Stereo- and Regioselective Introduction of 1- or 2-Hydroxyethyl Group via Intramolecular Radical Cyclization Reaction with a Novel Silicon-Containing Tether. An Efficient Synthesis of 4′α-Branched 2′-Deoxyadenosines[1]

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An efficient method for the synthesis of 4′α-branched 2′-deoxyadenosines starting from 2′-deoxyadenosine has been developed utilizing a novel radical cyclization reaction with a silicon tether. The radical reaction of 4′*β*-(phenylseleno)-3′-*O*-diphenylvinylsilyl adeninenucleoside derivative **17** with Bu_3SnH and AIBN, followed by Tamao oxidation, gave selectively either the 4′α-(2-hydroxyethyl) derivative **21** or 4′α-(1-hydroxyethyl) derivative **19**, depending on the reaction conditions. With a lower Bu_3SnH concentration, the reaction gave the 4′α-(2-hydroxyethyl) derivative **21**, via a 6-*endo*-radical cyclized product **20**, as the sole product in 72% yield. The reaction of **17** in the presence of excess Bu_3SnH gave **19** quantitatively, via a 5-*exo*-cyclized product **18**, as a diastereomeric mixture. The reaction mechanism was examined using Bu_3SnD. The results demonstrated that the 5-*exo* cyclized (3-oxa-2-silacyclopentyl)methyl radical (**C**) was formed initially which was trapped when the concentration of Bu_3SnH(D) was high enough. With lower concentrations of Bu_3SnH(D), radical **C** rearranged into the ring-enlarged 4-oxa-3-silacyclohexyl radical (**D**) which was then trapped with Bu_3SnH(D) to give *endo*-cyclized product **F**.

Introduction

Considerable attention has been focused on branched-chain sugar nucleosides because of their biological importance.[2−10] We have developed stereoselective synthetic methods for 2′- and 3′-branched-chain sugar nucleosides and have prepared a variety of 2′- and 3′-modified nucleoside analogues.[5,6] We found that 1-(2-deoxy-2-methylene-*β*-D-*erythro*-pentofuranosyl)cytosine (DMDC, **1**),[5s−v] 1-(2-*C*-cyano-2-deoxy-*β*-D-*arabino*-pentofuranosyl)cytosine (CNDAC, **2**),[5w−z] and 1-(3-*C*-ethynyl-*β*-D-*ribo*-pentofuranosyl)cytosine (ECyd, **3**)[6b−d] were potent antitumor nucleosides which significantly inhibited the growth of various human solid tumor cells both in vitro and in vivo.

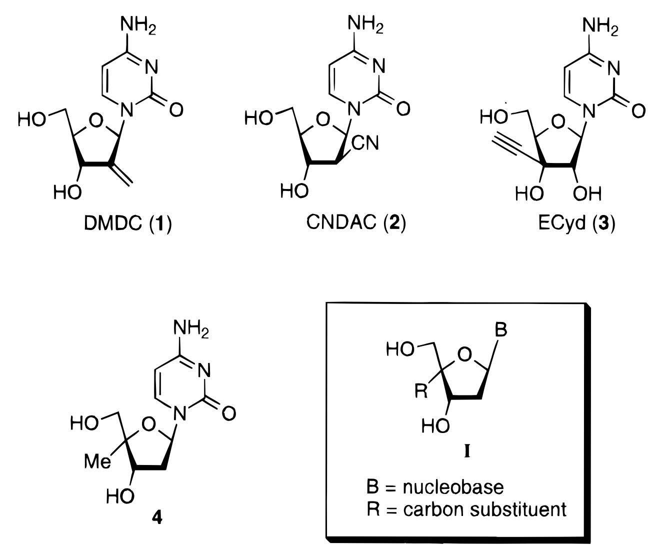

Figure 1.

However, only a few examples of 4′-branched nucleosides have been reported,[7−10] and their biological activities have not yet been investigated in a systematic manner. This may be because efficient synthetic methods for 4′-branched nucleosides had not been developed.[7] Recently, Ohrui and co-workers synthesized several 4′α-

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branched nucleoside derivatives and found that 4′α-*C*-methyl-2′-deoxycytidine (**4**) has very strong growth inhibitory activity against leukemic cells.[8] They synthesized **4** by deoxygenating the 2′-position of the corresponding 4′-branched ribonucleoside analogue, which was prepared via a glycosylation reaction of the corresponding 4α-*C*-methyl sugar synthesized from D-glucose.[8] As a result of the very long reaction steps, the overall yield was low. Consequently, the antileukemic activity of **4** was investigated in vitro only. To examine the biological effects of various 4′-branched nucleosides, the development of more straightforward synthetic methods is needed. In this paper, we describe an efficient synthetic method for 4′α-branched-2′-deoxyadenosines, using an intramolecular radical cyclization reaction with a novel silicon-containing tether[11] as a key step.

Radical cyclization is a highly versatile method for forming C−C bonds.[12] There has been growing interest in the use of silicon-containing tethers for intramolecular radical cyclization reactions.[13] These are very useful for regio- and stereoselective introduction of a carbon substituent based on a temporary silicon connection. Recently, we developed a regio- and stereoselective method for introducing 1-hydroxyethyl or 2-hydroxyethyl groups at the β-position of a hydroxyl group in halohydrins or α-(phenylseleno)alkanols using an intramolecular radical cyclization reaction with dimethyl- or diphenylvinylsilyl group as a radical acceptor tether (Scheme 1).[11] The selective introduction of both a 1-hydroxyethyl and a 2-hydroxyethyl groups can be achieved via a 5-*exo*-cyclization intermediate (**E**) or a 6-*endo*-cyclization intermediate (**F**), respectively, after oxidative ring-cleavage by treating the cyclization products under Tamao oxidation conditions,[14] as shown in Scheme 1. With a 2-bromoindanol derivative as a substrate, we also demon-

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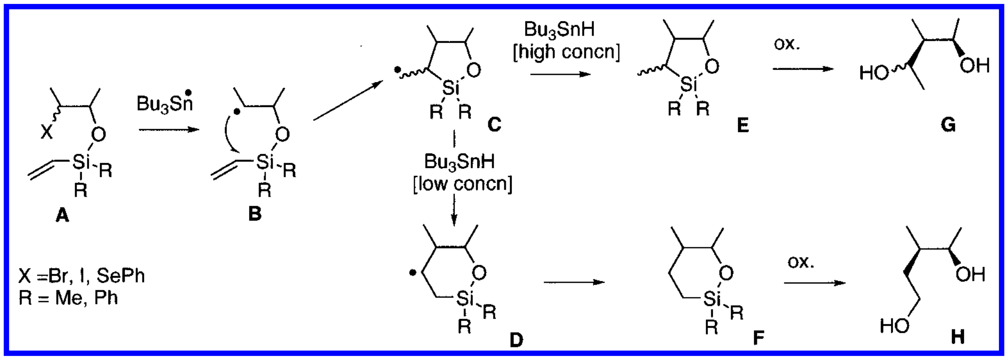
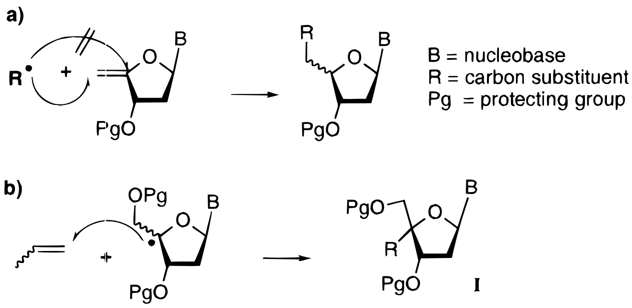
Scheme 1



