A Novel Ring-Enlargement Reaction of (3-Oxa-2-silacyclopentyl)methyl Radicals into 4-Oxa-3-silacyclohexyl Radicals. Stereoselective Introduction of a Hydroxyethyl Group *via* Unusual 6-*Endo*-Cyclization Products Derived from 3-Oxa-4-silahexenyl Radicals and Its Application to the Synthesis of a 4′-α-Branched Nucleoside[1]

Satoshi Shuto,* Makiko Kanazaki, Satoshi Ichikawa, and Akira Matsuda*

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan

Received May 15, 1997

Radical cyclization is a highly versatile method for forming C−C bonds.[2] There has been growing interest in the use of a silicon-containing tether for intramolecular radical cyclization reactions,[3] which are very useful for the regio- and stereoselective introduction of a carbon substituent based on a temporary silicon connection. We report here an efficient method for introducing a 2-hydroxyethyl group *via* a radical cyclization reaction with a silicon-containing tether. During this study, we identified a novel ring-enlargement reaction of (3-oxa-2-silacyclopentyl)methyl radicals into 4-oxa-3-silacyclohexyl radicals.

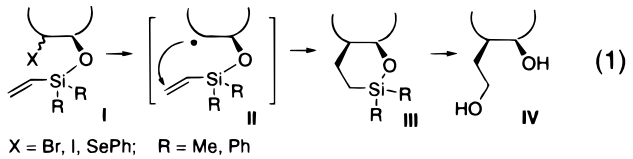
Over the past few years, we have studied antisense oligonucleotides with modified nucleoside units.[4] This work has required a 2′-deoxy-4′-α-(2-hydroxyethyl)adenosine derivative, such as **1** (eq 4), as a novel, modified nucleoside unit to be incorporated into oligonucleotides.

Table 1. Synthesis of 6 and 7 *via* Radical Cyclization Reaction of 3a or 3b[a]

entry	substrate	method[b]	temp, °C	% yield (**6** + **7**)	ratio[d] (**6**:**7**)
1	**3a**	A	80	71[c]	6:1
2	**3a**	B	80	72[d]	15:1
3	**3a**	C	26	91[d]	1:11
4	**3a**	D	80	84[d]	1:17
5	**3b**	A	80	70[d]	2.8:1
6	**3b**	C	26	72[d]	1:23
7	**3b**	D	80	81[d]	1:31

[a] Compounds **6** and **7** were obtained after treating the crude reaction mixture of the radical reaction under Tamao oxidation conditions. [b] A: To a solution of substrate (0.01 M) in benzene was added a mixture of Bu_3SnH (1.1 equiv) and AIBN (0.6 equiv) in benzene slowly over 4 h. B: To a solution of substrate (0.002 M) in benzene was added a mixture of Bu_3SnH (1.1 equiv) and AIBN (0.6 equiv) in benzene slowly over 7 h. C: To a solution of substrate (0.01 M) in benzene were simultaneously added a solution of Bu_3SnH (1.1 equiv) in benzene and a solution of Et_3B (0.6 equiv) in benzene over 4 h. D: To a mixture of substrate (0.01M) and Bu_3SnH (3.0 equiv) in benzene was added AIBN (0.6 equiv) in benzene over 2 h. [c] Isolated yield. [d] Determined by HPLC.

Although several methods for preparing 4′-branched nucleosides have been reported,[5] these methods are not stereoselective and only limited types of carbon substituents can be introduced. Therefore, we explored an efficient method for introducing a 2-hydroxyethyl group stereoselectively *via* a radical cyclization reaction using a silicon-containing tether bearing a radical acceptor. Our synthetic plan is outlined in eq 1. Halohydrins or α-(phenylseleno)alkanols are converted to the corresponding vinylsilyl ethers (**I**). If radical intermediate **II**, generated from **I**, is cyclized to 6-*endo*-product **III**, stereoselective introduction of a 2-hydroxyethyl group at the *β*-position of the hydroxyl can be achieved, after an oxidative ring-cleavage reaction.[6]



(1)

