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# C-1′ radicals in nucleosides

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**Abstract**

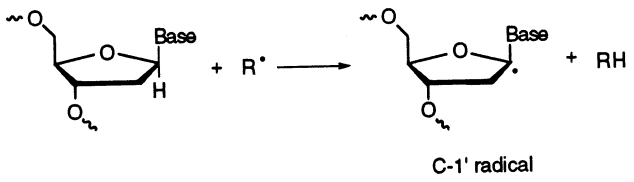
C-1′ radicals in modified nucleosides have been generated by a variety of methods. Synthetic methodologies based on radical cascade reactions for the preparation of anomeric spironucleosides have been developed. Structural information on C-1′ radicals has been obtained and their fate in anoxic or aerobic conditions has been studied. 

*Keywords:* Radicals; Nucleosides; Spiro compounds

## 1. Introduction

A number of agents are able to react with DNA and generate macromolecular radical species [1–4]. These processes are of considerable importance since they can lead to base modifications or strand scissions. In fact, abstraction of a hydrogen atom from deoxyribose produces carbon-centered radicals on the sugar which can be transformed into strand scissions. As research progresses in the area of the mechanism of attack of oxidative DNA cleavers, it becomes evident that hydrogen abstraction from the C-1′ position is involved in many cases (Scheme 1) [2–4].

For example, abstraction of a hydrogen atom from the C-1′ position of specific cytidine residues of the sugar backbone of DNA corresponds to a minor event in the action mechanism of neocarzinostatin, a member of the enediyne family of antibiotics [5]. Coupled with a major lesion involving hydrogen abstraction from the C-5′ position of a thymidine residue in the opposing strand, this event can lead to a double strand scission or site-selected mutagenesis. Evidence has also been presented which indicates that the glutathione-activated neocarzinostatin chromophore also generates bistranded lesions in DNA–RNA hybrids, involving C-1′ hydrogen abstraction from the targeted ribonucleotide and C-5′ chemistry at the targeted deoxyribonucleotide [6]. There are several other known cleavers which are able to generate C-1′ radicals. It is worth mentioning the action of dynemicin and bis(1,10-phenanthroline)-copper, two DNA cleavers which primarily abstract hydrogens from the C-1′ position [7]. The fate of the C-1′ radicals under either anoxic or aerobic conditions is currently under dispute [2,3].




Scheme 1.

On the other hand, it is envisaged from the recent literature in the nucleoside area that C-1′ radicals may constitute useful intermediates which can generate valuable chemistry currently unexplored but potentially important in medicinal chemistry. In fact, there are a number of natural products reminiscent of nucleosides which contain modifications in the C-1′ position. Examples can be found in angustamycin C (**1**) which has interesting antiviral and antitumor properties [8] or in hydantocidin (**2**) a natural spironucleoside with herbicidal and plant growth regulatory activities [9]. Anomeric spironucleosides are useful modifications of natural nucleosides in that they contain the base unit in a fixed conformation around the *N*-glycosidic bond. This property has made them good candidates in structure–activity studies for determining the ideal torsion angle around the *N*-glycosyl bond for optimal biological activity [10]. However, the availability of anomeric spironucleosides is limited since the presence of the base

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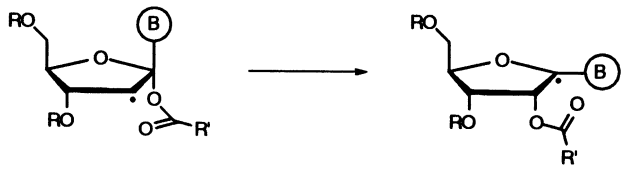
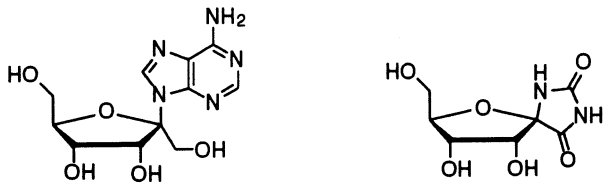


Scheme 2.

in the anomeric C-1′ position of nucleosides complicates any synthetic plan for direct modification on that position.



1 2

In order to understand better the fate of C-1′ radicals as well as their usefulness in the synthesis of complex molecules, we have undertaken a systematic investigation by utilizing modified nucleosides as models which allow for the specific generation of C-1′ radicals. Herein we summarize recent results from our laboratory.