Scheme 2



strated that the radical cyclization was irreversible, and that kinetically favored 5-*exo*-cyclized radical **C**, formed from radical **B**, was trapped when the concentration of Bu_3SnH was high enough to give **E**. At lower concentrations of Bu_3SnH and higher reaction temperatures, radical **C** rearranged into the more stable ring-enlarged 4-oxa-3-silacyclohexyl radical **D** which was then trapped with Bu_3SnH to give **F**.[11]

Tanaka and co-workers reported that intermolecular carbon radical addition reactions on 4′,5′-dehydro nucleoside derivatives did not give 4′-addition products but gave 5′-addition products exclusively as a diastereomeric mixture at the 4′-position (Scheme 2a).[7c] This result suggested generation of a radical at the 4′-position of nucleosides which subsequently added to an olefinic bond thereby introducing carbon substituents at the 4′-position (Scheme 2b). Therefore, we planned to explore a new method for producing 4′α-branched nucleosides via intramolecular radical cyclization reactions of the diphenylvinylsilyl group as a radical acceptor tether. Our synthetic strategy is outlined in Scheme 3.[15] If the radical cyclization reaction with 4′-(phenylseleno)-2′-deoxynucleoside derivatives **II** or **III** proceeds as we expect, these would give the corresponding ring-closure products, **IV** and/or **V**, or **VI** and/or **VII**, respectively. Subsequent oxidative ring-cleavage reactions of the products would give the desired 4′α-branched nucleoside analogues **VIII** and/or **IX**.

Results and Discussion

We used 2′-deoxyadenosine as a starting material, since a method for introducing a phenylseleno group at the 4′-position of 3′-*O*-acetyl-N^6,N^6-dibenzoyl-2′-deoxyadenosine has been developed by Giese and co-workers.[16] We used N^6,N^6,3′-*O*-tribenzoyl-2′-deoxyadenosine (**5**) as a protected nucleoside for further derivatization because of its easy preparation from 2′-deoxyadenosine. Thus, **5** was treated under Swern oxidation conditions followed by treatment with PhSeCl and Et_3N in CH_2Cl_2,[16] which afforded the 4′-(phenylseleno) derivative **6** in 72% yield as a diastereomeric mixture at the 4′-position. When the formyl group was reduced with Bu_4NBH_3CN in THF,[16] the resulting diastereomeric mixture was successfully separated by silica gel column chromatography to give the 4′β-(phenylseleno) derivative **7** and 4′α-(phenylseleno) derivative **8** in yields of 72% and 21%, respectively (Scheme 4). The 4′β-(phenylseleno) derivative **7** was treated with diphenylvinylchlorosilane and Et_3N in the presence of DMAP in toluene[17] to give vinylsilyl derivative **9**, a substrate for the radical reaction, in 84% yield.

A solution of 1.5 equiv of Bu_3SnH and AIBN in benzene was added slowly over 8 h, using a syringe-pump, to a solution of **9** in benzene at 80 °C. The resulting crude product was subsequently treated under Tamao oxidation conditions, to give cyclonucleoside **11** in 35% yield as the major product. The structure of **11**, including stereochemistry, was confirmed by HMBC and NOESY spectra after converting it into the corresponding triacetate **12**. Although the radical reaction of **9** was investigated under various conditions, the desired 4′-branched nucleosides were not obtained. This result suggests a tandem radical cyclization mechanism, shown in Scheme 5: a 5-*exo*-cyclized radical intermediate was first produced from the 4′-radical which did not react with Bu_3SnH to give the desired **13** or **14** but rapidly added to the 8-position of the adenine moiety. The 8-hydrogen was subsequently abstracted by a phenylseleno radical to afford **10**. Similar formations of cyclo-adenine nucleosides via intramolecular radical additions at the adenine 8-position have been previously reported by our laboratory (Scheme 6).[18]

We subsequently introduced the silicon tether at the 3′-hydroxyl group of the 4′-(phenylseleno) adeninenucleoside derivative and investigated its radical reactions (Scheme 7). The primary hydroxyl group of 4′β-(phenylseleno) nucleoside **15**, prepared from **7**, was selectively protected by a dimethoxytrityl (DMTr) group to give **16** quantitatively. Treatment of **16** with diphenylvinylchlorosilane under similar conditions to those described above gave **17**, a substrate for the radical reaction, in 93% yield.

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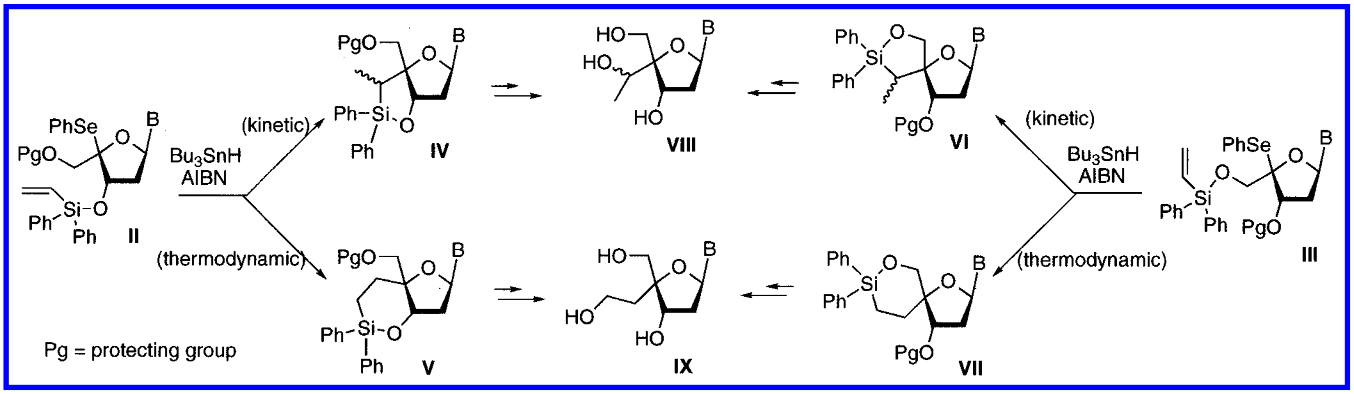
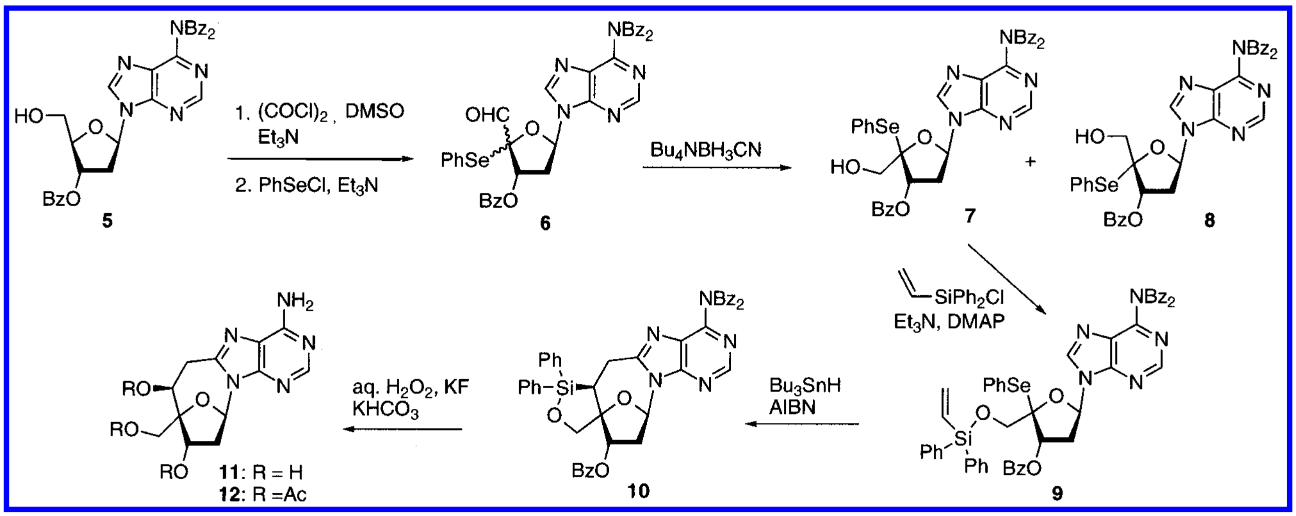
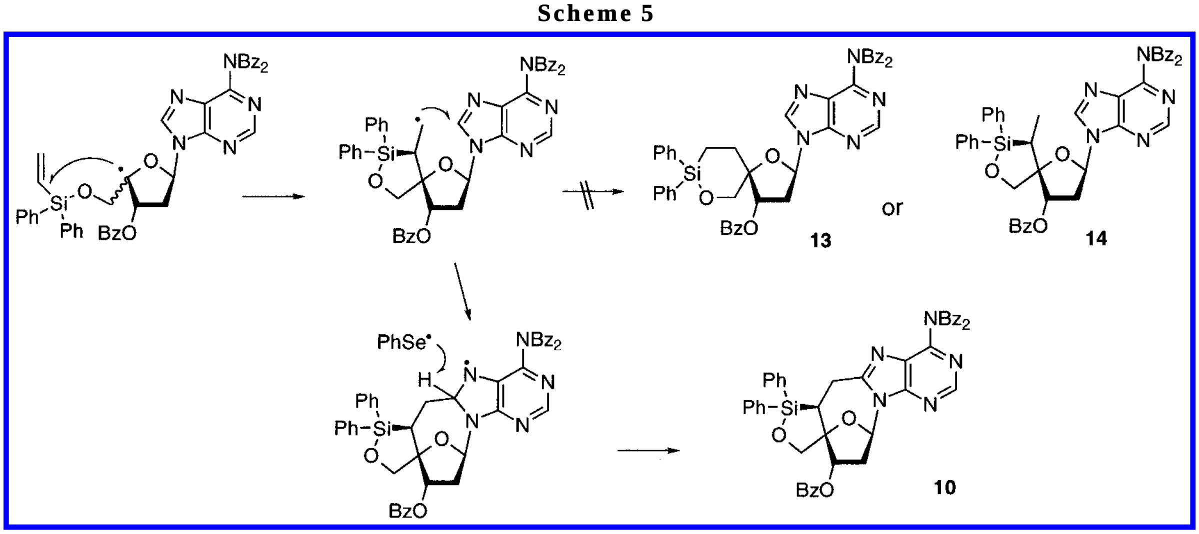
Scheme 3