We investigated the reaction with the diphenyl- and dimethylvinylsilyl ethers **3a** and **3b**, prepared from commercially available (±)-*trans*-2-bromo-1-indanol (**2**).[7] Radical reactions were performed with Bu_3SnH and either AIBN or Et_3B in benzene, followed by Tamao oxidation,[6] to give a mixture of diols **6** and **7**,[8] and the results are summarized in Table 1.[9] First, a mixture of Bu_3SnH (1.1 equiv) and AIBN in benzene was added slowly over 4 h to a solution of **3a** in benzene (0.01 M) under reflux, to give the desired 2-hydroxyethyl derivative **6** *via* 6-*endo* cyclization product **4a**, as a major product, along with **7** *via* 5-*exo* cyclization product **5a** (entry 1; 71%, **6**:**7** = 6:1). The selectivity for the formation of **6** increased significantly when a lower concentration of Bu_3SnH was employed (entry 2; 72%, **6**:**7** = 15:1). Interestingly, when the reaction was performed at room temperature, the regioselectivity was almost completely reversed to give **7** preferentially (entry 3; 91%, **6**:**7** =

(1) This paper constitutes Part 165 of Nucleosides and Nucleotides. Part 164: Nomura, Y.; Ueno, Y.; Matsuda A. *Nucleic Acids Res.* **1997**, in press.

(2) (a) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301. (b) Motherwell, W. B.; Crich, D. *Free-Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 715−831. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (e) Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385. (f) Laird, E. E.; Jorgensen, W. L. *J. Org. Chem.* **1990**, *55*, 9.

(3) (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Stork, G; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (c) Magnol, E.; Malacria, M. *Tetrahedron Lett.* **1986**, *27*, 2255. (d) Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098. (e) Walkup, R. D.; Kane, R. R.; Obeyesekere, N. U. *Tetrahedron Lett.* **1990**, *31*, 1531. (f) Myers, A. G.; Gin, D. Y.; Widdowson, K. L. *J. Am. Chem. Soc.* **1991**, *113*, 9661. (g) Hutchinson, J. H.; Daynard, T. S.; Gillard, J. W. *Tetraheron Lett.* **1991**, *32*, 573. (h) Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 8175. (i) Koot, W.-J.; van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetraherdon Lett.* **1991**, *32*, 401. (j) Stork, G.; Suh, H. S. Kim. G. *J. Am. Chem. Soc.* **1991**, *113*, 7054. (k) Zhen, X.; Rong, J.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 5255. (l) Martinez-Grau, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 8332.

(4) (a) Ono, A.; Dan, A.; Matsuda, A. *Bioconjugate Chem.* **1993**, *4*, 499. (b) Dan, A.; Yoshimura, Y.; Ono, A.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1992**, *3*, 615. (c) Ono, A.; Haginoya, N.; Kiyokawa, M.; Minakawa, N.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1993**, *4*, 361. (d) Nara, H.; Ono, A.; Matsuda, A. *Bioconjugate Chem.* **1995**, *6*, 54.

(5) (a) Secrist, J. A., III; Winter, W. J., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2554. (b) Youssefyeh, R. D.; Verheyden, P. H.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 1301. (c) O-Yang, C.; Wu, H. Y.; Frase-Smith, W. B.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 37. (d) Johnson, C. R.; Esker, J. L.; Van Zandt, M. C. *J. Org. Chem.* **1994**, *59*, 5854. (e) Haraguchi, K.; Tanaka, H.; Itoh, Y.; Yamaguchi, K.; Miyasaka, T. *J. Org. Chem.* **1996**, *61*, 851. (f) Waga, T.; Ohrui, H.; Meguro, H. *Nucleosides Nucleotides* **1996**, *15*, 287. (g) Marx, A.; Erdmann, P.; Senn, M.; Korner, S.; Jungo, T.; Petretta, M.; Imwinkelried, P.; Dussy, A.; Kulicke, K. J.; Macko, L.; Zehnder, M.; Giese, B. *Helv. Chim. Acta* **1996**, *79*, 1980.

(6) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2121.

