A new class of anomeric spironucleosides

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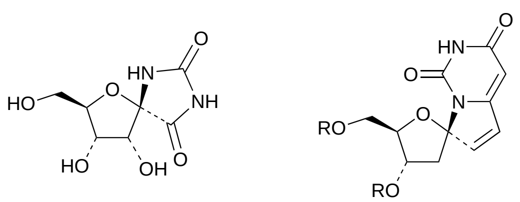
A 1,5-hydrogen migration of a conveniently situated alkoxyl radical affords spironucleosides which possess an unusual orthoamide structure at the anomeric position; X-ray crystallography establishes the configuration of the C-1′ position.

Anomeric spironucleosides are useful modifications of natural nucleosides in that they contain the base unit in a fixed conformation around the *N*-glycosidic bond.[1] In recent years, they have gained in importance with the discovery of hydantocidin[2] **1**, a natural spironucleoside with herbicidal and plant growth regulatory activities, and generally, with the notion that important pharmaceutical leads can be found among modified nucleoside analogues.



1 **2**

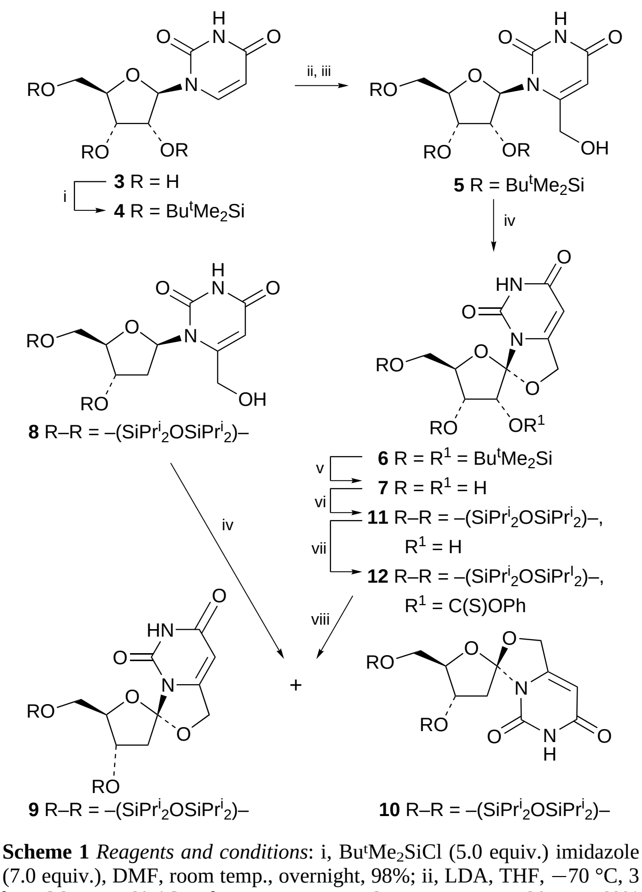
The first anomeric spironucleosides to be synthesized were derivatives of psiconucleosides.[3,4] All recent developments on the synthesis of anomeric spironucleosides are based on free-radical chemistry.[3b,5,6]

Modification of the anomeric position of nucleosides can also be attained *via* the intermediacy of C-1′ radicals.[7] We recently reported the first example of this kind of transformation for the preparation of compound **2**.[8] We report herein the synthesis of a new class of anomeric spironucleosides *via* a [1,5]-radical translocation of alkoxyl radicals to the anomeric position.

When the protected 6-hydroxymethylribouridine **5**, prepared from the corresponding protected uridine **4** by fine tuning of literature procedures,[9] was treated under the standard Suárez conditions[10] a major product was obtained in moderate (36%) yield after flash column chromatography (Scheme 1). The structure of the product could be assigned to compound **6** based on its ^{1}H NMR spectrum, in which 2′-H appeared as a doublet and the 7-Hs appeared as a well resolved AB quartet. This, coupled with the lack of a 1′-H or 7-OH signal, corroborated the assignment of an orthoamide function to the product nucleoside, although the configuration of the anomeric centre remained ambiguous. Deprotection of the silyl groups provided the water soluble compound **7**. A single crystal of this material grown from MeOH–H_2O with mp 172–173 °C was subjected to X-ray diffraction analysis in order to determine unambiguously the stereochemistry of the C-1′ position.

The independent part of the cell contains two formula units. An ORTEP diagram of **7** (molecule 1) is shown in Fig. 1. All atoms in molecule 1 were well defined, while atom O(5A) in molecule 2 exhibited a split image, as a consequence of two-fold rotational disorder around the C(4A)–C(5A) axis. An occupation factor for the latter was refined for O(5A) and the accompanying hydrogens, the final value being 0.57(1). The two independent molecules have strictly comparable parameters. In both molecules the stereogenic centre C(1A) is in the *R* configuration. The oxazolo[3,4-*c*]pyrimidine moiety is flat [maximum deviation from the average plane is 0.137(3) and 0.171(3) Å for atom O(7) in molecules 1 and 2, respectively]. The dihedral angle between the five membered ring and the fused pyrimidine moiety is 82.3(2) and 86.5(2)° for molecules 1 and 2, respectively.

