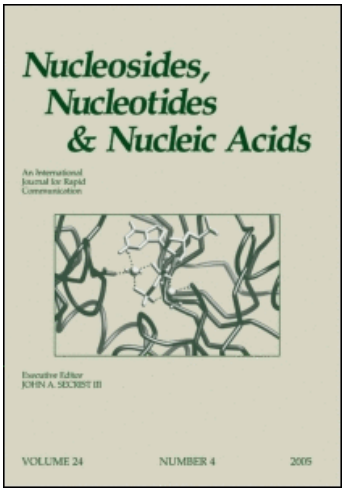

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1,5-TRANSLOCATION STRATEGY FOR NUCLEOSIDE ANOMERIC RADICALS

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ABSTRACT A new method for generating nucleoside anomeric radicals utilizing radical 1,5-translocation was developed. Two kinds of β-halogenovinyl groups at the C6-position of uracil nucleosides were found to be a good radical source, which subsequently forms a nucleoside anomeric radical. The following 5-*endo-trig* cyclization gave anomeric spiro nucleosides as products.

In the case of carbohydrates, anomeric radicals can be generated simply by using glycosyl halides as precursors. Giese and Dupuis reported that a pyranosyl anomeric radical undergoes a reaction at the α-face with high stereoselectivity, strongly affected by an anomeric effect.[1] This finding was utilized by Kahne *et al.* to construct a β-glycosyl linkage from an α-glycoside.[2] Unlike carbohydrates, it is difficult to design a precursor of a nucleoside anomeric radical because the anomeric position is preoccupied by a base moiety, which tends to act as a leaving group. Recently, we reported a unique process to generate the nucleoside anomeric radical by using 1,2-acyloxy migration, which was successfully applied to the synthesis of C1'-carbon-branched β-nucleosides.[3]

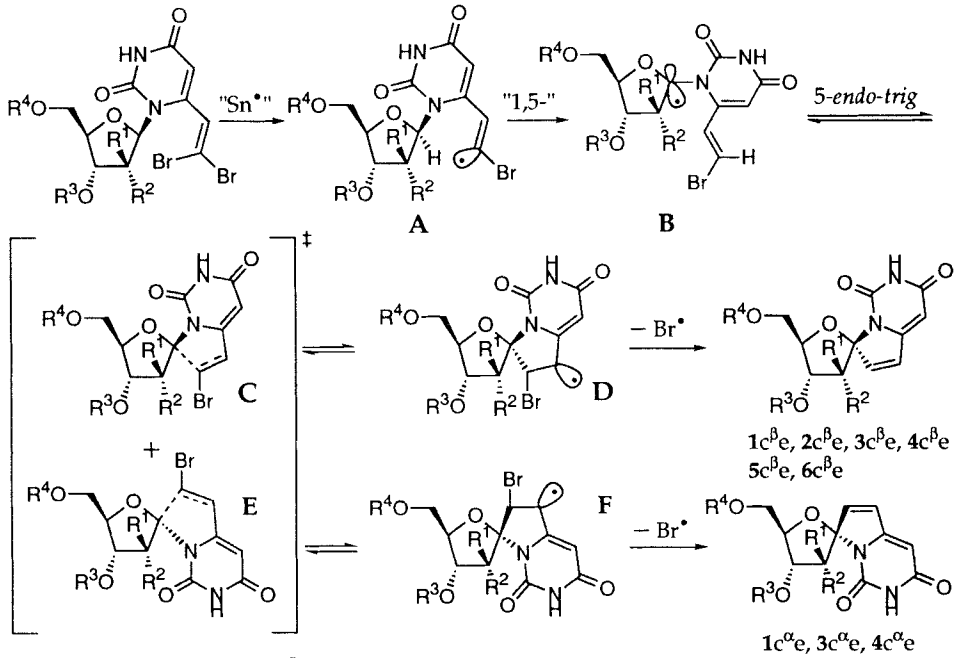
In this paper, we wish to report an alternative method to generate the anomeric radicals based on the radical 1,5-translocation,[4] which resulted in the formation of anomeric spiro nucleosides. Namely, a vinyl radical generated from a β,β-dibromovinyl (or (*E*)-β-iodovinyl) group at the C6-position of uracil nucleosides undergoes 1,5-translocation to yield an anomeric radical, which then further reacts in a 5-*endo-trig* manner[5] to give anomeric spiro nucleosides.[6] A similar reaction of a 6-chloropurine nucleoside was also carried out.