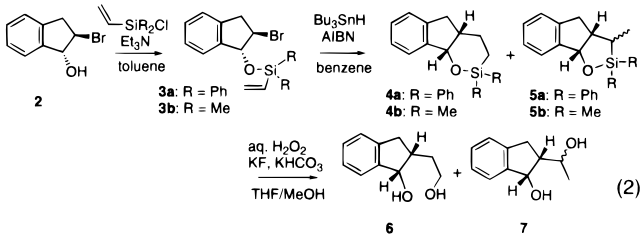
(7) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279.

(8) Compound **7** was obtained as an epimeric mixture of the 2-(1-hydroxyethyl) moiety.

(9) Isolation of the radical reaction products **4** and **5** was attempted, but they were not obtained in a pure form due to contamination with compounds derived from Bu_3SnH.

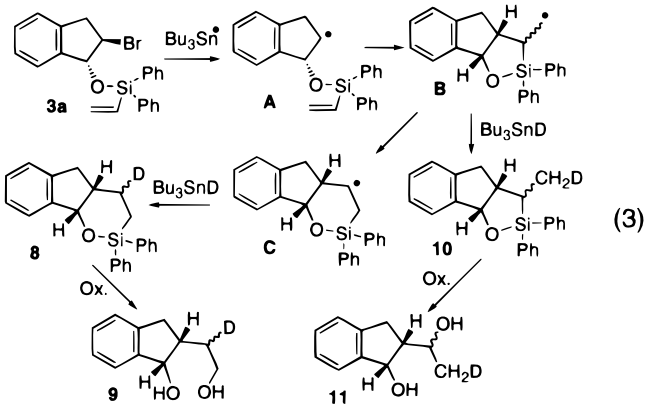
S0022-3263(97)00867-0 CCC: $14.00

1:11). Furthermore, the radical reaction of **3a** in the presence of excess of Bu_3SnH at 80 °C also gave **7** with high selectivity (entry 4; 84%, **6**:**7** = 1:17). Similar results were obtained when dimethylvinylsilyl derivative **3b** was used as a substrate (entry 5−7). These results suggest that the formation of the 6-*endo* product **4** may not be kinetic but thermodynamic, since the ratio of the *endo* and *exo* products should be independent of the concentration of Bu_3SnH if the reaction is controlled kinetically. These results conflict with well-known findings (Baldwin−Beckwith rule) that the cyclization reactions of hexenyl radicals and their equivalents are controlled kinetically to give 5-*exo* cyclization products preferably over 6-*endo* cyclization products.[10] Two pathways may explain the selective formation of 6-*endo* cyclization product **4**: (1) the cyclization reaction is reversible, or (2) 5-*exo* cyclized radical **B**, which is initially formed, is rearranged to give **C** (eq 3). However, it is unlikely that the cyclization is reversible, since reversible radical cyclizations of hexenyl radical or their equivalents have been observed only when radical centers are attached to radical-stabilizing groups, such as carbonyl groups.[11]



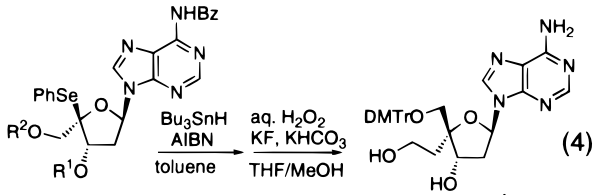
(2)

To examine the reaction mechanism, the reaction was performed with Bu_3SnD under the same conditions as for entry 1 (at 80 °C). After Tamao oxidation, it could be shown by ^1H NMR spectrum that in product **9** only the protons β to the primary hydroxyl were exclusively replaced by deuterium.[12] On the other hand, product **11**, which was produced *via* a radical reaction as shown for entry 3 (at 26 °C), was deuterated exclusively at the methyl group.[12] These results suggest that this cyclization would be irreversible and that the 5-*exo* cyclized radical **B** would be formed first and is mainly trapped when the concentration of $Bu_3SnH(D)$ is high enough or the reaction is done at room temperature; under a low $Bu_3SnH(D)$ concentration at a higher reaction temperature, radical **B** is rearranged into the ring-enlarged radical **C**,[13] which is then trapped with $Bu_3SnH(D)$ (eq 3). To the best of our knowledge, such a ring-enlarging 1,2-radical rearrangement of β-silyl carbon-centered radicals has not been previously reported.[14−17]



