Pergamon

Tetrahedron Letters, Vol. 37, No. 16, pp. 2801-2804, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00433-9

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

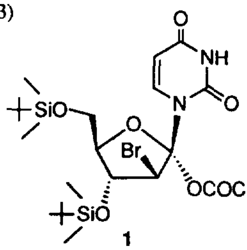
Atsushi Kittaka, Hiromichi Tanaka,* Naoki Yamada, and Tadashi Miyasaka

School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142

Key Words: anomeric radical; 1,5-translocation; nucleoside; 5-*endo-trig* cyclization; anomeric spiro structure

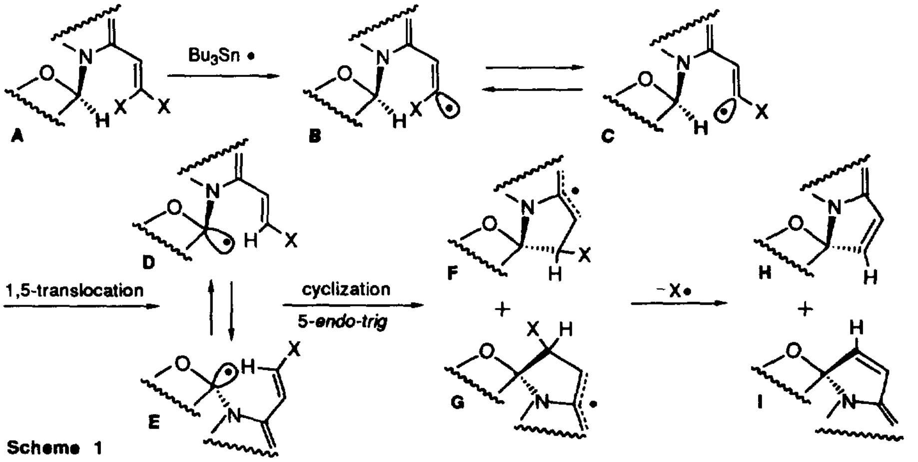
Abstract: *A method for generating anomeric radicals of nucleosides was developed based on a 1,5-translocation strategy. A vinyl radical derived from uracil nucleosides having a β,β-dibromovinyl group at the C6 position undergoes the 1,5-translocation to form an anomeric radical, which then cyclizes 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-(β-D-ribofuranosyl)purine derivative was also briefly examined.*

The finding that anomeric radicals of carbohydrates prefer α-facial reaction,1) irrespective of the C2-configuration, has offered a great advantage over conventional ionic processes especially in constructing the β-glycosidic linkage.2) 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.3) 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.4)



1

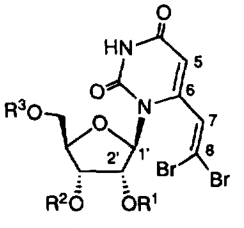
Our whole idea is visualized in Scheme 1. Reaction of a tin radical with **A** having a structure $CH=CX_2$ at the C6 position of pyrimidine nucleoside (or C8 of purine nucleoside) gives a vinyl radical **B**, which then forms **C** through radical inversion. Provided that the 1,5-translocation of **C** 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,5,6) 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



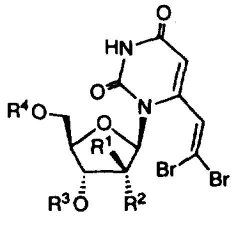
Scheme 1

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 β-spironucleoside H serves as a conformationally fixed model of naturally occurring nucleosides.[7]

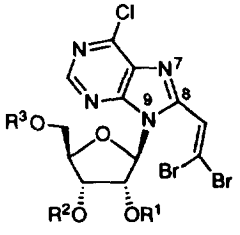
The β,β-dibromovinyl group was selected as a vinyl radical source, and **2**-**8** were synthesized by way of lithiation[8] (for introduction of a formyl group) followed by the Wittig reaction.[9] Radical reaction of these compounds was carried out by adding a mixture of Bu_3SnH (2.5 equiv) and AIBN (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 β-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 ^{1}H NMR spectrum: a high field shift of H-4' (δ 3.44 ppm), which is located above the phenyl ring, was observed (*cf.* H-4' of **9**: δ 4.29 ppm). When this reaction was repeated using Bu_3SnD, 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