Scheme 4

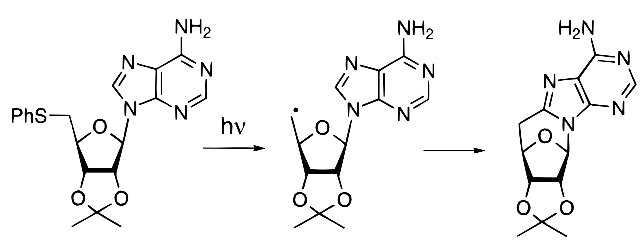


Scheme 5



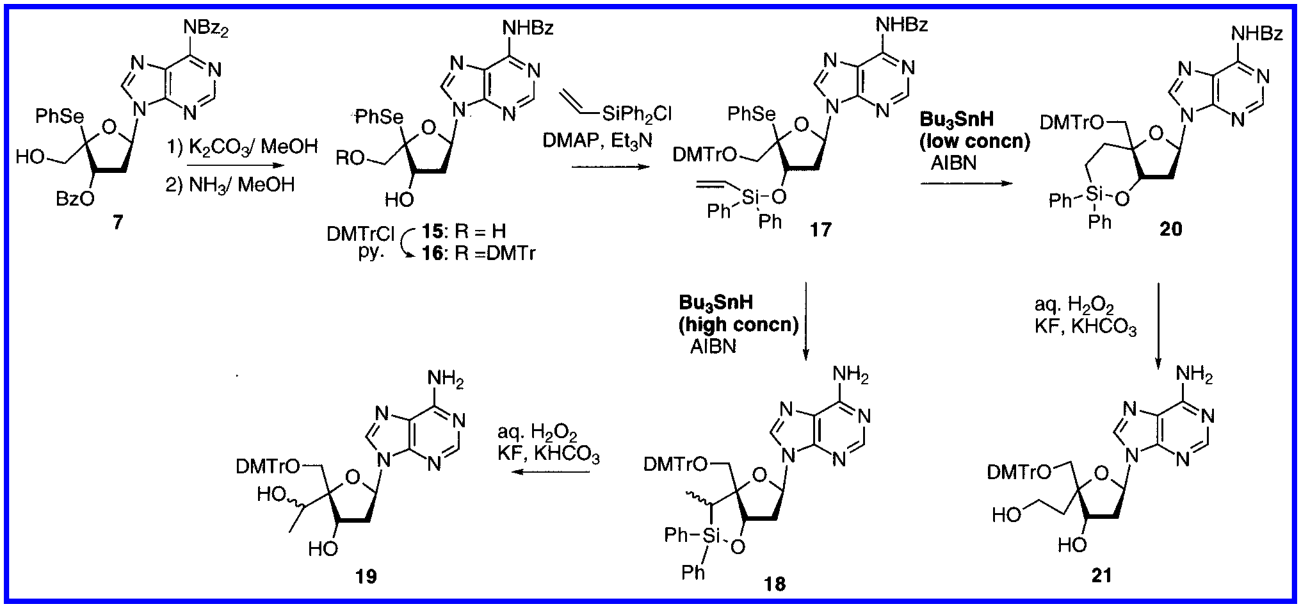
Treatment of **17** with 3.0 equiv of Bu_3SnH at 80 °C in benzene in the presence of AIBN, followed by Tamao oxidation gave a diastereomeric mixture of 4′α-(1-hydroxyethyl) derivatives **19** (the ratio of major and minor diastereomers was 2:1 from the ^1H NMR spectrum) which were derived from a 5-*exo*-cyclized product **18**, in almost quantitative yield. When a solution of 1.1 equiv of Bu_3SnH and AIBN (0.17 equiv) in toluene was added slowly over 4 h to a solution of **17** in toluene at 110 °C, the regioselectivity was completely reversed. The reaction did not give **18** at all, but rather 6-*endo*-cyclized **20**

Scheme 6

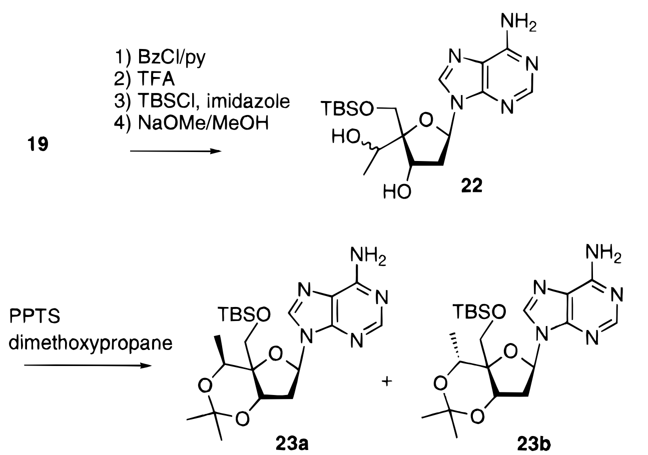


in 91% yield. Tamao oxidation of **20** gave 4′α-(2-hydroxyethyl) derivative **21** in 79% yield (Scheme 7).