## 2. Indirect formation: 1,2-migration of an acyloxy group

One of our first attempts to generate C-1′ radicals involved a β-(acyloxy)alkyl rearrangement of a C-2′ radical into the anomeric position (Scheme 2) [11,12].

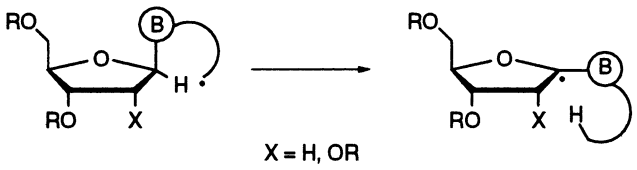
The C-2′ radicals were obtained by reaction of the halopivaloates **4** and **5** with tributyltin hydride under radical chain conditions (Scheme 3). By applying free-radical clock methodology the rate constants for these rearrangements were measured and found to be the same within experimental error upon substitution of uracil with adenine in the same diastereotopic configuration [12]. These results suggest that (i) polar effects play a very important role in enhancing the rates and (ii) C-1′ radicals are stabilized substantially by the presence of the base and that the degree of stabilization is similar for purine and pyrimidine moieties.

## 3. Indirect formation: 1,5-radical translocation

In this section we report a 1,5-hydrogen transfer as outlined in Scheme 4 used as protocol to access C-1′ radical intermediates in both ribo and 2′-deoxyribo series [13–15].

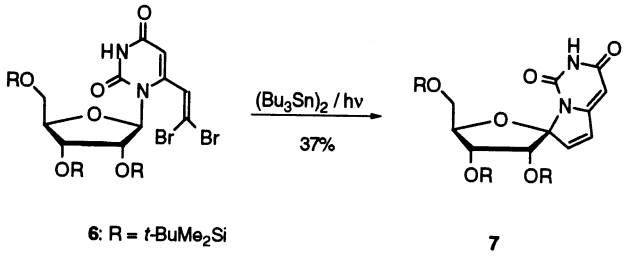
Reaction of compound **6** with the $Bu_3Sn^{\bullet}$ radical, generated by photolysis of hexabutylditin with 300 W of visible light, provided the spironucleoside **7** as the sole product in 37% yield (Scheme 5) [15].

When the same conditions were applied to the protected 2′-deoxynucleoside **8**, a mixture of anomeric spironucleosides **9** and **10** was obtained in a 2:1 ratio (Scheme 6) [13,15].



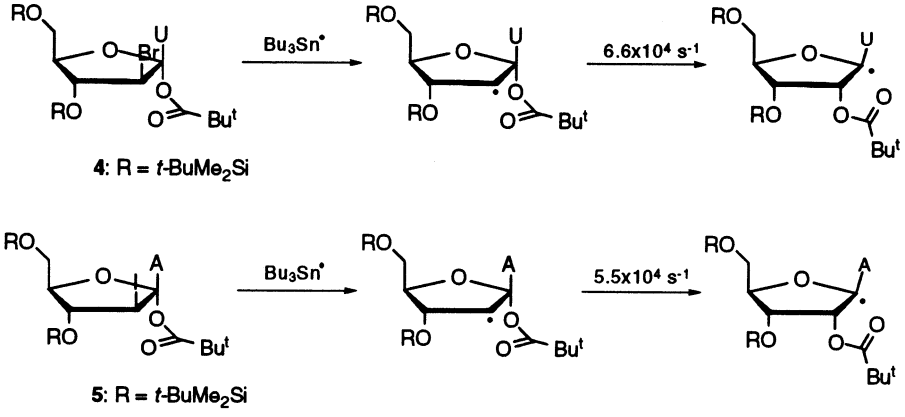
X = H, OR

Scheme 4.



6: R = *t*-BuMe$_2$Si 7

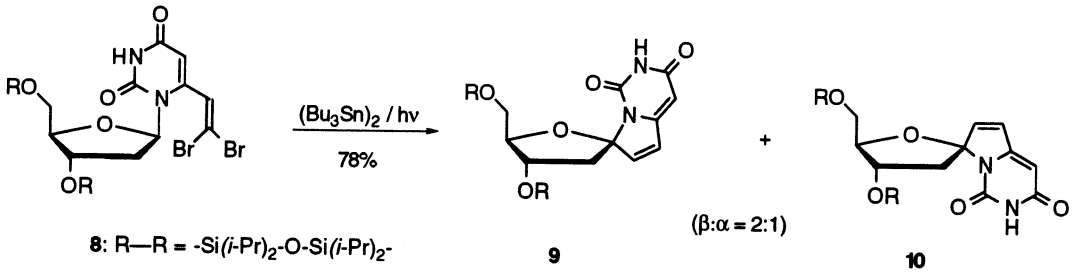
Scheme 5.