To introduce the β,β-dibromo- and β-iodovinyl groups, protected uridine was first lithiated selectively at the C6-position,[7] and subsequently treated with DMF for formylation. The crude aldehyde obtained in 97% yield next reacted with $Ph_3P{=}CBr_2$ and $Ph_3P{=}CHI$ to afford substrates **1** and **7** in 57 and 11% yields, respectively. Other uridine derivatives protected with tris(TBDMS) and triacetyl groups, **2** and **3**, were also synthesized from **1**. For a 2'-deoxyuridine derivative, the formylation occurred in 58% yield and the following Wittig reaction gave **4** in 73% yield. In the case of an arabinofuranosyl uracil nucleoside, it is necessary to convert the base moiety to 4-ethoxy-2-pyrimidinone for the effective lithiation at the C6-position.[7c] The formylathion and the following Wittig reaction proceeded in 70 and 86% yields, respectively. Treatment with aqueous HCl in MeOH and subsequent protection with 3',5'-bis(TBDMS) and triacetyl groups gave the substrates **5** and **6** in 56 and 78% yields.

TABLE 1. Radical-mediated cyclization of **1**-**7**.

entry	substrate	cyclized products isolated by HPLC (% yield)			combined yield (%)	β/α
1	**1**	**1**c$^{\beta}$e (40)		**1**c$^{\beta}$a^{Ph} (3)	46	14/1
		1c$^{\alpha}$e (3)				
2	**2**	**2**c$^{\beta}$e (50)	**2**c$^{\beta}$a^{H} (3)	**2**c$^{\beta}$a^{Ph} (5)	65	8/1
			2c$^{\alpha}$a^{H} (4)	**2**c$^{\alpha}$a^{Ph} (3)		
3	**3**	**3**c$^{\beta}$e (40)	**3**c$^{\beta}$a^{H} (1)	**3**c$^{\beta}$a^{Ph} (13)	62	7/1
		3c$^{\alpha}$e (7)		**3**c$^{\alpha}$a^{Ph} (1)		
4	**4**	**4**c$^{\beta}$e (23)	**4**c$^{\beta}$a^{H} (7)		47	2/1
		4c$^{\alpha}$e (16)	**4**c$^{\alpha}$a^{H} (1)			
5	**5**	**5**c$^{\beta}$e (11)	**5**c$^{\beta}$a^{H} (8)	**5**c$^{\beta}$a^{Ph} (12)	57	1/1
		5c$^{\alpha}$e (26)				
6	**6**	**6**c$^{\beta}$e (10)	**6**c$^{\beta}$a^{H} (5)	**6**c$^{\beta}$a^{Ph} (9)	67	1/2
		6c$^{\alpha}$e (21)	**6**c$^{\alpha}$a^{H} (10)	**6**c$^{\alpha}$a^{Ph} (14)		
7	**7**		**8** (65)		65	1/-

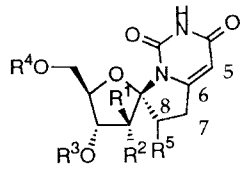
For example, **1**c$^{\beta}$e (or **1**c$^{\beta}$a^{Ph}) refers to the cyclized β-nucleoside with the 6,1'-etheno (or 6,1'-(1"-phenyl)ethano) bridge from **1**.



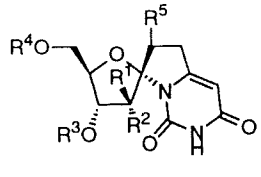
D-ribofuranosyl series: R^1=H, R^2=OR
1: R&R^3=isopropylidene, R^4=TBDMS
2: R=R^3=R^4=TBDMS
3: R=R^3=R^4=Ac

2'-deoxyuridine
4: R^1=R^2=H, R^3&R^4=TIPDS

D-arabinofuranosyl series: R^1=OR, R^2=H
5: R=H, R^3=R^4=TBDMS
6: R=R^3=R^4=Ac

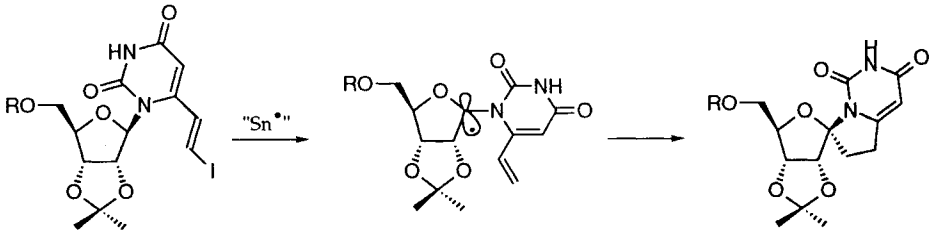


2c$^{\beta}$a^{H}, 3c$^{\beta}$a^{H}, 4c$^{\beta}$a^{H},
5c$^{\beta}$a^{H}, and 6c$^{\beta}$a^{H}: R^5=H
1c$^{\beta}$a^{Ph}, 2c$^{\beta}$a^{Ph}, 3c$^{\beta}$a^{Ph},
5c$^{\beta}$a^{Ph}, and 6c$^{\beta}$a^{Ph}: R^5=Ph