Scheme 7



Scheme 8



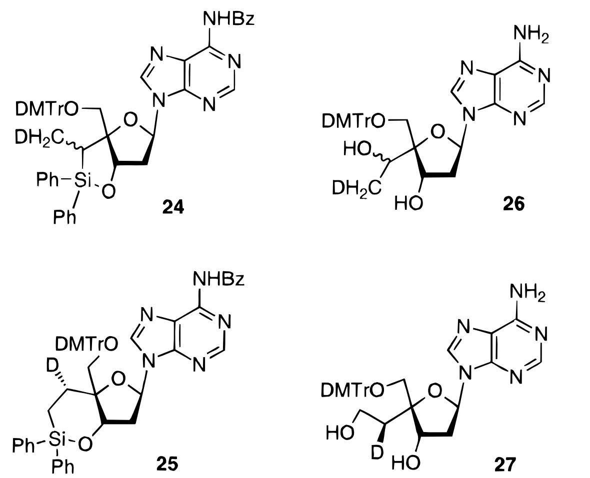


Figure 2.

The diastereomeric mixture **19** was converted to the corresponding isopropylidene derivatives which were successfully separated into the major diastereomer **23a** and the minor **23b** by silica gel column chromatography (Scheme 8). From the NOESY spectra, the stereochemistries at the 4′-branched moiety of **23a** and **23a** were determined as *S* and *R*, respectively.[19]

From the results of the radical reaction, it appeared that formation of the 6-*endo* product **20** was not kinetic but possibly thermodynamic, since the ratio of the *endo*- and *exo*-products should be independent of the concentration of Bu_3SnH, if the reaction is kinetically controlled.

To clarify the reaction mechanism, we performed the reaction with Bu_3SnD. The reaction of **17** in the presence of excess of Bu_3SnD gave 5-*exo* cyclized **24**[20,21] (Figure 2) with high selectivity which was deuterated exclusively at the methyl position. With a much lower Bu_3SnD concentration, the reaction gave **25**[21] (Figure 2) as the sole product, in which one methylene proton at the β-position of the silicon was exclusively replaced by deuterium based on its ^1H NMR spectrum. It is interesting that the proton which has a trans-configuration to the 5′-methylene group, of the methylene protons β to the silicon was exclusively replaced by a deuterium in **25** (Figure 2). This may be explained by substrate control.[12b] With regard to the radical intermediate, conformer **J** would be favored over **I**, due to steric repulsion between the axial phenyl group and tetahydrofuran ring in **I**. The bulky axial phenyl group of **J** may lead to equatorial attack of $Bu_3SnD(H)$ (Scheme 9).

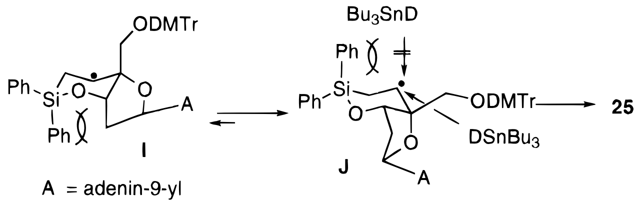
From these results, a radical reaction mechanism with an adenine nucleoside as a substrate, as shown in Scheme 10, was suggested, and the mechanism is consistent with that with 2-bromoindanol derivatives.[11] Therefore, it was suggested that this rearrangement reaction may be general in (3-oxa-2-silacyclopentyl)methy radicals. To the best of our knowledge, such a ring-enlarging 1,2-radical rearrangement reaction of β-silyl radicals has not been previously reported.[22−25] Thereaction mechanism of this rearrangement is not fully understood. However, it is known that β-silyl carbon-

(19) An evident cross peak between the H-1′ and the methine proton of the 4′α-branched chain siganals was observed in the NOESY spectrum of **23a**.

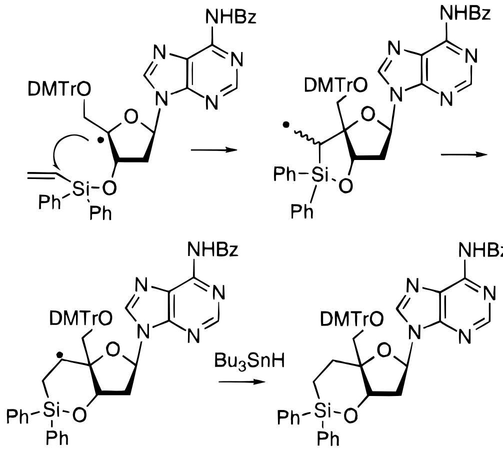
(20) Isolation of the radical reaction products was attempted, but was difficult due to contamination with compounds derived from Bu_3SnH.

(21) The structures of **24** and **25** were further confirmed from the instrumental analyses of their Tamao oxidation products **26** and **27**.

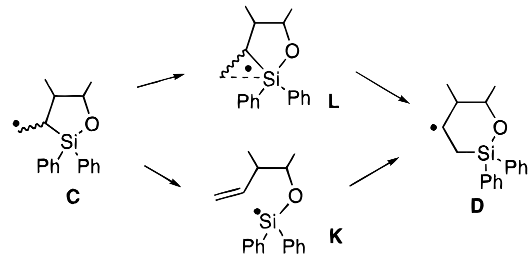
Scheme 9



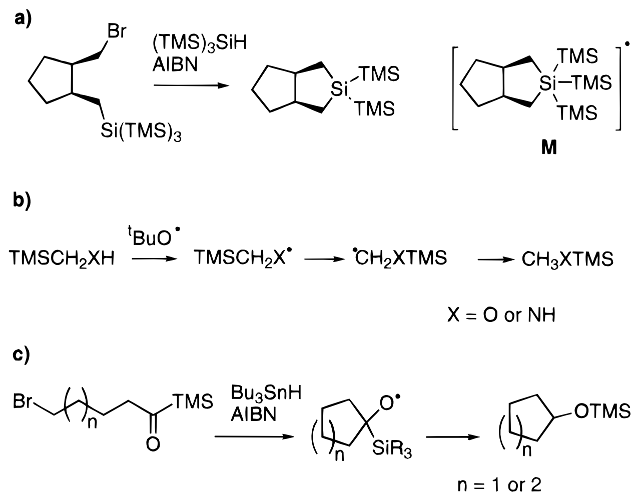
Scheme 10



Scheme 11



Scheme 12



centered radicals are easily generated and are stable compared with their all-carbon analogues.[26] Also, the Si−C bond (69−76 kcal mol^{-1}) is weaker than the C−C bond (83 kcal mol^{-1}),[27] and these effects may affect this rearrangement. Two intermediates, a fragmentation intermediate **K** and a silicon-bridging one **L**, may be postulated (Scheme 11). Recently, Giese and co-workers described a novel radical substitution reaction and proposed a silicon-bridging intermediate **M** (Scheme 12a)[28] that is analogous to the intermediate **L**. Pentavalent-like silicon radicals have also been suggested as intermediates of free radical 1,2-silicon shifts from carbon to nitrogen or oxygen by Harris and co-workers (Scheme 12b).[25a] On the other hand, Tsai and Cherng reported a radical Brook rearrangement as shown in Scheme 12c.[25b] Although, Tsai and Cherng did not discuss the mechanism in their paper, the rearrangement may also proceed via pentavalent-like silicon radical intermediates, since the rearrangement cannot proceed via a fragmentation mechanism. This kind of interaction between silicon and the unpaired electron in a β-silyl radical has been suggested[29] through kinetic study,[26a,29a] MO calculation,[29b] and ESR study.[29c,d] Accordingly, the rearrangement of β-silyl radicals found in this study, as well as the previous results of Giese et al., Harris et al., and Tsai et al., may suggest the participation of pentavalent-like silicon intermediates in radical reactions of some organosilicon compounds.