4: R = *t*-BuMe$_2$Si

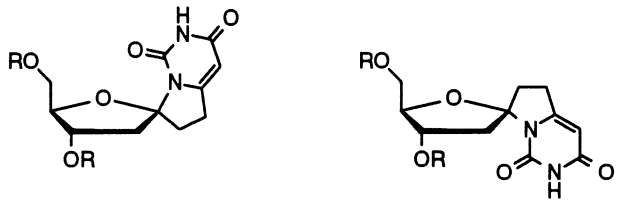
5: R = *t*-BuMe$_2$Si

Scheme 3.




Scheme 6.

The mechanism that we conceived for these transformations comprises a cascade of free radical reactions involving bromine abstraction from C-8 by the stannyl radical to generate the vinyl radical species, followed by a 1,5-radical translocation to the anomeric position, a 5-*endo*-*trig* cyclization of the anomeric radical onto the proximal double bond and, finally, product formation by bromine atom ejection. Kinetic information for both the 1,5-radical translocation and the 5-*endo*-*trig* cyclization was obtained and the factors controlling the stereochemistry of this cyclization were discussed [15]. Furthermore, compounds **9** and **10** were converted to spironucleosides **11** and **12** in 75 and 68% yield, respectively, by selective hydrogenation of the double bond using a 5% Rh/Al catalyst in methanol [15].



**11** **12**

When compound **13** was subjected to photolysis with visible light in the presence of $PhI(OAc)_2$ and $I_2$ in cyclohexane at room temperature, a major product was obtained in 49% yield (Scheme 7) whose structure **14** was determined by X-ray crystallography [15].

When the same conditions were applied to the protected 2′-deoxyribo analogous **15**, a mixture of anomeric spironuleosides **16** and **17** was obtained in 65% yield and in the anomeric composition $\beta{:}\alpha = 1{:}1$ (Scheme 8) [14,15].

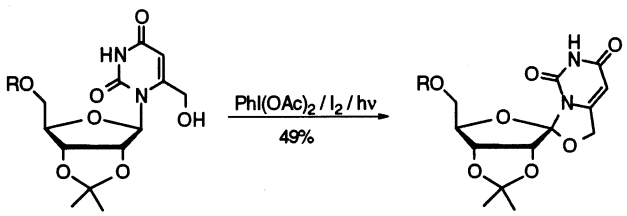
The suggested mechanism involves photolysis of the initially formed hypoiodite generating an alkoxy radical intermediate which undergoes a Barton-type hydrogen migration to generate the anomeric C-1′ radical. Reaction of the C-1′ radical with iodine generates the unstable C-1′ iodo derivative which undergoes anionic cyclization with the generation of the observed product.

It is worth pointing out that the steric hindrance induced by the C-2′ substituent is most probably responsible for the stereospecificity of the cyclization in the ribo series.

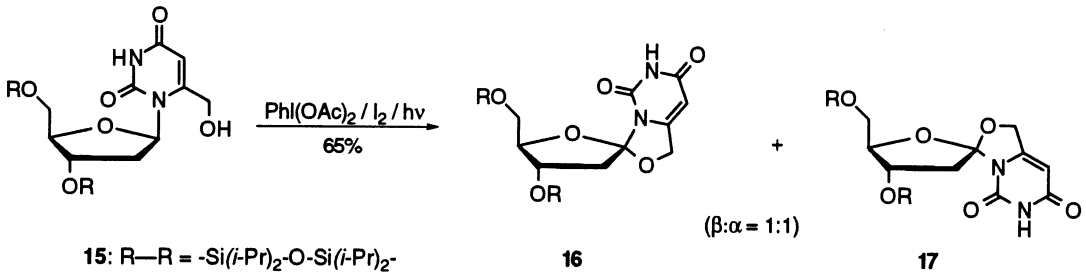
## 4. Direct formation: photolysis of C-1′ *tert*-butyl ketone

Ketone **18** was synthesized either by revising a reported procedure starting from D-fructose (11 steps) or from a new route starting from uridine (seven steps) and with a much higher overall yield [16,17]. Then, ketone **18** was used for the photolytic generation of specific C-1′ radicals which were studied spectroscopically (Scheme 9). Electron spin resonance data combined by theoretical studies indicate that the configuration of the C-1′ radical is strongly bent and that the unpaired electron is poorly delocalized in the uracil moiety [18].