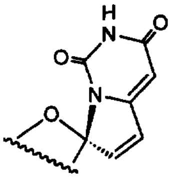
2 R^1& R^2 = isopropylidene, R^3 = TBDMS
3 R^1 = R^2 = R^3 = TBDMS
4 R^1 = R^2 = R^3 = Ac



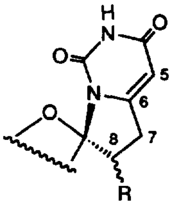
5 R^1 = R^2 = H, R^3& R^4 = TIPDS*
* 1,1,3,3-tetraisopropyldisiloxan-1,3-diyl
6 R^1 = OAc, R^2 = H, R^3 = R^4 = Ac
7 R^1 = OH, R^2 = H, R^3 = R^4 = TBDMS



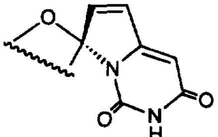
8 R^1 = R^2 = R^3 = TBDMS



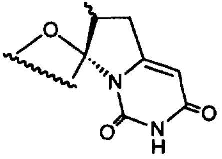
9 sugar = 5-*O*-TBDMS-2,3-*O*-isopropylidene-D-ribofuranosyl
12 sugar = 2,3,5-tris-*O*-TBDMS-D-ribofuranosyl
17 sugar = 2,3,5-tri-*O*-acetyl-D-ribofuranosyl
22 sugar = 2-deoxy-3,5-*O*-TIPDS-D-ribofuranosyl
26 sugar = 2,3,5-tri-*O*-acetyl-D-arabinofuranosyl
30 sugar = 3,5-bis-*O*-TBDMS-D-arabinofuranosyl



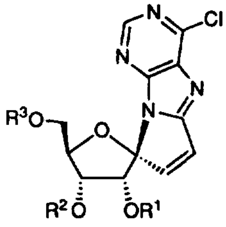
10 sugar = 5-*O*-TBDMS-2,3-*O*-isopropylidene-D-ribofuranosyl, R = Ph
13 sugar = 2,3,5-tris-*O*-TBDMS-D-ribofuranosyl, R = H
14 sugar = 2,3,5-tris-*O*-TBDMS-D-ribofuranosyl, R = Ph
18 sugar = 2,3,5-tri-*O*-acetyl-D-ribofuranosyl, R = H
19 sugar = 2,3,5-tri-*O*-acetyl-D-ribofuranosyl, R = Ph
23 sugar = 2-deoxy-3,5-*O*-TIPDS-D-ribofuranosyl, R = H
27 sugar = 2,3,5-tri-*O*-acetyl-D-arabinofuranosyl, R = Ph
31 sugar = 3,5-bis-*O*-TBDMS-D-arabinofuranosyl, R = H
32 sugar = 3,5-bis-*O*-TBDMS-D-arabinofuranosyl, R = Ph



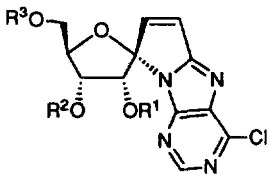
11 sugar = 5-*O*-TBDMS-2,3-*O*-isopropylidene-D-ribofuranosyl
20 sugar = 2,3,5-tri-*O*-acetyl-D-ribofuranosyl
24 sugar = 2-deoxy-3,5-*O*-TIPDS-D-ribofuranosyl
28 sugar = 2,3,5-tri-*O*-acetyl-D-arabinofuranosyl
33 sugar = 3,5-bis-*O*-TBDMS-D-arabinofuranosyl



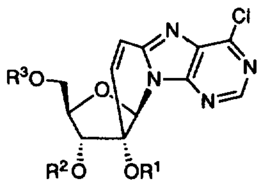
15 sugar = 2,3,5-tris-*O*-TBDMS-D-ribofuranosyl, R = H
16 sugar = 2,3,5-tris-*O*-TBDMS-D-ribofuranosyl, R = Ph
21 sugar = 2,3,5-tri-*O*-acetyl-D-ribofuranosyl, R = Ph
25 sugar = 2-deoxy-3,5-*O*-TIPDS-D-ribofuranosyl, R = H
29 sugar = 2,3,5-tri-*O*-acetyl-D-arabinofuranosyl, R = Ph



