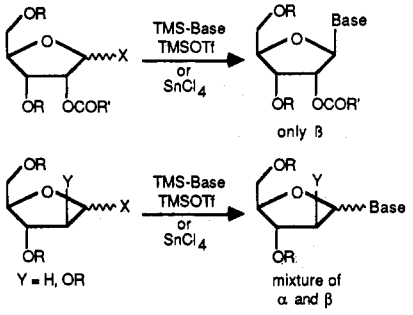
Michael E. Jung*,[2] and Claire Castro[3]

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

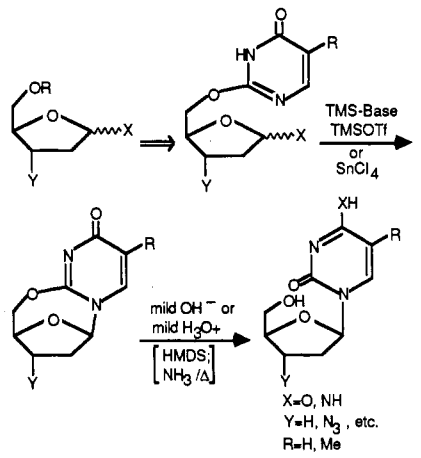
Received November 12, 1992

Summary: Silylation of the O^2,5'-linked nucleoside **7** followed by treatment with trimethylsilyl triflate affords the O^2,5'-anhydro nucleoside **9** and its hydrolysis product the β-anomer of the 2'-deoxyuridine **10** in good yield in the first example of an oxygen-bridged intramolecular Vorbrüggen coupling.

Modified nucleosides are used ever increasingly as therapeutic agents, especially as antiviral agents (e.g., AZT, ddI, ddC) and antitumor agents (ara-C). The Vorbrüggen modification[4] of the Hilbert–Johnson[5] reaction has been used to prepare many modified nucleosides by reaction of silylated bases with sugar derivatives having leaving groups at the anomeric center. It works well (giving almost exclusively the desired β-anomers) only when there is an α-acyloxy group at C2 of the sugar derivative (because of stabilization of the anomeric cation on the α-face by the acyloxy group). This synthesis process is much less useful for preparing modified nucleosides, e.g., 2'-deoxy, 2',3'-dideoxy, or aranucleosides, since approximately 1:1 mixtures of α and β anomers are usually formed with substrates lacking a 2α-acyloxy group.[6] We report here a method for potentially overcoming this anomeric mixture in pyrimidine nucleosides by the use of an intramolecular Vorbrüggen reaction.



We reasoned that if one attached the pyrimidine base at its 2-position to the 5-hydroxyl of a 2-deoxyribose derivative, addition to the anomeric center could occur only from the β-face. Final mild hydrolysis of the O^2,5'-anhydro nucleoside is known and gives only the desired β-anomer in good yield.[7] Thus, by a relatively simple process one could convert a 2-deoxyribose derivative into solely the desired β-nucleoside.



Although the synthesis of some carbon-bridged cyclonucleosides has been reported by Ueda and his group,[8] the closest analogy to our proposed chemistry is that of Mizuno's group[9] which involves cyclization of a 5'-sulfur-linked purine–sugar hybrid under strongly acidic conditions. A five-step sequence was required to convert the thio-anhydro nucleoside into the desired β-nucleoside.[9b] Very recently, Abushanab et al.[10] published the synthesis of 2,2',5'-trideoxynucleosides by the use of a 5'-sulfur-linked pyrimidine–sugar hybrid, although they were unable to prepare simple 2'-deoxynucleosides by this route. Our successful approach begins with the 3-*O*-methylribal **2** prepared in six steps from D-ribose (**1**) by an application of known chemistry.[11] Formation of 2-methylthiouracil[12] from 2-thiouracil (**3**) proceeded in good yield and

(1) Presented at the CATG Meeting, NIH/NIAID, Washington, DC, April 1991 and at the 33rd GECO Conference, Corsica, France, Sept 1992.