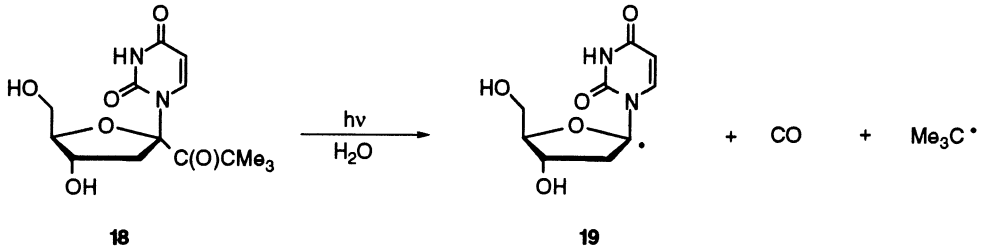
Radical **19** reacts fast with alkylthiols to give mixtures of α and β anomers of 2′-deoxyuridine (Scheme 10) [19]. The bimolecular rate constant for the reaction of radical **19** with glutathione was found to be $4.4 \times 10^6$ $M^{-1}$ $s^{-1}$ at 20°C [20]. Radicals **19** in the presence of oxygen produced 2′-deoxyribonolactone and uracil (Scheme 10) [19]. A detailed investigation of the reaction mechanism for the formation of 2′-deoxyribonolactone was performed by labelling experiments and kinetic studies using laser flash photolysis [19,20]. Scheme 10 shows in some details the reaction mechanism. C-1′ radical adds to molecular oxygen with a rate constant of $1 \times 10^9$ $M^{-1}$ $s^{-1}$ to give the peroxyl radical **20**. In its turn, the radical **20** eliminates the superoxide radical anion with a rate constant of $2 \times 10^4$ $s^{-1}$ to give the corresponding carbocation **21** which reacts with water to produce the observed products.



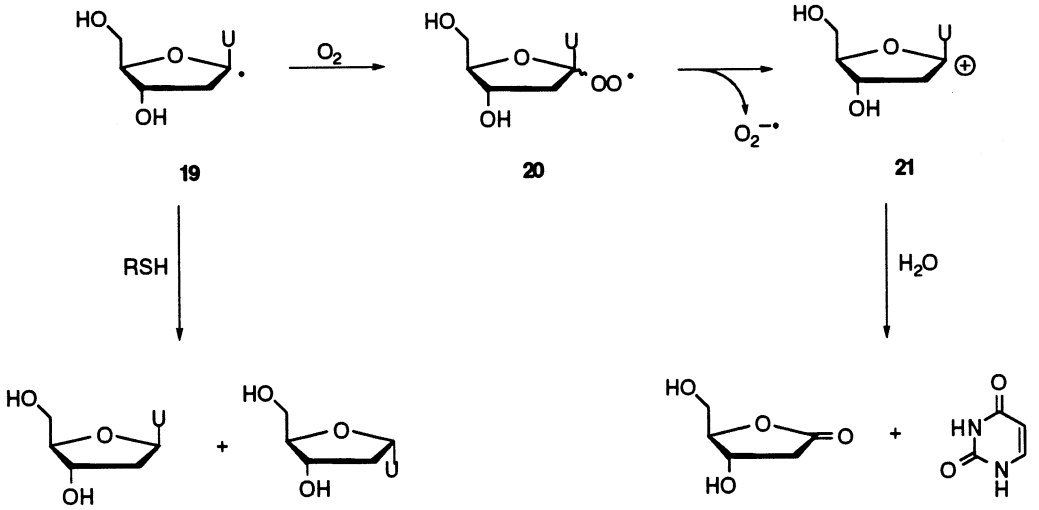

Scheme 7.




Scheme 8.




Scheme 9.




Scheme 10.

## 5. Conclusions

C-1′ radicals are no longer elusive intermediates and can be generated by a variety of methods. We have shown that C-1′ radicals can play an important role in the radical cascade synthesis of anomeric spironucleosides. In the near future we expect to see more application of this kind in the synthesis of modified nucleosides. The specific generation of C-1′ radicals allowed us to better understand their fate under anoxic or aerobic conditions; however, investigation of their chemistry in more complex systems like oligonucleotides will be of great importance.

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