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Spirocyclic Restriction of Nucleosides. An Analysis of Protecting Group Feasibility while Accessing Prototype *anti*-1-Oxaspiro[4.4]nonanyl Mimics

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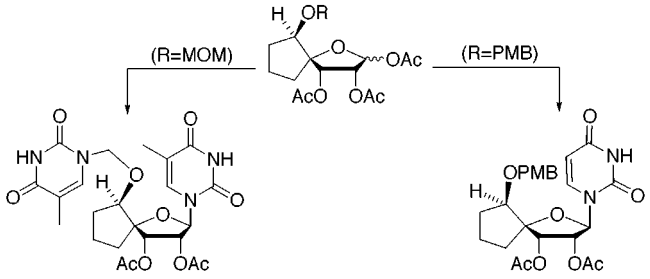
ABSTRACT



The first spirocyclic nucleoside featuring a β-hydroxyl (anti) at C5′ has yielded to synthesis. While the OMOM functionality proved to be sensitive to the conditions necessary to incorporate heterocyclic bases, PMB protection of the carbinol was readily accommodated. The remarkably similar minimum-energy conformations of the title compounds relative to natural thymidine as deduced by Amber calculations in the gas phase are noted.

The torsion angles around the bond of the sugar−phosphate DNA backbone are of decisive importance for the secondary structure of DNA as well as for base recognition.[1] Effective inhibitors of protein expression in vivo have also to resist the action of DNA-degrading enzymes and bind to their target *m*RNA sequences with high affinity and in a sequence-specific manner.[2] Since three sequential enzymatic steps are required to convert the nucleoside to its 5′-triphosphate, the complexity of the anabolic process is also an issue. Optimally, identification of the conformational preferences exhibited by the nucleoside at each step is warranted. Although idealized conformations have been identified,[3] the inherent flexibility of the furanose ring, which normally equilibrates rapidly in solution between two extreme forms of ring pucker,[4] often constitutes a major obstacle to identification of the idealized conformation for a particular interaction.

In the preceding paper,[5] we introduced the concept of spirocyclic restriction. For the 1-oxaspiro[4.4]nonane series represented by **B** and **C**, fully minimized Amber calculations in the gas phase have revealed a striking similarity to the low-energy conformation adopted by natural thymidine (**A**, Figure 1). The overlay of **B** on **A** is notably remarkable (RMS = 0.007). For **C**, the departure from direct superimposition is greater (RMS = 0.058) but still very acceptable. In both spirocyclic analogues, the hydroxyl substituent on the cyclopentane ring is expectedly disposed pseudoequatorially. Consequently, the structural change evidenced in proceeding from **B** ($\gamma = +sc$) to **C** ($\gamma = ap$) holds

(1) Eschenmoser, A.; Dobler, M. *Helv. Chim. Acta* **1992**, *75*, 218.
(2) (a) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543. (b) Milligan, J. F.; Matteucci, M. D.; Martin, J. C. *J. Med. Chem.* **1993**, *36*, 1923.
(3) Van Roey, P.; Taylor, E. W.; Chu, C. K.; Schinazi, R. F. *Ann. N. Y. Acad. Sci.* **1990**, *616*, 29.
(4) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205.

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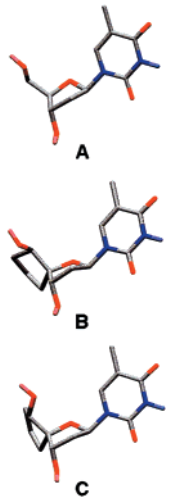


Figure 1. The minimum-energy conformations of thymidine (**A**), **B**, and **C**.

considerable interest. The torsion angles for the homo dimers of **A**−**C** are compiled in Table 1. Herein, we report the first