Derivatization of **19** and **21** into various 4′α-branched-chain sugar nucleosides and their biological evaluations are under investigation.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 270 or 500 MHz (^{1}H) and at 125 MHz (^{13}C) and are reported in ppm downfield from TMS. *J* values are given in hertz. Mass spectra were obtained by electron ionization (EI) or fast atom bombardment (FAB) method. Thin-layer chromatography was done on Merck coated plate 60F$_{254}$. Silica gel chromatography was done with Merck silica gel 5715. Reactions were carried our under an argon atmosphere.

***N*^{6},*N*^{6},*O*-Tribenzoyladenosine (5).** A mixture of 2′-deoxyadenosine (5.0 g, 20 mmol) and DMTrCl (15.7 g, 46 mmol) in pyridine (50 mL) was stirred at room temperature for 5 h. To the solution was added BzCl (11.6 mL, 100 mmol), and the resulting mixture was stirred at room-temperature overnight. The resulting solution was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. After the residue was

(22) There is no precedent for the ring-enlarging 1,2-rearrangement of a carbon-centered β-silyl radical analogous to this reaction, except for our recent communication (ref 11).

(23) Known 1,2-rearrangement of carbon-centered radicals: (a) Wilt, J. W.; Pawlikowski, W. W., Jr. *J. Org. Chem.* **1975**, *40*, 3641−3644. (b) Goermer, R. N.; Cote P. N., Jr.; Bittimberga, B. M. *J. Org. Chem.* **1977**, *42*, 19−28. (c) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829−2881. (d) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565−2575. (e) Dowd, P.; Ahang, W. *Chem. Rev.* **1993**, *93*, 2091−2115.

(24) 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*, 4215−4218.

(25) Carbon to oxygen or carbon 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. Organomet. Chem.* **1991**, *403*, C25−C28. (b) Tsai, Y.-M.; Cherng, C.-D. *Tetrahedron Lett.* **1991**, *32*, 3515−3518.

(26) (a) Auner, N.; Walsh, R.; Westrup, J. *J. Chem. Soc., Chem. Commun.* **1986**, 207−208. (b) Davidson, I. M. T.; Barton, T. J.; Hughes, S.; Ijadi-Maghsoodi, S.; Revis, J.; Paul, G. C. *Organometallics* **1987**, *6*, 644−647.

(27) Hess, G. G.; Lampe, F. W.; Sommer, L. H. *J. Am. Chem. Soc.* **1965**, *87*, 5327−2533.

(28) Kulicle, K. J.; Chatgiliatoglu, C.; Kopping, B.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 935−939.

(29) (a) Jackson, R. A.; Ingold, K. U.; Griller, D.; Nazran, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 208−211. (c) Pitt, C. G. *J. Organomet. Chem.* **1973**, *61*, 49−70. (c) Shen, K. S.; Kochi, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 1383−1391. (d) Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6715−6720.

dissolved in CH_2Cl_2 (300 mL), TFA (7.6 mL, 100 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was cooled in an ice-bath, aqueous $NaHCO_3$ (saturated, 100 mL) was added, and then the mixture was partitioned. The organic layer was washed with aqueous $NaHCO_3$ (saturated), H_2O, and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% EtOAc in hexane) to give **5** (7.4 g, 66%) as a foam: ^1H NMR (270 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 8.20 (s, 1 H), 8.10−7.35 (m, 15 H), 6.46 (dd, 1 H, J = 9.8, 5.4), 5.81 (m, 1 H, J = 5.6), 4.46 (m, 1 H), 4.01 (s, 2 H), 3.28 (ddd, 1H, J = 9.8, 14.3, 5.6), 2.64 (dd, 1 H, J = 5.4, 14.3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.02, 165.73, 151.76, 151.51, 144.21, 133.75, 133.46, 133.05, 129.84, 129.57, 129.36, 129.27, 128.70, 128.63, 128.46, 87.49, 87.30, 77.21, 63.14, 38.08, 36.50; EI-MS *m/z* 563 (M^+). Anal. Calcd for $C_{31}H_{25}N_5O_6{\cdot}3/2H_2O$: C, 63.05; H, 4.78; N, 11.86. Found: C, 63.20; H, 4.49; N, 11.67.

A Diastereomeric Mixture of 9-(3-*O*-Benzoyl-2-deoxy-4-(phenylseleno)-α-L-*threo*-pento-5-aldo-1,4-furanosyl)-*N*[6],*N*[6]-dibenzoyladenine and 9-(3-*O*-Benzoyl-2-deoxy-4-(phenylseleno)-*β*-D-*erythro*-pento-5-aldo-1,4-furanosyl)-*N*[6],*N*[6]-dibenzoyladenine (6). A mixture of oxalyl chloride (0.86 mL, 8.8 mmol) and DMSO (1.54 mL, 22 mmol) in CH_2Cl_2 (8 mL) was stirred at −78 °C for 10 min, and a solution of **5** (2.5 g, 4.4 mmol) in CH_2Cl_2 (15 mL) was added, and the resulting mixture was further stirred at the same temperature for 30 min. Et_3N (2.42 mL, 17.6 mmol) was added, and the resulting mixture was stirred at the same temperature for 1.5 h. The resulting solution was used directly for the next selenation reaction.

After a solution of PhSeCl (2.53 g, 13.2 mmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C, Et_3N (3.63 mL, 26.4 mmol) was added, and the resulting solution was added slowly to the above prepared solution. The resulting mixture was stirred at −78 °C for 30 min and then at 0 °C for 1.5 h. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 50% EtOAc in hexane) to give **6** (2.25 g, 72%) as a foam: ^1H NMR (270 MHz, $CDCl_3$) δ 9.37 (s, 1 H), 8.70 (s, 1 H), 8.60 (s, 1 H), 7.98−7.22 (m, 20 H), 6.95 (dd, 1 H, J = 8.4, 6.4), 6.17 (dd, 1 H, J = 5.1, 1.4), 3.59 (ddd, 1 H, J = 8.4, 14.0, 5.1), 3.03 (ddd, 1 H, J = 6.4, 14.0, 1.4); FAB-MS *m/z* 718 (MH^+). Anal. Calcd for $C_{37}H_{27}N_5O_6Se{\cdot}H_2O$: C, 60.49; H, 3.98; N, 9.53. Found: C, 60.35; H, 3.61; N, 9.41.

9-(3-*O*-Benzoyl-2-deoxy-4-(phenylseleno)-α-L-*threo*-pento-1,4-furanosyl)-*N*[6],*N*[6]-dibenzoyladenine (7) and 9-(3-*O*-Benzoyl-2-deoxy-4-(phenylseleno)-*β*-D-*erythro*-pento-1,4-furanosyl)-*N*[6],*N*[6]-dibenzoyladenine (8). To a solution of **6** (2.25 g, 3.1 mmol) in THF (30 mL) was added a solution of Bu_4NBH_3CN (1.58 g, 5.6 mmol) in THF (30 mL) at −78 °C, and the mixture was stirred at the same temperature for 15 min and then at 0 °C for 1.5 h. After aqueous tartaric acid (5%) was added, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 50% EtOAc in hexane) to give **7** (1.58 g, 72%) and **8** (0.46 g, 21%) as forms. **7**: ^1H NMR (270 MHz, $CDCl_3$) δ 8.61 (s, 2 H), 8.06−7.29 (m, 20 H), 6.89 (dd, 1 H, J = 7.9, 6.7), 6.01 (dd, 1 H, J = 5.4, 2.1), 3.82 (m, 2 H), 3.45 (ddd, 1 H, J = 14.0, 7.9, 5.4), 2.96 (ddd, 1 H, J = 14.0, 6.7, 2.1), 2.30 (t, 1 H, J = 6.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.04, 165.16, 152.82, 152.31, 151.88, 143.20, 136.67, 133.89, 133.67, 132.88, 129.68, 129.40, 129.31, 128.71, 128.59, 128.51, 127.35, 125.33, 97.37, 84.52, 77.82, 77.19, 63.06, 38.18; FAB-MS *m/z* 720 (MH^+). Anal. Calcd for $C_{37}H_{29}N_5O_6Se{\cdot}H_2O$: C, 60.33; H, 4.24; N, 9.51. Found: C, 60.04; H, 3.87; N, 9.31. **8**: ^1H NMR (270 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 8.25 (s, 1 H), 8.19−7.30 (m, 20 H), 6.60 (dd, 1 H,J = 6.7, 6.7), 6.24 (dd, 1 H, J = 7.2, 4.1), 4.02 (d, 1 H, J = 12.4), 4.79 (d, 1 H, J = 12.4), 3.33 (ddd, 1 H, J = 7.2, 6.7, 10.8), 2.83 (ddd, 1 H, J = 6.7, 4.1, 10.8); FAB-MS *m/z* 720 (MH^+). Anal. Calcd for $C_{37}H_{29}N_5O_6Se{\cdot}H_2O$: C, 60.33; H, 4.24; N, 9.51. Found C, 60.21; H, 4.00; N, 9.34.

