1,5-Radical Translocation Protocol for the Generation of C-1′ Radicals in Nucleosides. Synthesis of Spiro Nucleosides through a Rare 5-*endo-trig* Cyclization

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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 mechanism of action of neocarzinostatin, a member of the enediyne family of antibiotics.[1] 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, both important steps in radical-induced DNA damage.[1a] Recently, direct evidence has been presented which indicates that 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.[2] A similar C-1′ radical generation has been demonstrated to be effected by the bleomycins on deoxyoligonucleotide substrates containing a single ribo or arabino cytidine modification.[3] Finally, C-1′ radical chemistry is one of the major pathways involved in the oxidative DNA cleavage induced by bis(1,10-phenenthroline)copper[1c,4] and cationic metalloporphyrins.[1c]

Furthermore, it is envisaged from the recent literature in the nucleoside area[5] that C-1′ radicals may constitute useful intermediates which can generate rich chemistry currently unexplored but potentially important in medicinal chemistry. This overall picture has prompted us to undertake a systematic investigation of the radical chemistry associated with the C-1′ position. One of our first attempts to generate such radicals involved a β-(acyloxy)alkyl radical rearrangement of a C-2′ radical into the anomeric position (Scheme 1, method A). This successful methodology led to the formation of a model C-1′ ribouridyl radical.[6] Herein, we report a [1,5]-hydrogen transfer as outlined in Scheme 1 (method B) used as a protocol to access C-1′ radical intermediates in model deoxyribonucleosides. This well-precedented carbon-to-carbon radical migration has been recently utilized in synthetic design by Curran and others[7] and has been more appropriately termed 1,5-radical translocation.

Scheme 1

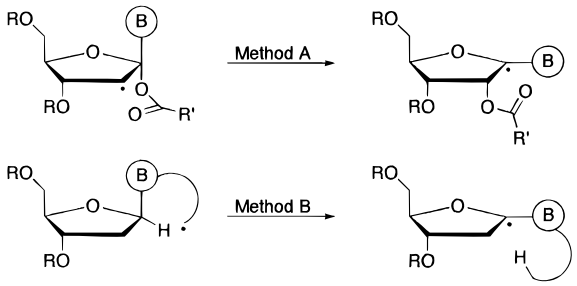

Table 1. Reaction of Compound 1[a] with a Variety of Reagents at 80 °C under Free Radical Conditions

			yield,[b] %	
entry	reagent	condns	**3** (*E*:*Z*)	**7** + **8** (**7**:**8**)
1	Bu_3SnH	*c*, *d*	44 (1:2)	36 (2:1)
2	Bu_3SnH	*e*, *d*	26 (1:2)	52 (2:1)
3	$(TMS)_3SiH$	*f*, *d*	25 (1:2)[g]	57 (2:1)
4	$Bu_3SnSnBu_3$	h		78 (2:1)
5	Bu_3SnD	*i*, *d*	42 (1:2)[j]	32 (2:1)

[a] Starting concentration of **1** was 0.05 M in benzene. [b] Yields after isolation of pure compounds. [c] 1.5 equiv; 3 h. [d] AIBN (10 mol %); a second portion of AIBN (10 mol %) was added after 1.5 h. [e] 2.2 equiv; syringe-pump addition in 3 h followed by an additional 1 h reflux. [f] 4.0 equiv; 5 h. [g] 7% of starting material was recovered. [h] Photoinitiation with 300 W of visible light; 12 h under reflux. [i] 2.5 equiv; 3 h. [j] Deuterium incorporation ca. 80%; see ref 14.

The radical precursor, the protected 6-(2,2-dibromovinyl)uridine (**1**), was prepared by the Corey−Fuchs protocol[8] for the introduction of the dibromovinyl function on the appropriate carboxaldehyde[9] in 42% yield. Upon reaction of compound **1** with Bu_3SnH under standard free radical conditions (see entry 1 in Table 1 and Scheme 2), we obtained four products which were isolated *via* preparative TLC and characterized (80% combined yield). The structure and anomeric composition of the monoreduced vinyl bromides (*E*)-**3** and (*Z*)-**3** were deduced from a combination of NMR experiments including ^1H, ^{13}C, homonuclear decoupling, and 1D-NOE[10] as well as from a comparison of the collected data with these of similar reported compounds.[11] Similar treatment of the spectroscopic data of the other two more polar components of the initial reaction mixture revealed the structures of the anomeric spiro nucleosides **7** and **8** obtained in a 2:1 ratio (Scheme 2). We were aided in the structure determination of the last two compounds by the recent report by Tanaka and co-workers of the preparation of some similar anomeric spiro nucleosides.[5b] In fact, deprotection of the silyl groups in **7** with Bu_4NF in THF led to the known free nucleoside, 2′-deoxy-6,1′-ethenouridine, the spectroscopic data of which were in complete agreement with the reported data.[5b]

In order to obtain further mechanistic information and to improve the yield of spiro nucleosides, the reaction was performed under a variety of free radical conditions. Table 1 summarizes these results. Entries 2 and 3 show that by decreasing the hydrogen donation ability of the reducing agent, either by slow addition of Bu_3SnH or by using $(TMS)_3SiH$,[12] the amount of vinyl bromides **3** decreases substantially in favor of spiro nucleosides **7** and