(3)

This reaction was applied to the stereoselective synthesis of our target nucleoside unit **1**. A known 4′-phenylseleno derivative of 2′-deoxyadenosine **12**[18] was converted to the 3′-*O*-vinylsilyl derivative **13**. When **13** was treated under the conditions similar to those for entry 2 in Table 1, 4′-α-hydroxyethyl nucleoside **1**[19] was obtained successfully in 72% yield. Thus, this radical reaction with a vinylsily tether may be applicable to a variety of halohydrins and related compounds for introducing a hydroxyethyl group at the β-position of the hydroxyl with a *cis*-configuration.



(4)

Acknowledgment. We are grateful to Dr. Tamotsu Yamamoto (Asahi Chemical Industry) for mass spectra measurement.

Supporting Information Available: Experimental details, characterization data for compounds, and ^1H NMR and mass spectral charts of **6**, **7**, **9**, and **11** (17 pages).

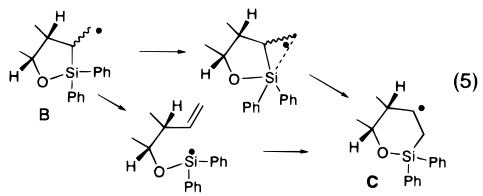
JO970867O

(10) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (c) Beckwith, A. L. J. Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (d) Spellmeyer, S. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(11) (a) Julia, M. *Pure Appl. Chem.* **1967**, *15*, 167. (b) Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust, J. Chem.* **1972**, *25*, 1081. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(12) The deuterium contents were also assayed by mass spectroscopy: **9**, 99.9%; **11**, 97.9%.

(13) Although the reaction pathway of the radical **B** to **C** is unclear, two intermediates may be postulated: as shown below, (1) a fragmentation intermediate and (2) an intermediate assisted by a bridging interaction between silicon and the unpaired electron of the β-silyl radical [this kind of bridging interaction has been suggested through both kinetic studies (Auner, N.; Walsh, R.; Westrup, J. *J. Chem. Soc., Chem. Commun.* **1986**, 207−208), and MO calculation (Pitt, C. G. *J. Organomet. Chem.* **1973**, *61*, 49.)].



(5)

(14) Known 1,2- rearrangement of carbon-centered radicals: (a) Wilt, J. W.; Pawlikowski, W. W., Jr. *J. Org. Chem.* **1975**, *40*, 3641. (b) Goermer, R. N.; Cote, P. N., Jr.; Vittimberga, B. M. *J. Org. Chem.* **1977**, *42*, 19. (c) Stork, G.; Mook Jr., R. *J. Am. Chem. Soc.* **1987**, *109*, 2829. (d) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565. (e) Dowd, P.; Ahang, W. *Chem. Rev.* **1993**, *93*, 2091.

(15) A gas phase 1,2-migration of trimethylsilyl group in an aromatic β-silyl biradical has been reported: Johnson, G. C.; Stofko, J. J., Jr.; Lockhart, T. P.; Brown, D. W.; Bergman, R. G. *J. Org. Chem.* **1979**, *44*, 4215.

(16) Carbon to oxygen or to nitrogen 1,2-silicon migrations in oxygen- or nitrogen-centered β-silyl radicals have been known: (a) Harris, J. M.; MacInnes, I.; Walton, J. C.; Maillard, B. *J. Organometal. Chem.* **1991**, *403*, C25. (b) Tsai, Y.-M.; Cherng, C.-D. *Tetrahedron Lett.* **1991**, *32*, 3515.

(17) An intramolecular homolytic substituent of δ-silyl carbon-centered radicals at the silicon in liquid phase has been reported: Kulicle, K. J.; Chatgiliatoglu, C.; Kopping, B.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 935.

(18) Giese, B.; Erdmann, P.; Schafer, T.; Schwitter, U. *Synthesis* **1994**, 1310.

(19) The stereochemistry of **1** was determined by NOE experiments.