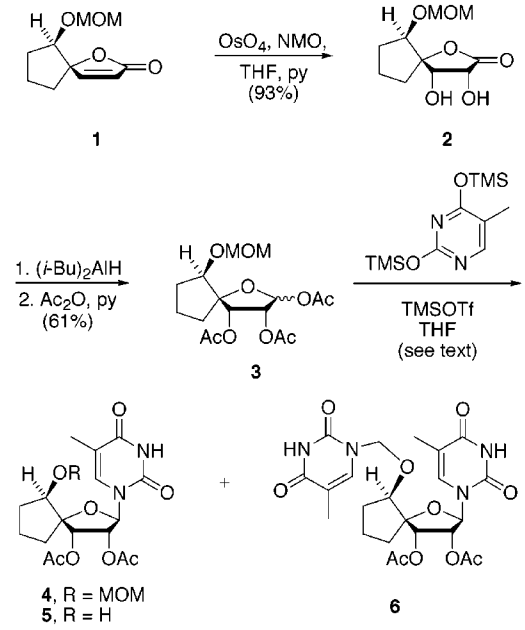
Table 1. Relevant Torsional Angles for [Thymidine]$_2$, **B**^{2}, and **C**^{2} (Values in Degrees)

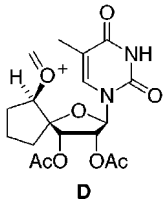
angle	**A**^{2}	**B**^{2}	**C**^{2}
α	−63.1	−57.4	124.7
β	178.4	116.6	−89.7
γ	58.2	45.6	152.7
δ	126.2	144.4	76.3
ϵ	175.3	−171.3	−97.0
ζ	−85.9	−37.4	−88.0

successful access to nucleosides of type **B** and thereby extend the range of candidates amenable to further scrutiny. Unlike the syn series where the MOM protecting group was well tolerated,[5] this substituent proved to be more problematic when dealing with the somewhat more elevated steric congestion resident in the anti diastereomers.

Our primary interest was the possible inhibitory steric effect induced by the protected 5′-hydroxyl on proper formation of the nucleosidic bond. Initially, attention was paid to **1**, a spirobutenolide building block available in racemic and enantiopure forms.[6] Although the efficiency of the dihydroxylation of **1** proved to be somewhat variable, this transformation provided a reliable means for establishing the C2′−C3′ configurational pattern defined in **2** (Scheme 1). The success of the ensuing reductive acetylation with generation of **3** rests significantly on a direct quench of the reaction of the Dibal-H reaction mixture with acetic anhydride and pyridine. Failure to execute this protocol leads instead to tight complexation of the aluminum ion to the triad of hydroxyl groups. For formation of the spirocyclic nucleoside analogues, we chose to involve the Lewis acid-induced coupling of **3** to persilylated thymine[7] as in the syn series.[5] The three chromatographically separated products generated in this reaction were produced in relative yields that varied widely as a function of the quality of the trimethylsilyl triflate. The greater the level of adventitious triflic acid that develops upon prolonged storage of this reagent (through hydrolysis and degradation), the more elevated are the proportions of **5** and especially **6**. The finding that the structurally unusual **6** could be made predominant provided support for the conclusion that oxonium ion **D** can indeed be generated transitorily. Irreversible capture of the activated nucleoside base subsequently materializes.