34 $R^1 = R^2 = R^3 = $ TBDMS



35 $R^1 = R^2 = R^3 = $ TBDMS



36 $R^1 = R^2 = R^3 = $ TBDMS

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

Entry	Substrate	Cyclized product (% yield by HPLC isolation)	Combined yield (%)	Ratio of β- and α-isomers (β / α)
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	*ca.* 1 / 1
7	**8**	**34** (18), **35** (14), **36** (5)	37	*ca.* 1 / 1

stereochemistry is readily assignable based on an anisotropic effect of C2-carbonyl group to H-2' which is observable only in β-isomers (chemical shifts of H-2' in $CDCl_3$ δ ppm: **17**, 6.44; **18**, 6.39; **19**, 6.19 and 6.40; **20**, 5.53; **21**, 5.28).[10)]

It is conceivable that ribofuranosyl anomeric radicals prefer α-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.[11)] As shown in entry 4 by the formation of **22**-**25**, when the α-face is less crowded, a significant decrease in the β/α ratio was an actual issue.

As can be anticipated from steric hindrance of the 2'-*O*-substituent, proportion of β-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 β/α ratio.[12)] Finally, reaction of the ribofuranosylpurine derivative **8** was examined (entry 7). Although we have no clear explanation about the decreased β/α 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(13) of a vinyl radical.

Acknowledgement. The authors would like to thank Dr. Martin Slater (Glaxo-Wellcome Research & Development, U. K.) for proof reading of this manuscript.

REFERENCES AND NOTES

1) a) Giese, B.; Dupuis, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 622. b) Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984**, *25*, 1349. c) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944.
2) a) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716. b) Crich, D.; Hermann, F. *Tetrahedron Lett.* **1993**, *34*, 3385.
3) a) Haraguchi, K.; Matsumoto, K.; Itoh, Y.; Tanaka, H.; Miyasaka, T. *Nucleic Acids Symposium Series* **1994**, *31*, 29. b) Itoh, Y.; Haraguchi, K.; Tanaka, H.; Matsumoto, K.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1995**, *36*, 3867. c) Gimisis, T.; Ialongo, G.; Zamboni, M.; Chatgilialoglu, C. *Tetrahedron Lett.* **1995**, *36*, 6781.
4) For 1,5-translocation of radicals: Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051 and references cited therein.
5) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
6) For a recent example of 5-*endo-trig* cyclization: Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Am. Chem. Soc.* **1995**, *117*, 9653.
7) Yoshimura, Y.; Otter, B. A.; Ueda, T.; Matsuda, A. *Chem. Pharm. Bull.* **1992**, *40*, 1761.
8) a) Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron* **1982**, *38*, 2635. b) Tanaka, H.; Uchida, Y.; Shinozaki, M.; Hayakawa, H.; Matsuda, A.; Miyasaka, T. *Chem. Pharm. Bull.* **1983**, *31*, 787. c) Shimizu, M.; Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron Lett.* **1990**, *31*, 1295.
9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
10) The structures of several products (**9**, **12**, **17**, **22**, **23**, **24**, **30**, and **31**) were also confirmed by conversion to reported derivatives: a) Kittaka, A.; Tanaka, H.; Odanaka, Y.; Ohnuki, K.; Yamaguchi, K.; Miyasaka, T. *J. Org. Chem.* **1994**, *59*, 3636. b) Kittaka, A.; Tsubaki, Y.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Nucleosides Nucleotides* **1996**, *15*, in press.
11) In the following report, which describes the reaction of a psicofuranos-2-yl radical with Bu_3SnH, ratio of the products (α- and β-anomers) was explained on the basis of both stereoelectronic and steric effects: Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210.
12) Attempted preparation of 1-(2,3,5-tris-*O*-TBDMS-β-D-arabinofuranosyl)-6-(2,2-dibromovinyl)uracil failed (TBDMSCl/imidazole/DMF), giving **7** as the sole product.
13) For a recent example of radical 1,6-translocation: Yamazaki, N.; Eichenberger, E.; Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6623.

(*Received in Japan* 25 *January* 1996; *revised* 27 *February* 1996; *accepted* 29 *February* 1996)