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Spirocyclic Restriction of Nucleosides. Synthesis of the First Exemplary *syn*-1-Oxaspiro[4.4]nonanyl Member

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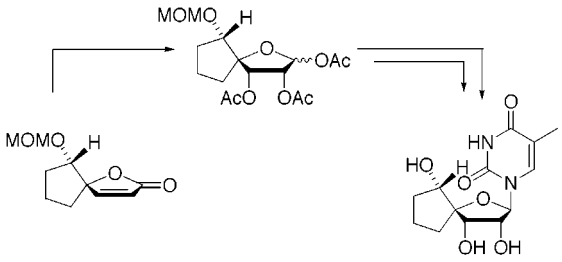
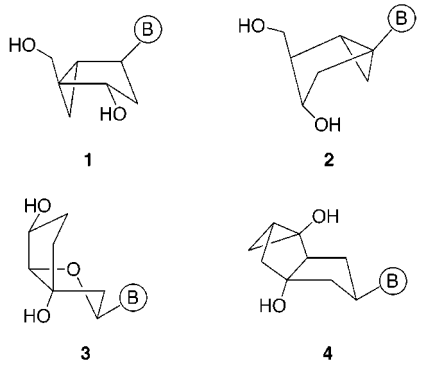
ABSTRACT



The potential benefits associated with the spirocyclic restriction of nucleosides are summarized. Following exploration of a π-allylpalladium route to 5′-α- or syn-dideoxy examples, we evaluated MOM protection of the 5′-hydroxyl as being suited to the synthesis of the first member of this new class of nucleoside mimic.

Structurally modified nucleosides continue to attract synthetic and biological interest because select members are amenable to treating diseases where the normal and diseased states differ with regard to the enzymes involved in the processing of nucleic acids. This is particularly true for viral diseases. Seemingly, the relevant enzymes possess strict conformational requirements, with binding to the nucleoside analogue occurring only when the furanose ring adopts a well-defined conformation.[1] In recent years, increasing attention has been focused on structural modifications that feature restrictions in conformational flexibility in order to better attain optimal puckering.[2] These include, but are not restricted to, the bicyclo[3.1.0]hexane-derived carbocyclic pseudosugars **1** and **2** devised by the Altmann[3] and Marquez groups[4] and Leumann's bi- and tricyclodeoxynucleosides **3** and **4**.[5] A subset of related molecules that have not been accorded prior attention involves those nucleoside mimics such as **5**−**8** that are



spiroannulated at C4′. The following are some of the advantages offered by this structural class: (a) the glycosyl torsion angle about the C4′−C5′ bond is fixed such that this key functional group is now specifically oriented anti (*a*

(1) (a) Prota, A.; Vogt, J.; Pilger, B.; Perozzo, R.; Wurth, C.; Marquez, V. E.; Russ, P.; Schulz, G. E.; Folkers, G.; Scapozza, L. *Biochemistry* **2000**, *39*, 9597. (b) Jacobson, K. A.; Ji, X.; Li, A.; Melman, N.; Siddiqui, M. A.; Shin, K. J.; Marquez, V. E.; Ravi, R. G. *J. Med. Chem.* **2000**, *43*, 2196. (c) Nandanan, E.; Jang, S.-Y.; Moro, S.; Kim, H. O.; Siddiqui, M. A.; Russ, P.; Marquez, V. E.; Busson, R.; Herdewijn, P.; Harden, T. K.; Boyer, J. L.; Jacobson, K. A. *J. Med. Chem.* **2000**, *43*, 829. (d) Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Hernandez, S.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H., Jr. *Helv. Chim. Acta* **1999**, *82*, 2119. (e) Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Shin, K. J.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H., Jr. *Nucleosides Nucleotides* **1999**, *18*, 521.

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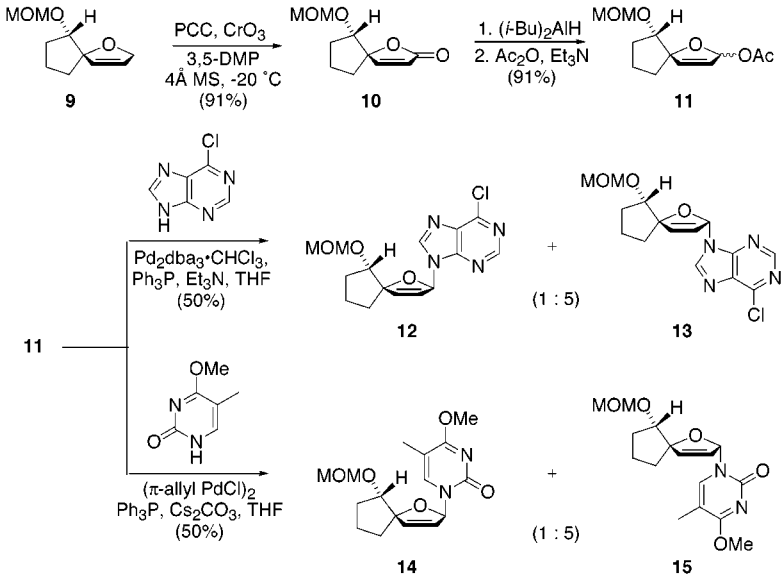
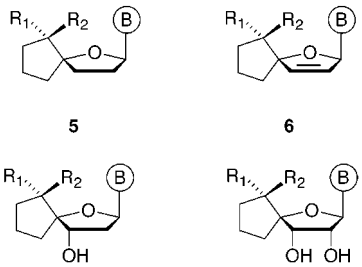
Scheme 1