When the Suárez conditions,[10] were applied to the 2′-deoxynucleoside analogue **8**, prepared from the corresponding protected 2-deoxyuridine,[9] two spironucleoside products were isolated in 71% combined yield and in a 1.1 : 1 ratio after flash column chromatography (Scheme 1). The structures of the products were assigned to compounds **9** and **10** based on their ^{1}H NMR spectra, in which the two diastereotopic 2′-Hs appeared as well resolved doublets of doublets and the 7-Hs appeared as an AB quartet. The determined absolute configuration of the anomeric centre in the spiroribonucleoside **7** was linked with that of the 2′-deoxy analogues through a straightfor-



Scheme 1 *Reagents and conditions*: i, Bu^{t}Me$_2$SiCl (5.0 equiv.) imidazole (7.0 equiv.), DMF, room temp., overnight, 98%; ii, LDA, THF, −70 °C, 3 h; HCO_2Et, −60 °C, 2 h; iii, $NaBH_4$, MeOH, room temp., 30 min, 68% based on consumption of **4**; iv, $PhI(OAc)_2$, I_2, cyclohexane, *hν*, 28 °C, 5 h, 36% for **6**, 71% for **9** and **10**; v, Bu_4NF on SiO_2, THF, room temp., 2 h, 90%; vi, $(Pr^i_2SiCl)_2O$, pyridine, room temp., overnight, 61%; vii, PhOC(S)Cl, DMAP, CH_2Cl_2, 1 h, room temp., 84%; viii, $(Me_3Si)_2SiH$, AIBN, toluene, 80 °C, 6 h, 95%

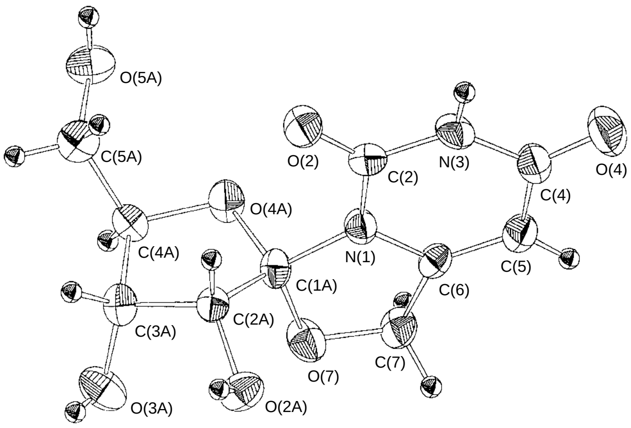
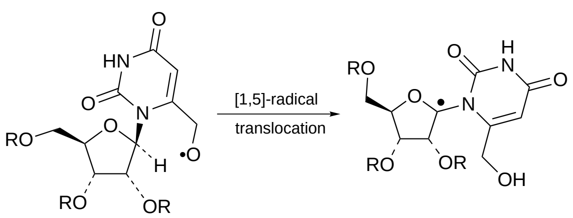


Fig. 1 ORTEP drawing of one of the independent molecules of **7** (molecule 1) in the unit cell

ward, three-step chemical transformation, as outlined in Scheme 1. Standard regioselective protection of the 3′- and 5′-positions with the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl group to afford **11**, followed by transformation of the 2′-hydroxy group to give the thiocarbonate **12**,[11] and finally Barton–McCombie radical deoxygenation in the presence of $(Me_3Si)_3SiH$[12] produced the chromatographically less polar stereoisomeric 2′-deoxyspironucleoside **9**. These transformations, apart from establishing unequivocally the configuration of the C-1′ anomeric centre in **9** and **10**, also demonstrated the inherent stability of the orthoamide structure.

The mechanism for the formation of the spironucleoside involves generation, under the Suárez conditions, of the alkoxyl radical intermediate **13** which undergoes a [1,5]-radical translocation reaction[13] to yield the anomeric C-1′ radical intermediate **14** [eqn. (1)], which in turn produces the observed



13 **14** (1)

orthoamide **6** after oxidation and cyclization. It is worth pointing out that the steric hindrance induced by the bulky 2′-substituent in the ribo series is likely responsible for the stereospecificity of the cyclization. The absence of the epimeric spironucleoside with *S* configuration in the reaction product can be attributed to the steric interaction between the carbonyl in the 2-position of the base and the bulky-2′ substituent as can be envisaged by inspection of the crystal structure in Fig. 1.

The spironucleosides reported herein correspond to the first spiro[tetrahydrofuran-2,3′-(1,5,6,7-tetrahydro-3*H*-[1,3]-oxazolo[3,4-*c*]pyrimidine)] nucleosides, possessing a remarkably stable orthoamide modification of the C-1′ anomeric position. Further work on the preparation and chemical transformations of this class of compounds is in progress.

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Footnote and References

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