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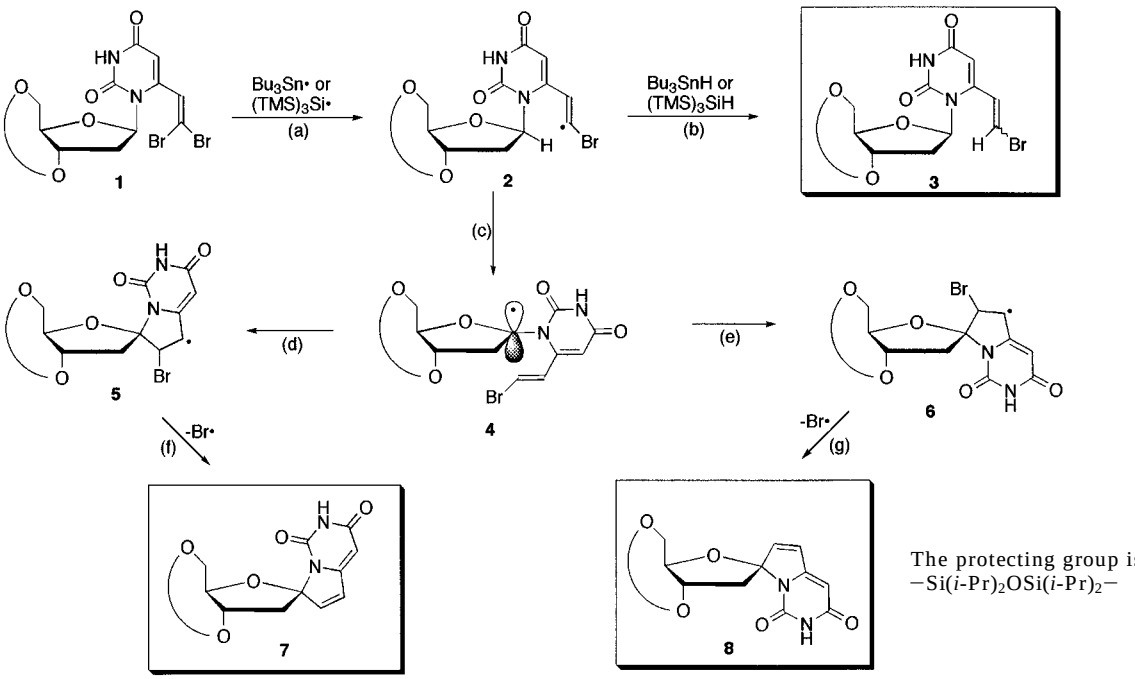
Scheme 2



8. An experiment utilizing hexabutylditin as the radical source[13] and photoinitiation using 300 W of visible light (entry 4, Table 1) provided not only a set of synthetically useful conditions (clean production of the spiro nucleosides **7** and **8** as the sole products in 78% yield) but also evidence that no hydride was necessary for the formation of **7** and **8**. Entry 5 (Table 1) shows an experiment analogous to entry 1 (Table 1) using 2.5 equiv of tributyltin deuteride; the same four compounds were obtained with the relative amounts of the vinyl bromides and spiro nucleosides very similar to entry 1, indicating a deuterium isotope effect $k_H/k_D = 1.7$.[14]

The mechanism that we conceived for these reactions is outlined in Scheme 2. It is comprised of a cascade of free radical reactions involving bromine abstraction from C-8 by stannyl or silyl radical to generate the vinyl radical species **2** (step a), followed by a 1,5-radical translocation to the anomeric position (step c), a rare 5-*endo-trig* cyclization of the anomeric radical **4** onto the proximal double bond (steps d and e), and finally product formation by bromine atom ejection (steps g and f).[15] In the presence of a hydride, radical intermediate **2** can also undergo reduction to the bromides **3** (step b). Although there is ample precedence for 1,5-hydrogen transfer reactions,[7] 5-*endo-trig* free radical cyclizations onto carbon continue to obey the Baldwin−Beckwith rules[16] and remain relatively rare.[17] The correct geometrical arrangement coupled with the stability of the C-7-produced radical could account for the success of this exceptional cyclization.

Furthermore, some kinetic information for both the 1,5-radical traslocation (step c) and the 5-*endo-trig* cyclization (steps d and e) can be deduced. By applying free-radical clock methodology[6,18] in entry 1 (Table 1, second order kinetics) we were able to find $k_c/k_b = 0.045$ M, where k_b is the rate constant for the reaction of radical **2** with Bu_3-SnH. Assuming $k_b > 10^7$ M^{-1} s^{-1},[18] we estimate the radical traslocation (step c) to be larger than 4×10^5 s^{-1}. On the other hand, the lack of hydrogen abstraction from the hydrides by radical **4** to give anomeric mixtures of bromides **3** suggests that the 5-*endo-trig* cyclization is a relatively fast process. However, the factors controlling the stereochemistry of this cyclization are not straightforward. Radical **4** is initially generated in the orientation which would lead exclusively to radical **5** (step d). For the formation of radical **6** a half-rotation of the C1′−N1 bond is needed prior to cyclization (step e). Therefore, the spiro nucleosides ratio **7**:**8** = 2:1 should reflect either the competition between cyclization and C1′−N1 bond rotation or the relative populations of the two rotamers in the case in which the C1′−N1 bond rotation in radical **4** is much faster than cyclization.

In summary, a 1,5-radical translocation protocol has been developed for the generation of a C-1′ radical in a model nucleoside. It has led, through an unusual 5-*endo-trig* cyclization, to a practical synthesis of anomeric spiro nucleosides which compares favorably to the previously published method. The possibility of using such a system as a trap for C-1′ radicals in biological systems is currently under investigation.

Supporting Information Available: Experimental procedures and characterization data (6 pages).

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(14) There was ca. 80% deuterium incorporation on the C-8 position of (*E*)-**3** and (*Z*)-**3** but no measurable (<4%) deuterium incorporation in the anomeric C-1′ position of either compound. Furthermore, there was no deuterium incorporation observed in **7** or **8**.

(15) Bromine atom either abstracts hydrogen from hydride or reacts in an S_H2 fashion with ditin to regenerate the silyl or stannyl radicals, thus completing the cycle of these chain reactions.

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