series) or syn (*b* series) to the furanose oxygen, (b) no nonbonded steric superimposition is expected from occupation by the tetramethylene bridge of the void space below C4′ as gauged by extensive crystallographic data recorded for DNA and RNA fragments,[6] and (c) the possibility of free radical-induced degradation by hydrogen atom abstraction at C4′ is now precluded by the substitution pattern.[7]



a, R_1 = H, R_2 = OH; **b**, R_1 = OH, R_2 = H

In addition to these positive features, the spirocyclic array in **5b**−**8b** strives to project the hydroxyl substituent on the cyclopentane ring pseudoequatorially, thereby attaining the highly desirable *ap* torsion angle.[8] For **7b**, very good overlay of the furanose sector upon that of natural thymidine is also seen.[9]

The present synthetic effort started with the conveniently accessible dihydrofuran **9**.[10,11] To bring about the allylic oxidation of **9** to lactone **10** in a reasonably efficient manner, we developed conditions involving the combined action of pyridinium chlorochromate (5 equiv), chromium trioxide (5 equiv), and 3,5-dimethylpyrazole (10 equiv). Following reduction of **10** to the lactol and O-acetylation, we were prompted to examine first the stereoselectivity of the regiocontrolled introduction of bases at C1′. The stereodispositon of the acetate functionality in **11** could not be ascertained spectroscopically. However, if hydride delivery to **10** had occurred predominantly from the face distal to the MOM group, then conversion to a π-allylpalladium species and subsequent coupling to a heterocycle should be met with overall retention.[12] In the present instance, reaction of **11** with 6-chloropurine in the presence of Pd_2dba_3·$CHCl_3$, triphenylphosphine, and triethylamine effected smooth conversion to a 1:5 mixture of **12** and **13** (Scheme 1).

(2) Reviews: (a) Meldgaard, M.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3539. (b) Herdewijn, P. *Liebigs Ann.* **1996**, 1337.

(3) (a) Altmann, K.-*H*.; Imwinkelreid, R.; Kesselring, R.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 7625. (b) Altmann, K.-H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331.

(4) (a) Moon, H. R.; Ford, H., Jr.; Marquez, V. E. *Org. Lett.* **2000**, *2*, 3793. (b) Shin, K. J.; Moon, H. R.; George, C.; Marquez, V. E. *J. Org. Chem.* **2000**, *65*, 2172. (c) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 2780 and relevant references therein.

(5) (a) Keller, B. M.; Leumann, C. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2278. (b) Egger, A.; Leumann, C. J. *Synlett* **1999**, 913. (c) Meier, R.; Grüschow, S.; Leumann, C. J. *Helv. Chim. Acta* **1999**, *82*, 1813. (d) Steffens, R.; Leumann, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3249. (e) Steffens, R.; Leumann, C. J. *Helv. Chim. Acta* **1997**, *80*, 2426. (f) Steffens, R.; Leumann, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 11548. (g) Bolli, M.; Trafelet, H. U.; Leumann, C. J. *Nucleic Acids Res.* **1996**, *24*, 4660. (h) Tarköy, M.; Bolli, M.; Leumann, C. J. *Helv. Chim. Acta* **1994**, *77*, 716. (i) Tarköy, M.; Bolli, M.; Schweizer, B.; Leumann, C. J. *Helv. Chim. Acta* **1993**, *76*, 481.

(6) For examples of C4′ α′-homologated nucleosides, see: (a) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 746. (b) Crich, D.; Hao, X. *J. Org. Chem.* **1998**, *63*, 3796. (c) Crich, D.; Yao, Q. *Tetrahedron* **1998**, *54*, 305. (d) Hess, M. T.; Schwitter, U.; Petretta, M.; Giese, B.; Naegeli, H. *Biochemistry* **1997**, *36*, 2332. (e) Marx, A.; MacWilliams, M. P.; Bickle, T. A.; Schwitter, U.; Giese, B. *J. Am. Chem. Soc.* **1997**, *119*, 1131. (f) Hrebabecky, H.; Holy, A. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1128. (g) Marx, A.; Erdmann, P.; Senn, M.; Körner, S.; Jungo, T.; Petretta, M.; Imwinkelreid, P.; Dussy, A.; Kulicke, K. J.; Macko, L.; Zehnder, M.; Giese, B. *Helv. Chim. Acta* **1996**, *79*, 1980. (h) Giese, B.; Erdmann, P.; Giraud, L.; Gobel, T.; Petretta, M.; Schafer, T.; von Raumer, M. *Tetrahedron Lett.* **1994**, *35*, 2683. (i) Thrane, H.; Fensholdt, J.; Regner, M.; Wengel, J. *Tetrahedron* **1995**, *51*, 10389 and more recent work by the Wengel group.