Scheme 1

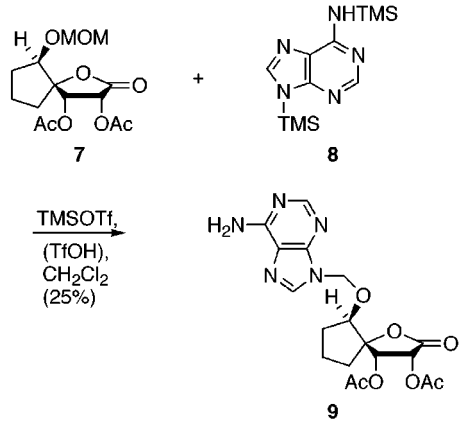




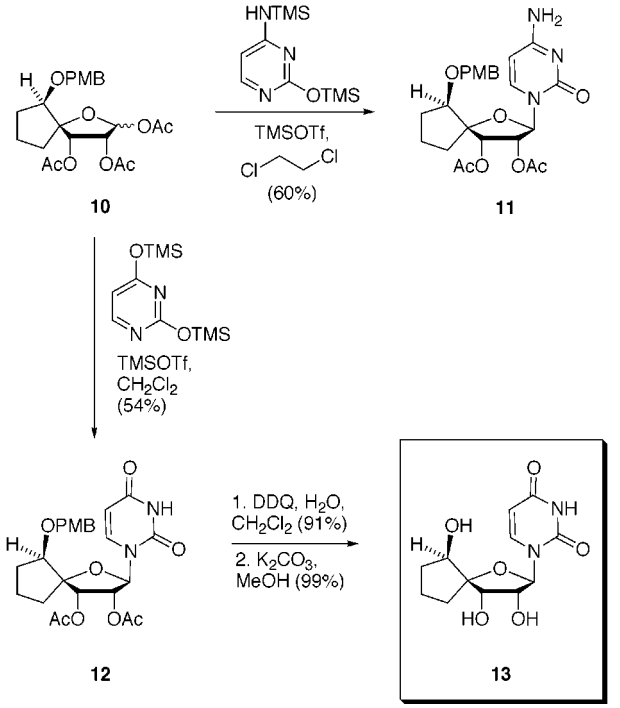
The mode of reaction observed for **3** is not limited to this specific spirocyclic pseudosugar but appears to be general for the β-oriented MOM series. Another representative example, displayed in Scheme 2, consists of the reaction of lactone **7** with bis(trimethylsilyl)adenine (**8**)[8] in the presence of trimethylsilyl triflate under otherwise comparable conditions. In this manner, ready access was gained to **9**. To our

(5) Paquette, L. A.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L. *Org. Lett.* **2001**, *3*, 4039.
(6) Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.* **2001**, *66*, 2828.
(7) Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279.
(8) Nishimura, T.; Iwai, I. *Chem. Pharm. Bull.* **1964**, *12*, 352.

Scheme 2



Scheme 3



knowledge, **6** and **9** represent prototypes of a unique series of nucleoside mimics that have not been accorded prior attention.[9]

To skirt this particular reactivity profile, the replacement of OMOM by an OPMB group was probed. Triacetate **10** was prepared in the predescribed manner from the levorotatory (>99% enantiomeric excess) butenolide[6] (Scheme 3). The first nucleosidation to be examined involved excess bis-(trimethylsilyl)cytosine[8] in the presence of 1 equiv of trimethylsilyl triflate in CH_2Cl_2 as the solvent. The formation of **11** appeared to fail until recourse was made instead to use 1,2-dichloroethane as the reaction medium, in line with the recommendation of others.[10] Under these circumstances, **11** could be readily isolated in an unoptimized 60% yield. No such solvent sensitivity was noted with persilylated uracil, which gave **12** as the sole nucleosidic product in 54% yield. In neither reaction was evidence obtained regarding possible complications arising from the presence of the OPMB substituent. While the removal of this protecting group by oxidation with ceric ammonium nitrate failed, excellent selectivity was realized through the use of DDQ. After mild saponification, the fully deprotected triol **13**, mp 209 °C, became available as the first example of a 5′β spirocyclic nucleoside.

(9) For a related observation involving an acyclic methylene acetal, consult: Chamberlain, S. D.; Biron, K. K.; Dornsife, R. E.; Averett, D. R.; Beauchamp, L.; Koszalka, G. W. *J. Med. Chem.* **1994**, *37*, 1371.

(10) For example: Steffens, R.; Leumann, C. *Helv. Chim. Acta* **1997**, *80*, 2426.

In summary, we have defined and prepared representatives of a new type of conformationally restricted nucleoside. Since DNA is, like RNA, involved in a wide array of biological functions, deoxy congeners of the spirocyclic type need also to be targeted for deliberate incorporation in a site-specific manner into nucleotide strands. This line of research is being actively pursued.

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Supporting Information Available: Representative experimental procedures and select spectral characterization for the compounds reported herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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