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Synthesis of a Novel Nucleoside Based on a Spiroacetal Framework*

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The first synthesis of a nucleoside analogue **1** is reported wherein the nucleobase 5-fluorocytosine is attached to a 1,6-dioxaspiro[5.5]undecane spiroacetal ring system. The spiroacetal system acts as a substitute for the sugar unit of natural nucleosides and provides a conformationally restricted framework upon which to append nucleobases in a well defined geometry. Trimethylsilyl triflate promoted Vorbrüggen-type coupling of bis(trimethylsilyl)-5-fluorocytosine **3** with spiroacetal acetate **2** provided spiroacetal nucleoside **1** in which the nucleobase occupied an equatorial position together with the ring opened (*Z*)-alkene **10**. Spiroacetal acetate **2** serves as the spiroacetal donor and was prepared from the readily available starting materials δ-valerolactone and but-3-yn-1-ol **4**.

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The synthesis of nucleosides (the formation of *N*-glycosides of the sugars D-ribose and 2-deoxyribose with heterocyclic bases) has received considerable attention[1–3] from synthetic chemists largely stimulated by the prospect of developing therapeutic analogues of naturally occurring nucleosides and nucleic acids. Analogues of the natural substrates for nucleic acid processing enzymes are a good source of antiviral agents which target the enzymes specific to the disease state.[4–6] Modified oligonucleotides have been synthesized with the aim of creating analogues able to bind complementary single-stranded RNA with high affinity and specificity enabling use of an antisense strategy to inhibit the biosynthesis of a disease-related protein.[7,8]

The two main sources of variation in the structure of nucleoside analogues, namely the sugar component and the heterocyclic base, have provided medicinal chemists with enormous scope for exploitation. Considerable interest has been focussed on the synthesis of nucleoside analogues wherein the sugar ring oxygen has been replaced by carbon,[9–15] nitrogen,[16] or sulfur.[17–22] Other modifications made in an effort to improve the chemotherapeutic potential include the introduction of a double bond into the 2′,3′-position of the ribose unit,[4] incorporation of this double bond into an aromatic structure,[23] and the preparation of bicyclic compounds[24,25] including cyclopropano homologues.[26]

The design of nucleosides to study the role of sugar conformation in the processes of recognition and binding of nucleosides, nucleotides, and oligonucleotides to their target enzymes has also prompted the synthesis of conformationally restricted nucleoside analogues mainly based on a furanose or a cyclopentane moiety.[27–29] Recently, the concept of spirocyclic restriction was developed by Paquette[30] and others[31] whereby the synthesis of 4′-spirocyclic nucleoside mimics provided a new direction in the design of antisense molecules.

Given the widespread occurrence of spiroacetals in nature and their ease of availability through synthesis,[32] we were attracted to the possibility of preparing nucleoside mimics using a spiroacetal framework as a pseudosugar. The 1,6-dioxaspiro[5.5]undecane ring system was particularly attractive due to its thermodynamic preference to adopt a *trans*-diaxial conformation in which there is a lone pair of electrons antiperiplanar to each C—O bond, thus gaining maximum stability from the anomeric effect[33] and providing a scaffold to which nucleobases can be attached in a precisely configured arrangement. Our initial work in this area focussed on the construction of nucleosides based on a spiroacetal framework (see Scheme 1), and we herein report the first synthesis of nucleoside mimic **1** using a spiroacetal framework as a pseudosugar.

A retrosynthetic analysis for a prototype spiroacetal nucleoside in which 5-fluorocytosine was chosen as the nucleobase is shown in Scheme 2. The synthetic strategy hinges on the Lewis acid mediated addition of a silyl-activated nucleobase **3** to an oxocarbenium ion generated from a spiroacetal **2** that bears an acetate leaving group at the anomeric position. Precedent for the successful generation of oxocarbenium ions from spiroacetal acetates, followed by trapping with allylstannanes, has been demonstrated by this research group[34] and Mead.[35]

The spiroacetal acetate **2** intermediate was prepared from but-3-yn-1-ol **4** and δ-valerolactone as outlined in Scheme 3. After standard protection of the alcohol as a benzyl ether **5**,

* Dedicated to Professor Lew Mander on the occasion of his 65th birthday.

