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## Nucleoside Anomeric Radicals via 1,5-Translocation: Facile Access to Anomeric Spiro Nucleosides

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Abstract: A method for generating anomeric radicals of nucleosides was developed based on a 1,5-translocation strategy. A vinyl radical derived from uracil nucleosides having a  $\beta$ , $\beta$ -dibromovinyl group at the C6 position undergoes the 1,5-translocation to form an anomeric radical, which then cyclizes with the resulting CH=CHBr group in a 5-endo-trig manner. The whole sequence has disclosed a facile access to anomeric spiro derivatives. A similar reaction of a 6-chloro-9-( $\beta$ -D-ribofuranosyl)purine derivative was also briefly examined. Copyright © 1996 Elsevier Science Ltd

The finding that anomeric radicals of carbohydrates prefer  $\alpha$ -facial reaction,<sup>1</sup>) irrespective of the C2configuration, has offered a great advantage over conventional ionic processes especially in constructing the  $\beta$ glycosidic linkage.<sup>2</sup>) These anomeric radicals were generated from carbohydrate derivatives having a suitable C1-radical source (halogen, SePh, *etc.*). Since the anomeric position of nucleosides is preoccupied by a base moiety, which sometimes acts as a leaving group, there has been no method available for the preparation of such C1'-substituted radical precursors. Therefore, different chemistry has to be developed for generating nucleoside anomeric radicals. Quite recently, we and Chatgilialoglu *et al.* independently reported the first example of a nucleoside anomeric radical in which a compound like 1 was used as a precursor.<sup>3</sup>) In this instance, initially formed C2'-radical undergoes 1,2-translocation with migration of the pivaloyl group to yield an anomeric radical. This communication describes an alternative approach for generating the anomeric radicals, which is based on the 1,5-translocation strategy.<sup>4</sup>)

Our whole idea is visualized in Scheme 1. Reaction of a tin radical with A having a structure  $CH=CX_2$  at the C6 position of pyrimidine nucleoside (or C8 of

purine nucleoside) gives a vinyl radical **B**, which then forms **C** through radical inversion. Provided that the 1,5-translocation of **C** takes place, a new method of generating an anomeric radical (**D** and **E**) can be developed. Although the subsequent intramolecular reaction leading to anomeric spiro nucleosides **H** and **I** is formally a disfavoured 5-*endo-trig* cyclization,<sup>5,6)</sup> there would be a good chance in this particular case to effect such a reaction pathway: conjugation of the CH=CHX group with an enone structure of uracil ring (or an



imine system of a purine base) would facilitate the formation of incipient radicals F and G which are stabilized by the resonance effect. It should be mentioned that the anomeric  $\beta$ -spironucleoside H serves as a conformationally fixed model of naturally occurring nucleosides.<sup>7</sup>

The  $\beta_i\beta_i$ -dibromovinyl group was selected as a vinyl radical source, and 2-8 were synthesized by way of lithiation<sup>8</sup>) (for introduction of a formyl group) followed by the Wittig reaction.<sup>9</sup>) Radical reaction of these compounds was carried out by adding a mixture of Bu<sub>3</sub>SnH (2.5 equiv) and AIBN (0.5 equiv) over 3 h by a syringe pump to a refluxing benzene solution of each substrate. The results are summarized in Table 1 with only cyclized products being listed. When 2 was used (entry 1), the spiro  $\beta$ -nucleoside 9 was isolated as the major product along with 10 and 11 after HPLC separation (hexane/EtOAc = 1/1-1/2). The 7,8-dihydro-8-phenyl derivative 10 was obtained as a single isomer. The C8-configuration of 10 was assumed to be *R*, based on its <sup>1</sup>H NMR spectrum: a high field shift of H-4' ( $\delta$  3.44 ppm), which is located above the phenyl ring, was observed (*cf.* H-4' of 9:  $\delta$  4.29 ppm). When this reaction was repeated using Bu<sub>3</sub>SnD, no deuterium incorporation was observed in 9. In entry 2, the major product 12 was accompanied with four 7,8-dihydro derivatives (13-16). Similar results are seen in entry 3 wherein 17-21 were obtained (compound 19 consists of (8*S*)- and (8*R*)-isomers). Since the glycosidic conformation of these products is fixed in the *syn*-range, their anomeric



2 R<sup>1</sup>& R<sup>2</sup> = isopropylidene, R<sup>3</sup> = TBDMS 3 R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = TBDMS 4 R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = Ac



 5 R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup>& R<sup>4</sup> = TIPDS\*
 1,1,3,3-tetraisopropyldisiloxan-1,3-diyi
 6 R<sup>1</sup> = OAc, R<sup>2</sup> = H, R<sup>3</sup> = R<sup>4</sup> = Ac

 $R^{1} = OH, R^{2} = H, R^{3} = R^{4} = TBDMS$ 





Table 1. Radical-Mediated Cyclization of 2-8.

Entry	Substrate	Cyclized product (% yield by HPLC isolation)	Combined yield (%)	Ratio of $\beta$ - and $\alpha$ -isomers ( $\beta / \alpha$ )
1	2	9 (40), 10 (3), 11 (3)	46	ca. 14/1
2	3	12 (50), 13 (3),14 (5), 15 (4), 16 (3)	65	ca. 8/1
3	4	17 (40), 18 (1), 19 (13), 20 (7), 21 (1)	62	ca. 7/1
4	5	22 (23), 23 (7), 24 (16), 25 (1)	47	ca. 2/1
5	6	26 (10), 27 (7), 28 (21), 29 (14)	52	1/2
6	7	30 (11), 31 (8), 32 (12), 33 (26)	57	<i>ca</i> . 1/1
7	8	34 (18), 35 (14), 36 (5)	37	<i>ca</i> . 1/1

stereochemistry is readily assignable based on an anisotropic effect of C2-carbonyl group to H-2' which is observable only in  $\beta$ -isomers (chemical shifts of H-2' in CDCl<sub>3</sub>  $\delta$  ppm: 17, 6.44; 18, 6.39; 19, 6.19 and 6.40; 20, 5.53; 21, 5.28).<sup>10</sup>

It is conceivable that ribofuranosyl anomeric radicals prefer  $\alpha$ -orientation as depicted in **D**, irrespective of the hydroxy protecting group, presumably due to unfavourable disposition of the bulky base moiety in **E** caused by the 2'-O-substituent.<sup>11</sup>) As shown in entry 4 by the formation of **22-25**, when the  $\alpha$ -face is less crowded, a significant decrease in the  $\beta/\alpha$  ratio was an actual issue.

As can be anticipated from steric hindrance of the 2'-O-substituent, proportion of  $\beta$ -isomers decreases when the arabinofuranosyl derivatives 6 and 7 were employed (entries 5 and 6). There may be a trend that increase in bulkiness of the 2'-O-protecting group results in decrease of the  $\beta/\alpha$  ratio.<sup>12</sup>) Finally, reaction of the ribofuranosylpurine derivative 8 was examined (entry 7). Although we have no clear explanation about the decreased  $\beta/\alpha$  ratio, the observed comparatively lower combined yield would be a reflection of the fact that the vinyl group is bound to a 5-membered imidazole ring and thus the distance between vinyl radical and H-1' is slightly longer than that of uracil cases. This assumption would be supported by the formation of 36 which is assumed to have resulted from 1,6-translocation<sup>13</sup>) of a vinyl radical.

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