9-(3-*O*-Benzoyl-2-deoxy-5-*O*-diphenylvinysilyl-4-(phenylseleno)-α-L-*threo*-pento-1,4-furanosyl)-*N*[6],*N*[6]-dibenzoyladenine (9). A mixture of **7** (1.0 g, 1.4 mmol), diphenylvinylchlorosilane (500 μL, 2.1 mmol), DMAP (30 mg, 0.28 mmol), and Et_3N (300 μL, 2.1 mmol) in toluene (25 mL) was stirred at room temperature for 30 min. After insoluble materials were filtered off, the filtrate was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% EtOAc in hexane) to give **9** (1.1 g, 84%) as a form: ^1H NMR (270 MHz, $CDCl_3$) δ 8.63 (s, 1 H, H-8), 8.48 (s, 1 H), 7.99−7.07 (m, 30 H), 6.63 (dd, 1 H, J = 6.9, 6.9), 6.32 (dd, 1 H, J = 15.0, 19.9), 6.17 (dd, 1 H, J = 15.0, 4.2), 6.08 (dd, 1 H, J = 6.2, 3.9), 5.80 (dd, 1 H, J = 19.9, 4.2), 4.21 (d, 2 H, J = 11.5), 3.24 (ddd, 1 H, J = 13.7, 6.9, 6.2), 2.89 (ddd, 1 H, J = 13.7, 6.9, 3.9); FAB-MS *m/z* 928 (MH^+). Anal. Calcd for $C_{51}H_{41}N_5O_6SeSi{\cdot}H_2O$: C, 64.82; H, 4.59; N, 7.41. Found: C, 64.54; H, 4.26; N, 7.54.

(5′*S*)-4′-*C*-(Hydroxymethyl)-2′-deoxy-8,5′-methanoadenosine (11). To a solution of **9** (185 mg, 0.20 mmol) in benzene (20 mL) at 80 °C was added a solution of Bu_3SnH (160 μL, 3.0 mmol) and AIBN (50 mg, 0.30 mmol) in benzene (20 mL) slowly over 8 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between MeCN and hexane. The MeCN layer was evaporated under reduced pressure, the residue was dissolved in MeOH/THF (1:1, 6 mL), aqueous H_2O_2 (30%, 112 μL, 1.0 mmol), KF (60 mg, 1.0 mmol), and $KHCO_3$ (32 mg, 0.32 mmol) were added, and the resulting mixture was stirred at room temperature for 15 h. Aqueous $Na_2S_2O_3$ (1 M, 20 mL) was added, and the resulting insoluble materials were filtered off. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 20% MeOH in $CHCl_3$) to give **11** (20 mg, 35%) as a syrup: HRMS (EI) calcd for $C_{12}H_{15}N_5O_4$ 293.1124, found 293.1116. This compound was acetylated as follows without further purification.

(5′*S*)-3′5′-Di-*O*-acetyl-4′-*C*-(acetoxymethyl)-2′-deoxy-8,5′-methanoadenosine (12). A solution of **11** (23 mg, 0.08 mmol), acetic anhydride (44 μL, 0.47 mmol), Et_3N (μL, 0.47 mmol), and DMAP (10 mg, 0.08 mmol) in MeCN (2 mL) was stirred at room temperature for 5 min. After EtOH was added, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% EtOAc in hexane) to give **12** (19 mg, 58%) as a solid: ^1H NMR (270 MHz, $CDCl_3$) δ 8.27 (s, 1 H, H-2), 6.78 (dd, 1 H, H-1′, J = 2.9, 7.6), 6.32 (s, 2 H, NH_2), 5.82 (dd, 1 H, H-3′, J = 6.7, 3.0), 5.36 (dd, 1 H, H-5′, J = 4.2, 11.6), 4.59 (d, 1 H, 4′α-CH_2OAc, J = 12.3), 4.20 (d, 1 H, 4′α-CH_2OAc, J = 12.3), 3.61 (dd, 1 H, 5′-CH_2-, J = 4.2, 15.6), 3.07 (dd, 1 H, 5′−CH_2-, J = 11.6, 15.6), 2.81 (m, 2 H, H-2′), 2.18, 2.12, 2.03 (each s, each 3 H), the assignments were in agreement with COSY spectrum; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.64, 170.03, 169.09, 154.94, 152.44, 145.71, 89.47, 81.84, 74.43, 67.21, 63.38, 42.60, 31.08, 21.29, 21.05, 20.82; HRMS (EI) calcd for $C_{18}H_{21}N_5O_7$ 419.1439, found 419.1430.

9-(2-Deoxy-4-(phenylseleno)-α-L-*threo*-pento-1,4-furanosyl)-*N*[6]-benzoyladenine (15). A mixture of **7** (2.6 g, 3.6 mmol) and K_2CO_3 (500 mg, 3.6 mmol) in MeOH (40 mL) was stirred at room temperature for 10 min, to which was added a solution of saturated NH_3 in MeOH (40 mL), and the resulting mixture was stirred for 10 min. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 16% MeOH in $CHCl_3$) to give **15** (1.3 g, 69%) as a white powder: ^1H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, 1 H), 8.84 (s, 1 H), 8.59 (s, 1 H), 8.06−7.19 (m, 10 H), 6.94 (dd, 1 H, J = 8.2, 6.7), 4.87 (m, 1 H), 3.93 (m, 2 H), 3.74 (d, 1 H, J = 3.7), 3.20 (ddd, 1 H, J = 13.7, 8.2, 5.1), 2.83 (ddd, 1 H, J = 13.7, 6.7, 1.5), 2.69 (m, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.40, 152.11, 151.54, 150.08, 142.70, 136.38, 133.18, 132.24, 128.56, 128.30, 126.75, 126.68, 125.45, 99.07, 83.75, 75.41, 62.56, 60.28. Anal. Calcd for $C_{23}H_{21}N_5O_4Se$: C, 54.12; H, 4.15; N, 13.72. Found: C, 53.99; H, 4.10; N, 13.57.