(2) UCLA McCoy Award recipient, 1992–92; UCLA Hanson–Dow Teaching Award recipient, 1992.

(3) BASF Graduate Fellow, UCLA, 1989–90; UCLA Mentorship Awardee, 1990–91; University of California Office of the President Dissertation Year Fellow, 1992–3.

(4) Vorbrüggen, H. et al. *Chem. Ber.* **1981**, *114*, 1234, 1256, 1279 among others.

(5) For review, see: Pliml, J.; Prystas, M. *Adv. Heterocycl. Chem.* **1967**, *8*, 115.

(6) There are some examples where specific substrates give higher than usual proportions of the desired β-anomers. Also if the α-anomer of the chlorosugar can be selectively prepared (for selective preparation via crystallization of the bis-toluoyl 2-deoxyribosyl chloride, see: Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777), then a simple S_N2 displacement using the anion of a purine nucleoside gives cleanly the desired β-anomer (see: Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379). However, this procedure is unfortunately not general for all 2-deoxy-3-substituted and 2,3-dideoxy sugars. For a good discussion of this area, see: Hubbard, A. J.; Jones, A. S.; Walker, R. T. *Nucleic Acids Res.* **1984**, *12*, 6827.

(7) (a) For a good review of cyclonucleosides, see: Ueda, T. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, 1988; p 49. (b) For example, 2',3'-isopropylidene-2,5'-anhydrouridine gives uridine on treatment with 25% acetic acid or 0.3 *N* NaOH at 25 °C for 4 h. Also reaction with methanolic ammonia gives the corresponding 2',3'-isopropylideneisocytidine. Brown D. M.; Todd, A. R.; Varadarajan, S. *J. Chem. Soc.* **1957**, 868. (c) Minamoto, K.; Azuma, K.; Fujiwara, N.; Eguchi, S. *J. Org. Chem.* **1989**, *54*, 4543. (d) Schram, K. H.; Ratcliff, S.; Neenan, J. *J. Label. Compd. Radiopharm.* **1981**, *19*, 399.

(8) (a) Yoshimura, Y.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1989**, *37*, 660; **1988**, *36*, 162; *Nucleosides Nucleotides* **1988**, *7*, 409. (b) For a conceptually similar approach to restricted pyrimidine nucleosides, see: Hsu, L.-Y.; Wise, D. S.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1992**, *57*, 3354.

(9) (a) Mizuno, Y.; Kaneko, C.; Oikawa, Y.; Ikeda, T.; Itoh, T. *J. Am. Chem. Soc.* **1972**, *94*, 4737. (b) Mizuno, Y.; Kaneko, C.; Oikawa, Y. *J. Org. Chem.* **1974**, *39*, 1440.

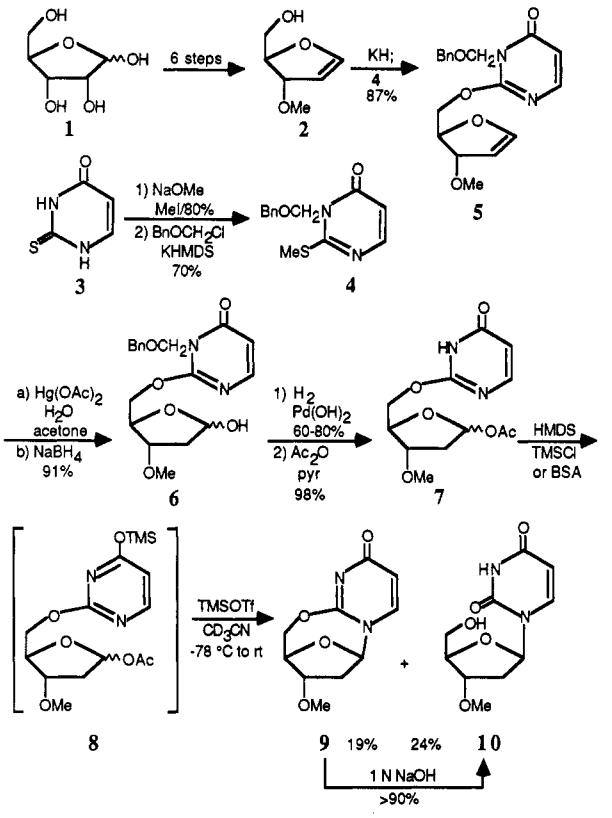
(10) El Subbagh, H. I.; Ping, L.-J.; Abushanab, E. *Nucleosides Nucleotides* **1992**, *11*, 603.