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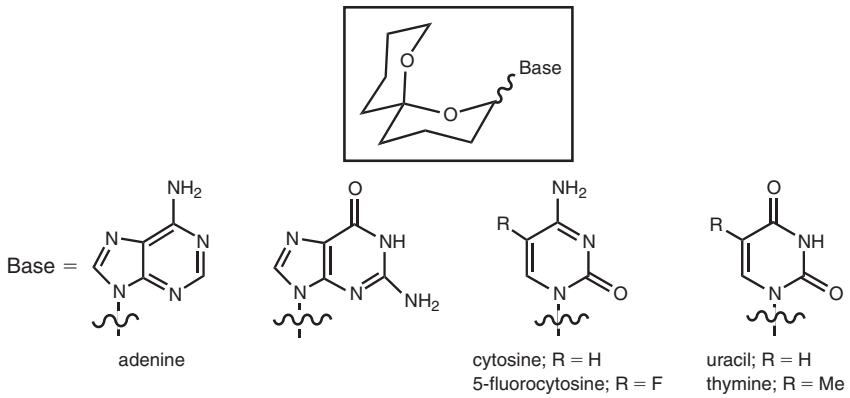
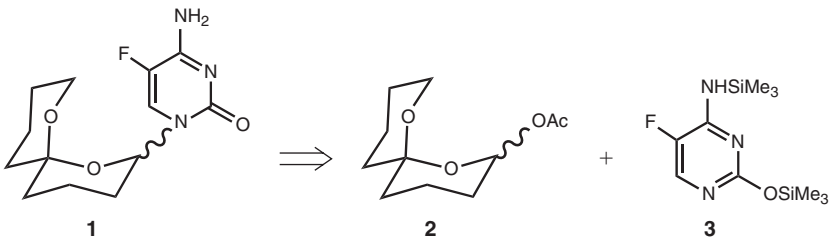
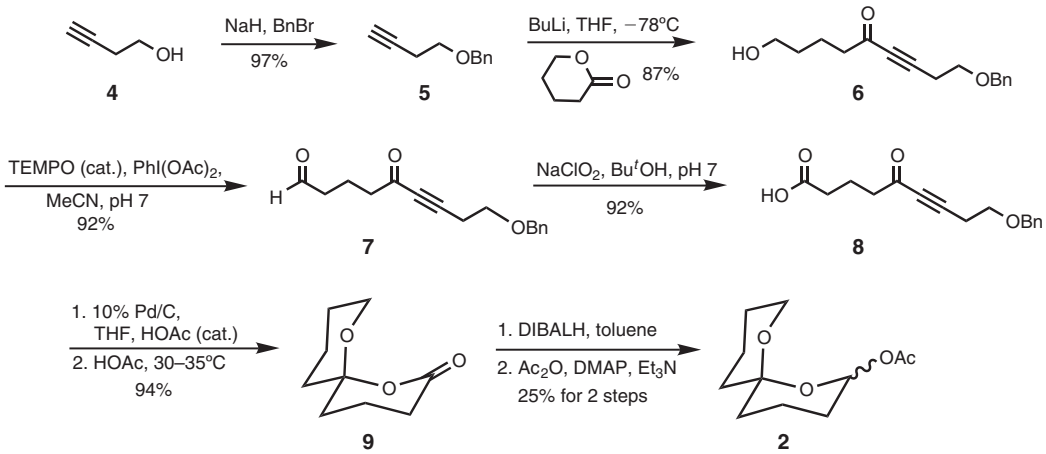


Scheme 1.



Scheme 2.

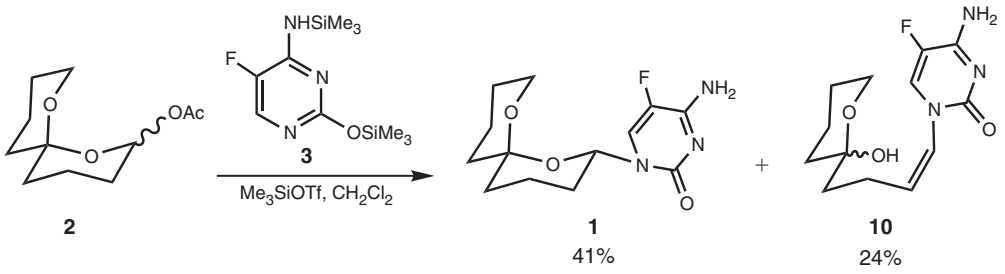


Scheme 3.

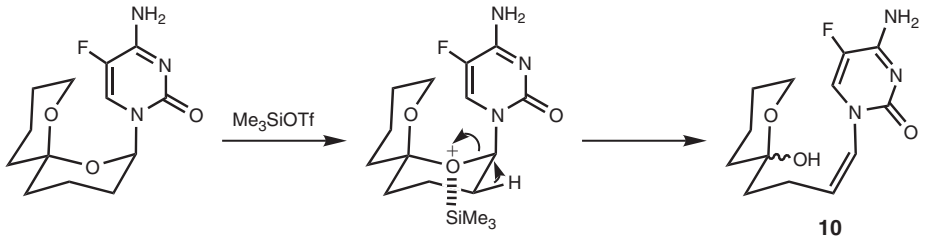
generation of the lithium acetylide followed by addition of δ-valerolactone afforded keto alcohol **6** in good yield. After much experimentation, TEMPO-catalyzed oxidation of alcohol **6** using iodobenzene diacetate afforded aldehyde **7** in 92% yield which underwent further oxidation to acid **8** also in 92% yield. One-pot hydrogenation of the acetylene and debenzylation of the benzyl ether proceeded using 10% palladium on charcoal as catalyst. The resultant keto acid then underwent smooth spirocyclization to oxaspirolactone **9** in 94% yield upon gentle heating in acetic acid.