9-(2-Deoxy-5-*O*-(dimethoxytrityl)-4-(phenylseleno)-α-L-*threo*-pento-1,4-furanosyl)-*N*[6]-benzoyladenine (16). A mixture of **15** (1.5 g, 3.0 mmol) and DMTrCl (1.2 g, 3.7 mmol) in pyridine (30 mL) was stirred at room temperature for 48 h. After EtOH (1 mL) was added, and the solution was stirred for 10 min. The resulting solution was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 2% MeOH−$CHCl_3$) to give **16** (2.5 g, quant): ^{1}H NMR (500 MHz, $CDCl_3$+D_2O) δ 8.81(s, 1 H), 8.48 (s, 1 H), 8.04−6.79 (m, 23 H), 6.87 (dd, 1 H, J = 7.4, 5.9), 4.82 (m, 1 H), 3.80 (s, 6 H), 3.66 (d, 1 H, J = 10.3), 3.55 (d, 1 H, J = 10.3), 3.04 (ddd, 1 H, J = 13.3, 7.4, 5.9), 2.75 (dd, 1 H, J = 13.3, 6.4); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 164.65, 158.67, 152.85, 151.93, 149.49, 143.90, 141.73, 135.56, 134.91, 134.81, 133.59, 132.72, 129.81, 129.06, 128.79, 128.52, 128.27, 128.05, 127.82, 127.06, 122.91, 113.38, 96.43, 87.22, 84.96, 77.95, 77.22, 64.96, 55.17, 40.22; FAB-MS m/z 814 (MH^+). Anal. Calcd for $C_{44}H_{39}N_5O_6Se{\cdot}1/2H_2O$: C, 64.31; H, 4.91; N, 8.52. Found: C, 64.30; H, 4.93; N, 8.35.

9-(2-Deoxy-5-*O*-(dimethoxytrityl)-3-*O*-(diphenylvinylsilyl)-4-(phenylseleno)-α-L-*threo*-pento-1,4-furanosyl)-*N*⁶-benzoyladenine (17). A mixture of **16** (1.8 g, 2.2 mmol), DMAP (54 mg, 0.44 mmol), Et_3N (590 μL, 4.4 mmol), and diphenylvinylchlorosilane (980 μL, 4.4 mmol) in toluene (30 mL) was stirred at room temperature for 15 h. Insoluble materials were filtered off, and the filtrate was evaporated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 60% EtOAc in hexane) to give **17** (1.7 g, 93%) as a foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.72 (s, 1 H), 8.19 (s, 1 H), 8.05−6.75 (m, 33 H), 6.65 (dd, 1 H, J = 6.5, 5.9), 6.23 (dd, 1 H, J = 20.0, 14.9), 6.13 (dd, 1 H, J = 14.9, 4.0), 5.71 (dd, 1 H, J = 20.0, 4.0), 4.88 (dd, 1 H, J = 5.9, 5.6), 3.87 (d, 1 H, J = 10.0), 3.77 (s, 6 H), 3.27 (d, 1 H, J = 10.0), 2.89 (ddd, 1 H, J = 13.0, 5.9, 5.9), 2.77 (ddd, 1 H, J = 13.0, 6.5, 5.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.44, 158.22, 152.48, 151.39, 149.25, 141.63, 138.11, 136.82, 135.79, 135.64, 135.01, 134.89, 133.57, 133.05, 132.38, 130.24, 130.18, 128.76, 128.58, 128.54, 128.26, 127.89, 127.86, 127.75, 127.67, 126.79, 126.59, 123.03, 112.97, 112.94, 96.28, 86.84, 84.36, 77.21, 65.81, 55.16, 39.37; FAB-MS m/z 1022 (MH^+). Anal. Calcd for $C_{58}H_{51}N_5O_6SeSi{\cdot}H_2O$: C, 67.04; H, 5.14; N, 6.74. Found: C, 66.83; H, 4.95; N, 6.64.

2′-Deoxy-5′-*O*-(dimethoxytrityl)-4′-*C*-(1-hydroxyethyl)-adenosine (19). A mixture of **17** (204 mg, 0.20 mmol), Bu_3SnH (160 μL, 0.60 mmol), and AIBN (10 mg, 0.06 mmol) in benzene (2 mL) was stirred at 80 °C for 30 min. The solvent was evaporated under reduced pressure, and the residue was partitioned between MeCN and hexane. The MeCN layer was evaporated under reduced pressure. A mixture of the residue, aqueous H_2O_2 (30%, 112 μL, 1.0 mmol), KF (60 mg, 1.0 mmol), and $KHCO_3$ (32 mg, 0.32 mmol) in MeOH/THF (1:1, 6 mL) was stirred at room temperature for 15 h. Aqueous $Na_2S_2O_3$ (1 M, 20 mL) was added, and the resulting insoluble materials were filtered off. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 8% MeOH in $CHCl_3$) to give **19** (118 mg, 98%) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.21 (s, minor H-8), 8.13 (s, major H-8), 7.77 (s, minor H-2), 7.76 (s, major H-2), 7.39−6.82 (m, major and minor Ph), 6.43 (m, major and minor H-1′), 5.69 (br s, major and minor NH_2), 4.97 (m, minor H-3′), 4.81 (d, major H-3′, J = 4.8), 4.42 (q, minor H-6′, J = 6.6), 4.21 (q, major H-6′, J = 6.6), 3.78 (s, major and minor OMe), 3.63 (d, major H-5′a, J = 10.0), 3.42 (d, major H-5′b, J = 10.0), 3.31 (d, minor H-5′, J = 9.6), 3.18 (d, minor H-5′b, J = 9.6), 3.03 (m, major H-2′a), 2.94 (m, minor H-2′a), 2.59 (m, minor H-2′b), 2.48 (m, major H-2′b), 1.15 (d, major and minor H-7′ J = 6.6), the assignments were in agreement with COSY spectrum, and the ratio of major and minor diastereomers was 2:1; HRMS (FAB) calcd for $C_{33}H_{36}N_5O_6$ 598.2664, found 598.2696. Similar reaction of **17** (102 mg, 0.10 mmol) with Bu_3SnD, instead of Bu_3SnH, gave deuterium-labeled **26** (55 mg, 50%): HRMS (FAB) calcd for $C_{33}H_{35}DN_5O_6$ 599.2727, found 599.2733.

6-*Endo*-Cyclization Product 20. To a solution of **17** (2.2 g, 2.2 mmol) in toluene (180 mL) at 110 °C, was added a solution of Bu_3SnH (820 μL, 3.00 mmol) and AIBN (50 mg, 0.30 mmol) in toluene (25 mL) slowly over 4 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between MeCN and hexane. The MeCN layer was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 50% EtOAc in hexane) to give **20** (1.7 g, 91%) as a white foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1 H, NH), 8.68 (s, 1 H, H-8), 8.00 (s, 1 H, H-2), 8.03−6.74 (m, 28 H, Ph), 6.52 (dd, 1 H, H-1′, J = 6.0, 8.4), 4.96 (m, 1 H, H-3′), 3.77 (s, 6 H, MeO x 2), 3.36 (d, 1 H, H-5′a, J = 9.7), 3.21 (d, 1 H, H-5′b, J = 9.7), 2.95 (ddd, 1 H, H-2′a, J = 13.7, 8.4), 2.68 (dd, 1 H, H-2′b, J = 13.7, 6.0), 2.44 (ddd, 1 H, H-6′a, J = 14.0, 10.4, 3.6), 2.16 (ddd, 1 H, H-6′b, J = 14.0, 8.7, 4.1), 1.41 (ddd, 1 H, H-7′a, J = 15.0, 10.4, 4.1), 1.12 (ddd, 1 H, H-7′b, J = 15.0, 8.7, 3.6), the carbons introduced at the 4′α-position were numbered C-6′ and C-7′, and the assignments were in agreement with COSY spectrum; NOE, irradiated H-3′, observed H-1′ (1.0%), H-5′a (1.6%), H-5′b (1.2%), H-2′a (3.5%), and H-2′b (1.2%); irradiated H-6′a, observed H-3′ (1.6%), H-5′a (0.4%), H-5′b (0.3%), H-6′b (16%), H-7′a (0.3%), and H-7′b (0.08%); irradiated H-6′b, observed H-1′ (1.7%), H-5′b (1.5%), H-6′a (16%), H-7′a (0.9%), and H-7′b (1.6%); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.41, 158.36, 158.34, 152.34, 151.32, 149.27, 144.22, 141.46, 135.37, 134.47, 134.31, 134.23, 134.15, 133.61, 132.61, 130.36, 130.18, 129.89, 129.83, 128.74, 128.10, 128.00, 127.97, 127.77, 127.71, 126.80, 123.39, 113.07, 87.94, 86.42, 84.99, 76.47, 67.40, 55.20, 40.91, 27.32, 4.84; HRMS (FAB) calcd $C_{52}H_{48}O_6N_5Si$ 866.3374, found 866.3394. Similar reaction of **17** (102 mg, 0.10 mmol) with Bu_3SnD, instead of Bu_3SnH, gave deuterium-labeled **25** (63 mg, 73%): HRMS (FAB) calcd $C_{52}H_{47}DO_6N_5Si$ 867.3433, found 867.3467.