(7) (a) Pratviel, G.; Bernadou, J.; Meunier, B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 746. (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (c) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. (d) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191.

The predominance of **13** was not unequivocally established but arrived at by comparison with the behavior of *O*-methylthymine under closely comparable reaction conditions with π-allylpalladium chloride as a promoter. In this example, a 5:1 mixture of spironucleotides was again produced, and the major anomer was confirmed to be **15** by X-ray crystallographic analysis (Figure 1). The implications here

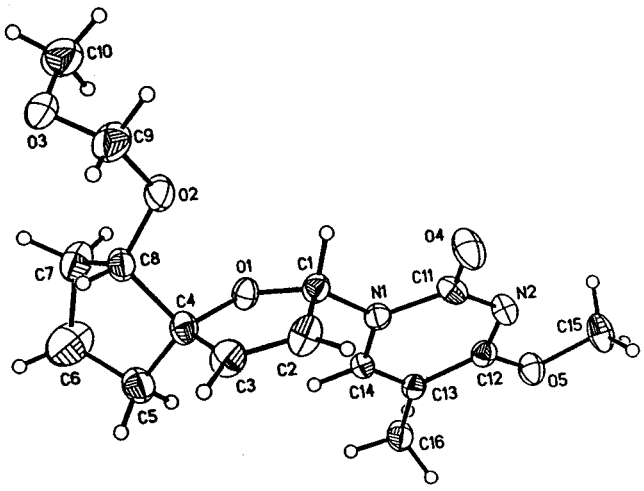
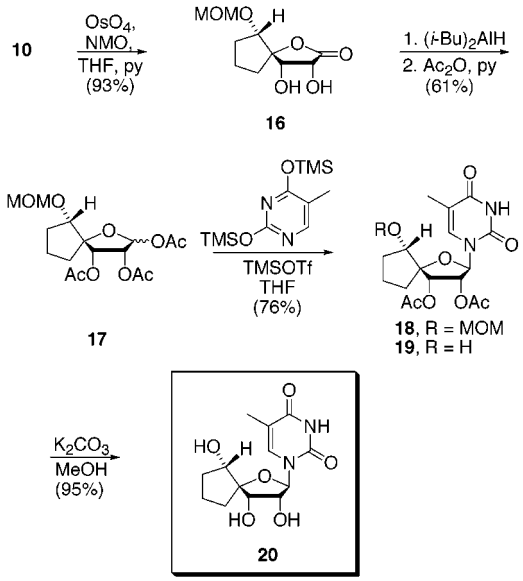


Figure 1. Computer-generated perspective drawing of **15** as determined by X-ray crystallography.

are that the spirocyclic systems undergo these Pd-catalyzed reactions productively and that the Dibal-H reduction followed by O-acetylation delivers predominantly the α-acetate.

In a different, more rewarding thrust, the unsaturated lactone **10** was dihydroxylated with osmium tetroxide under catalytic conditions in the presence of NMO to furnish only **16** (93%, Scheme 2). Evidently, the MOM substituent sterically and perhaps electronically impacts this process to render it highly diastereoselective. In a subsequent one-pot reaction, **16** was reduced with Dibal-H and directly acetylated to generate triacetate **17** as a diastereomeric mixture. Since the Vorbrüggen process[13] takes advantage of participation

Scheme 2



by the neighboring acetate group residing at C2′, the loss of stereochemical integrity at this point is only transitory. Indeed, treatment of **17** with bis-O-silylated thymine in the presence of trimethylsilyl triflate gave predominantly diacetate **18** or its deprotected alcohol congener **19** depending on the relative amount of promoter added. Saponification with potassium carbonate in methanol removed the remaining acetate units and afforded **20**.[14,15]

With arrival at **20**, the door has been opened for continuing experimental exploration of spirocyclic nucleosides having syn-hydroxyl orientation at C5′. These new mimics will hopefully hold interest as useful medicinal agents in their own right and impart interesting and valuable therapeutic properties when incorporated into nucleotide strands.

Acknowledgment. We thank Prof. Robin Rogers (University of Alabama) for the X-ray crystallography on compound **15**.

Supporting Information Available: Representative experimental procedures and ^{1}H and ^{13}C NMR data in addition to tables giving the crystal data and structure refinement information, bond lengths and angles, atomic and hydrogen coordinates, and isotropic and anisoptropic displacement coordinates for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Whereas **9** is available in racemic and enantiopure forms, the racemic modification was utilized in the pilot experiments defined herein.

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(13) Vorbrüggen, H.; Ruh-Pohlenz, C. *Org. React*. **2000**, *55*, 1.

(14) The authors thank D. R. Owen for conducting this experiment.

(15) All new compounds were of ≥95% purity as determined by ^{1}H and ^{13}C NMR as well as TLC analysis.