Oxaspirolactone **9** has previously been prepared[36] by Wittig reaction of a tetrahydropyranyl triphenylphosphonium ylide with methyl 3-formylpropionate followed by hydrolysis of the ester and cyclization. However, this procedure was undesirable due to the necessity to use HMPA in order to achieve a successful outcome in the initial Wittig olefination step. Conversion of lactone **9** into spiroacetal acetate **2** by reduction using diisobutylaluminium hydride followed by acetylation afforded spiroacetal acetate **2** as a 1 : 1 mixture of anomers in low yield due to the capricious nature of the product upon purification by chromatography.

With spiroacetal acetates **2** in hand, the final crucial Vorbrüggen coupling with bis(silylated)-5-fluorocytosine (Scheme 4) was investigated using a procedure adapted from those reported by Mann et al.[37] and Paquette et al.[38–40] Thus, treatment of the acetates **2** with trimethylsilyl triflate



Scheme 4.



Scheme 5.

generated an oxocarbenium ion that underwent reaction with the silylated 5-fluorocytosine* at the less hindered N1 position to give a mixture of the 5-fluorocytidine spiroacetal **1**† in 41% yield together with (*Z*)-enamide **10**‡ in 24% yield after purification by flash chromatography.

Assignment of the heterocyclic base to an equatorial position on the spiroacetal ring in **1** was determined by the observation that the pseudo-anomeric proton H2′ resonated as a doublet of doublets at δ_H 5.96 with coupling constants $J_{2'ax,3'eq}$ 2.2 Hz and $J_{2'ax,3'ax}$ 11.2 Hz. The magnitude of this latter coupling constant clearly established that the proton at the pseudo-anomeric position occupied an axial position placing the heterocyclic base in an equatorial position. The '*anti*-orientation' of the nucleobase and the oxygen atom of the second ring is determined by the adoption of the more stable *trans*-diaxial conformation of the spiroacetal ring system.

The magnitude of the vinylic coupling constant, *J* 8.4 Hz, observed for alkene **10** clearly established the (*Z*)-stereochemistry of the double bond. The formation of (*Z*)-alkene **10** as a by-product in the Vorbrüggen coupling step is thought to arise from the corresponding nucleoside spiroacetal in which the heterocyclic base occupies the more sterically hindered axial position. In this case the unstable spiroacetal undergoes an elimination–ring opening sequence to the (*Z*)-alkene in the presence of the electrophilic trimethylsilyl triflate (Scheme 5). If the elimination were stereospecific, one would expect the (*Z*)-alkene to be formed from the spiroacetal nucleoside in which the heterocycle is axial, as observed.

To conclude, the synthesis of the first nucleoside analogue based on a spiroacetal framework has been reported. Spiroacetal-based nucleosides such as **1** represent promising building blocks for the synthesis of artificial oligonucleotides and other complex molecules. This novel class of molecule also provides an interesting structural scaffold to probe for antiviral activity. Further work on the incorporation of additional nucleobases onto the 1,6-dioxaspiro[5.5]undecane ring system and efforts to improve the stereocontrol in the critical *N*-pseudoglycosylation step are currently underway in our laboratory.

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* Silylation of 5-fluorocytosine was achieved by heating with *N*,*O*-bis(trimethylsilyl)acetamide.

† Data for **1**: δ_H (400 MHz, $CDCl_3$) 7.55 (1 H, d, $^3J_{H,F}$ 6.0, H6), 5.96 (1 H, dd, *J* 11.2, 2.2, H2′), 5.55 (2 H, br s, NH_2), 3.75–3.62 (2 H, m, H8′), 2.05–1.98 (1 H, m, H3′A), 1.80–1.20 (11 H, m, H3′B, H4′, H5′, H9′, H10′, H11′). δ_C (100 MHz, $CDCl_3$) 156.5 (CF, d, $^1J_{C,F}$ 223, C5), 155.1 (quat., C2), 153.6 (quat., C4), 125.5 (CH, d, $^2J_{C,F}$ 31.4, C6), 98.5 (quat., C6′), 77.5 (CH, C2′), 61.0 (CH_2, C8′), 35.2 (CH_2, C5′ or C11′), 34.9 (CH_2, C11′ or C5′), 30.8 (CH_2, C3′), 24.8 (CH_2, C9′), 18.3 (CH_2, C4′ or C10′), 18.0 (CH_2, C10′ or C4′). *m*/*z* (EI^+) 283 ($M^{+\bullet}$, 0.4%), 155 (14), 136 (100), 129 (65), 108 (38), 98 (27), 86 (20), 79 (34), 66 (14), 51 (21), 41 (23), 39 (17). *m*/*z* (FAB^+) Found: 284.1433. Calc. for $C_{13}H_{19}FN_3O_3^+$ [M + H^+]: 284.1410.

‡ Data for **10**: δ_H (300 MHz, $CDCl_3$) 7.38 (1 H, d, $^3J_{H,F}$ 5.4, H6), 5.27 (1 H, d, *J*8.4, H2′), 4.81 (1 H, m, H3′), 4.02 (2 H, m, H8′), 2.13–1.20 (12 H, m, H3′, H4′, H5′, H9′, H10′, H11′).

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