2′-Deoxy-5′-*O*-(dimethoxytrityl)-4-*C*-(2-hydroxyethyl)adenosine (21). A mixture of **20** (430 mg, 0.50 mmol), aqueous H_2O_2 (30%, 280 μL, 2.5 mmol), KF (150 mg, 2.5 mmol), and $KHCO_3$ (80 mg, 0.80 mmol) in MeOH/THF (1:1, 10 mL) was stirred at room temperature for 15 h. Aqueous $Na_2S_2O_3$ (1 M, 20 mL) was added, and the resulting insoluble materials were filtered off. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 8% MeOH in $CHCl_3$) to give **21** (240 mg, 79%) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.87 (s, 1 H), 7.36−6.48 (m, 13 H), 6.48 (dd, 1 H, J = 6.6, 6.1), 5.61 (s, 2 H), 4.51 (dd, 1 H, J = 6.0, 3.0), 3.87 (m, 1 H), 3.78 (s, 6 H), 3.71 (m, 1 H), 3.39 (d, 1 H, J = 9.9), 3.24 (d, 1 H, J = 9.9), 2.93 (ddd, 1 H, J = 13.6, 6.6, 6.0), 2.55 (ddd, 1 H, J = 13.6, 6.1, 3.0), 2.18 (m, 2 H); FAB-MS m/z 596 (MH^+). Anal. Calcd for $C_{33}H_{35}N_5O_6{\cdot}MeOH$: C, 65.04; H, 5.94; N, 11.16. Found: C, 64.98; H, 6.07; 11.05. Similar reaction of **25** (44 mg, 0.050 mmol) gave **27** (28 mg, 94%): HRMS (FAB) calcd for $C_{33}H_{35}DO_6N_5Si$ 599.2727, found 599.2717.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-4-*C*-(1-hydroxyethyl)adenosine (22). A mixture of **19** (260 mg, 0.44 mmol) and BzCl (400 μL, 4.4 mmol) in pyridine (5 mL) was stirred at room temperature for 15 h. After MeOH was added, the resulting mixture was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. A solution of the residue and TFA (170 μL, 2.2 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h, aqueous $NaHCO_3$ (saturated, 10 mL) was added, and the resulting mixture was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The resulting residue, imidazole (177 mg, 2.6 mmol), and TBSCl (200 mg, 1.3 mmol) were dissolved in DMF (5 mL), and the resulting mixture was stirred at room temperature for 15 h. After MeOH was added, the resulting mixture was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. To the solution of the residue in MeOH (10 mL) was added NaOMe (5.2 M in MeOH, 85 μL, 0.44 mmol), and the resulting mixture was stirred at room temperature for 15 h. The mixture was neutralized with AcOH and then evaporated. The residue was purified by column chromatography (SiO_2, 8% MeOH in $CHCl_3$) to give **22** (98 mg, 54%) as a foam: ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, minor), 8.31 (s, major), 8.00 (s, minor), 7.91 (s, major), 6.50 (dd, minor, $J = 7.0$, 6.6), 6.43 (dd, major, $J = 9.4$, 5.5), 5.61 (br s, major and minor), 4.89 (d, minor, $J = 3.4$), 4.76 (d, major, $J = 5.1$), 4.28 (q, minor, $J = 6.6$), 4.15 (q, major, $J = 6.6$), 4.03 (d, minor, $J = 10.5$), 3.88 (d, major, $J = 10.0$), 3.74 (d, minor, $J = 10.5$ Hz), 3.62 (d, major, $J = 10.0$), 3.31 (m, major), 3.00 (m, minor), 2.60 (ddd, minor, $J = 13.6$, 6.6, 3.4), 2.51 (ddd, major, $J = 13.7$, 5.5, 5.1), 1.36 (d, major, $J = 6.6$), 1.33 (d, minor, $J = 6.6$), 0.92 (s, minor), 0.94 (s, major), 0.16, 0.15 (each s, major), 0.11, 0.09 (each s, minor), the ratio of major and minor diastereomers were about 2:1; HRMS (EI) calcd for $C_{18}H_{31}N_5O_4Si$ 409.2143, found 409.2136.

Acetonides 23a and 23b. A mixture of **22** (79 mg, 0.20 mmol), dimethoxypropane (74 μL, 0.57 mmol), and PPTS (33 mg, 0.13 mmol) in acetone (3 mL) was stirred at room temperature for 3 days. The resulting solution was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 4% MeOH in $CHCl_3$) to give **23a** (18 mg, 21%) and **23b** (6 mg, 7%) in pure forms, respectively. **23a**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1 H, H-8), 8.22 (s, 1 H, H-2), 6.66 (dd, 1 H, H-1′, $J = 7.4$, 7.4), 5.68 (br s, 2 H, NH_2), 4.44 (dd, 1 H, H-3′, $J = 3.0$, 3.0), 3.93 (m, 2 H, H-5′a and 4′-C*H*(OH)CH_3), 3.78 (d, 1 H, H-5′b, $J = 10.7$), 2.54 (m, 2 H, H-2′ab), 1.39, 1.37 (each s, each 3 H, Me), 1.13 (d, 3 H, 4′-CHCH_3, $J = 6.8$), 0.96 (s, 9 H, t-Bu), 0.16, 0.15 (each s, each 3 H, Me), the assignments were in agreement with COSY spectrum; HRMS (EI) calcd for $C_{21}H_{35}O_4N_5Si$ 449.2459, found 449.2472. **23b**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1 H, H-8), 7.92 (s, 1 H, H-2), 6.43 (dd, 1 H, H-1′, $J = 9.5$, 5.6), 5.58 (br s, 2 H, NH_2), 4.76 (d, 1 H, H-3′, $J = 3.8$), 4.41 (q, 1 H, 4′-C*H*CH_3, $J = 6.4$), 4.19 (d, 1H, H-5′a, $J = 10.8$), 3.57 (ddd, 1 H, H-2′a, $J = 13.6$, 9.5, 3.8), 3.48 (d, 1 H, H-5′b, $J = 10.8$), 2.37 (dd, 1 H, H-2′b, $J = 13.6$, 5.6), 1.53, 1.45 (each s, each 3 H, Me), 1.24 (d, 3 H, 4′-CHCH_3, $J = 6.4$), 0.94 (s, 9 H, *t*-Bu), 0.14, 0.11 (each s, each 3 H, Me), the assignments were in agreement with COSY spectrum; HRMS (EI) calcd for $C_{21}H_{35}O_4N_5Si$ ($M^+ - t$-Bu) 392.1754, found 392.1777.

Supporting Information Available: ^1H NMR, HMBC, and NOESY spectral charts of **12**, ^1H NMR and NOESY spectral charts of **23a**, and ^1H NMR spectral charts of **19**, **21**, **26**, and **27** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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