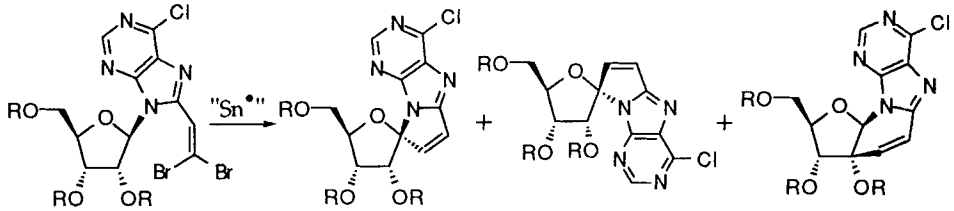


2c$^{\alpha}$a^{H}, 4c$^{\alpha}$a^{H},
and 6c$^{\alpha}$a^{H}: R^5=H
2c$^{\alpha}$a^{Ph}, 3c$^{\alpha}$a^{Ph},
and 6c$^{\alpha}$a^{Ph}: R^5=Ph

Scheme 1



Scheme 2



Scheme 3

6-Halogenovinyl uridine derivatives thus synthesized reacted under the radical conditions. In all cases a benzene solution containing 2.5 eq of Bu_3SnH and 0.5 eq of AIBN was added for over 3 h using a syringe pump to the refluxing benzene solution of each substrate. The cyclized products were isolated by HPLC; the results are summarized in Table 1. The spiro structures as well as the anomeric stereochemistry were unambiguously determined by the conversion of previously reported spiro nucleoside derivatives.[8] The structure of **3**$c\beta a^{Ph}$ with (8*S*)-configuration was confirmed by X-ray crystallographic analysis (data not shown).

The plausible reaction mechanism to produce 6,1'-ethenouridines is shown in Scheme 1. Since both dibromo and monoiodo olefins gave 6,1'-ethano uridine derivatives (Schemes 1 and 2), vinyl radical **A** may react with tin hydride or solvent C_6H_6 to afford a β-bromo- or β-bromo-β-phenylvinyl derivative[9] (equivalent to **7**), which reacts with a tin radical again to give 6,1'-ethanouridines, **2**$c\beta a^{H}$-**6**$c\beta a^{Ph}$ and **2**$c\alpha a^{H}$-**6**$c\alpha a^{Ph}$. Regarding the ratio of β-and α-isomers, at the transition state for the 5-*endo-trig* cyclization (C and E), it seems likely that the configuration and bulkiness of the C2'-substituent affect the α,β-orientation of the base moiety (entries 3, 4, and 6).

We next investigated a D-ribofuranosyl 6-chloropurine nucleoside. According to the same procedure as in the uridine case, the tris(TBDMS) protected derivative was led to 8-dibromovinyl compound **9** in 41% overall yield. The radical reaction afforded purine spiro nucleosides **10** and **11** in 18 and 14% yields (Scheme 3). Stereochemistry was determined

by taking the *N*3 anisotropic effect toward H2' for β-nucleoside[10] and H4' for α-nucleoside into consideration; in the case of **10**, the chemical shifts of H2' and H4' were 5.10 and 4.25 ppm, and for α-isomer **11**, they were 4.46 and 4.78 ppm, respectively. The β/α ratio was almost 1 to 1, and interestingly a 1,6-translocated product **12** was also obtained in 5% yield.[11] These results were different from the case of uridine derivatives, which could be explained by the distance between the vinyl radical and the anomeric hydrogen atom.

In conclusion, we have discovered a new radical cascade, involving the 1,5-translocation to produce nucleoside anomeric radicals and the subsequent 5-*endo-trig* cyclization process, which appears to be an efficient approach to both uracil and 6-chloropurine spiro nucleosides.

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8) (a) Kittaka, A.; Tanaka, H.; Odanaka, Y.; Ohnuki, K.; Yamaguchi, K.; Miyasaka, T. *J. Org. Chem.* **1994**, *59*, 3636-3641. (b) Kittaka, A.; Tsubaki, Y.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Nucleosides Nucleotides* **1996**, *15*, 97-107. During these studies on spiro nucleosides, we have found that the anisotropic effect of the C2 carbonyl group, which is always fixed in the *syn* region, toward the H2' and/or H4' could be taken into account for determination of the anomeric β/α configuration. For example, in β-nucleoside $3c^{\beta}e$ chemical shifts of H2' and H4' in $CDCl_3$ are 6.44 and 4.41 ppm, and those for appropriate α-nucleoside $3c^{\alpha}e$ are 5.53 and 5.23 ppm, respectively.

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