(11) Cheng, J. C.-Y.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778.

(12) Mizutani, M.; Sanemitsu, Y. *J. Org. Chem.* **1985**, *50*, 764.

0022-3263/93/1958-0807$04.00/0

selective protection of the nitrogen with (benzyloxy)methyl chloride afforded the desired 2-(methylthio)-3-(benzyloxymethyl)pyrimidinone (**4**). Reaction of the potassium



salt of **2** and **4** gave the O^2,5′-nucleoside hybrid **5** in 87% yield. Hydration of the alkene was accomplished by oxymercuration–reduction to give **6** as a 1:1 mixture of anomers (by ^{1}H NMR integration) in excellent yield. Hydrogenolytic removal of the benzyloxymethyl protecting group followed by acetylation furnished the desired substrate to test our method, namely acetate **7**, in good overall yield. Silylation of the base with hexamethyldisilazane/trimethylsilyl chloride or bis(trimethylsilyl)acetamide gave the (silyloxy)pyrimidine **8** which was not isolated (its formation was shown by ^{1}H NMR) but immediately subjected to treatment with trimethylsilyl triflate to produce a mixture of two products, the desired O^2,5′-anhydro nucleoside **9** and the hydrolysis product 2′-deoxy-3′-*O*-methyluridine **10** in yields of 19% and 24%, respectively. The anhydro nucleoside **9** was hydrolyzed under conditions similar to those used for analogous compounds in the literature[7] to give the β-anomer of the uridine derivative **10** in nearly quantitative yield. Thus, the overall yield of the desired β-anomer **10** from the intramolecular Vorbrüggen reaction is 43%. The structure of **9** was determined by comparison to an authentic sample prepared from the known[13] **10** by tosylation and treatment with DBU.[14] There was none of the corresponding α-anomer of **10** produced in this process.[15] This is the first example of an oxygen-bridged nucleoside–sugar hybrid undergoing an intramolecular coupling. The major byproduct in this reaction is the hydrolyzed sugar derivative and uracil, implying that the carbon–oxygen bond of the amidino ether is probably labile under the reaction conditions.

In summary, we have carried out the final intramolecular Vorbrüggen coupling of an oxygen-bridged nucleoside to produce after hydrolysis only the desired β-anomer of a 2′-deoxyuridine derivative.[16] We are currently working on optimizing the yield of this process and looking at other attachments of the base, e.g., at the 3-position of a xylo derivative to produce the O^2,3′-anhydro nucleosides which are known to be easily transformed into 3′-deoxy 3′-substituted nucleoside derivatives on treatment with strong nucleophiles.

Acknowledgment. We thank the National Institutes of Health (AI-26692 and GM-47228) for generous financial support.

Supplementary Material Available: Experimental procedures and characterization data (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Holy, A.; Votruba, I. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1646.

(14) Watanabe, K. A.; Reichman, U.; Chu, K. C.; Fox, J. J. In *Nucleic Acid Chemistry*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1978; p 273.

(15) A mixture of the α- and β-anomers of **10** was produced by a standard intermolecular Vorbrüggen reaction of bis(trimethylsilyl)uracil with α,β-methyl 2-deoxy-3-*O*-methyl-5-*O*-(*tert*-butyldimethylsilyl)ribosides followed by deprotection of the silyl ether.

(16) A conceptually similar process (intramolecular coupling at the anomeric center) has been used for the stereocontrolled synthesis of disaccharides. Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087.