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Anti versus Syn Opening of Epoxides Derived from 9-(3-Deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine with Me_3Al: Factors Controlling the Stereoselectivity

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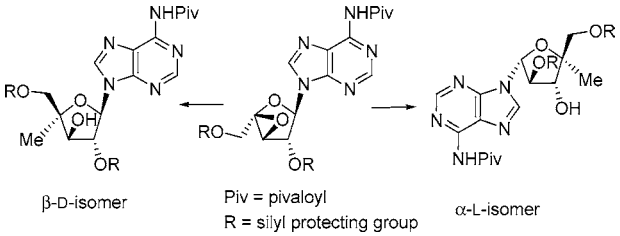


Upon epoxidation with dimethyldioxirane, the 2′,5′-bis-*O*-silyl derivatives of 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine gave the respective "3′,4′-up" epoxides exclusively. Reaction between these epoxides and Me_3Al was investigated in detail. It was found that the stereoselectivity of epoxide ring opening (anti versus syn) varied significantly upon changing the amount of Me_3Al, the solvent, the *O*-silyl protecting group, and the reaction temperature. A possible reaction mechanism is proposed.

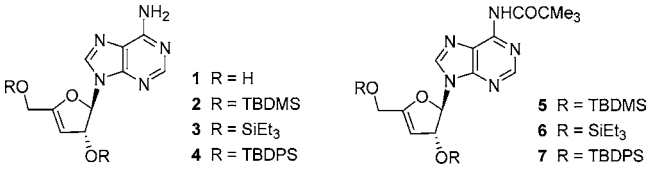
Introduction

Ring opening of epoxides with organoaluminum reagents is a useful operation for forming C−C bonds in organic synthesis. It is generally recognized that simple epoxides undergo anti opening with organoaluminum reagents;[1−3] however, there seem to be no clear explanations available for the stereochemical outcome, except for one report in the reaction of epoxy alcohols.[4]

Our recent synthetic endeavor has been focused on the preparation of 4′-carbon-substituted nucleosides based on ring opening of their epoxy intermediates.[5−7] A previous report has demonstrated that reaction of organoaluminum reagents with a nucleoside 4′,5′-epoxide constitutes an efficient entry to the analogues bearing sp^3-, sp^2-, and sp-hybridized carbon substituents.[6] It was readily anticipated that nucleoside 3′,4′-epoxides can also be used for the same purpose. Furthermore, such substrates upon reacting with organoaluminum reagents are expected to provide informative experimental results to further the understanding of the stereochemistry of epoxide ring opening. In the present study, reaction of Me_3Al with the 3′,4′-epoxides derived from 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**1**) was investigated in detail.

Results and Discussion

Epoxidation of 9-(3-Deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine Derivatives. The 3′,4′-unsaturated nucleoside **1** employed as a starting material in the present study was prepared from adenosine according to the procedure reported by Moffatt and co-workers: reaction of adenosine with 2-acetoxyisobutyryl bromide followed by DBN treatment of the resulting mixture of 2′,3′-vicinal halo acetates.[8] Compound **1** was silylated at the 2′- and 5′-hydroxyl groups to give **2**−**4**, which were further converted to the N^6-pivaloyl derivatives **5**−**7** to avoid *N*-oxide formation[9] during epoxidation.



(1) Mole, T.; Jeffery, E. A. *Organoaluminium Compounds*; Elsevier Publishing Company: Amsterdam; The Netherlands, 1972.
(2) Nagata, W.; Yoshioka, M.; Okamura, T. *Tetrahedron Lett.* **1966**, 847.
(3) Fried, J.; C.-H. Lin; Ford, S. H. *Tetrahedron Lett.* **1969**, 634 and 1379.
(4) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.
(5) Haraguchi, K.; Takeda, S.; Tanaka, H. *Org. Lett.* **2003**, *5*, 1399.
(6) Haraguchi, K.; Takeda, S.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3775.
(7) Haraguchi, K.; Kubota, Y.; Tanaka, H. *J. Org. Chem.* **2004**, *69*, 1831.

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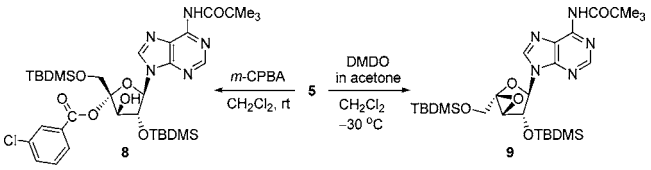
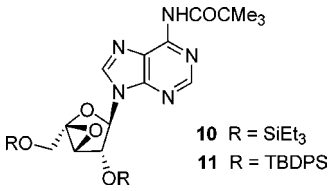
SCHEME 1



For the preparation of the desired 3′,4′-epoxide from **5**−**7**, one would anticipate that use of nucleophilic reagents and/or solvents should be avoided, since the presence of an enol ether structure renders their epoxide fairly susceptible to nucleophilic ring opening. This appeared to be the case as shown in Scheme 1. When **5** was reacted with *m*-CPBA (1.5 equiv) in CH_2Cl_2 for 1.5 h at room temperature, there were formed several products as evidenced by TLC (hexane/EtOAc = 1/1), among which one product was assumed to be the corresponding epoxide. However, silica gel column chromatography of the reaction mixture allowed only the isolation of 9-[4-(3-chlorobenzoyloxy)xylofuranosyl]adenine (**8**: 16%).[10]

In contrast to the reaction of *m*-CPBA, epoxidation of **5** with an acetone solution of dimethyldioxirane (DMDO)[11,12] carried out in CH_2Cl_2 at −30 °C for 0.5 h gave the corresponding epoxide **9** in quantitative yield, simply by evaporation of the solvents. Although **9** was not stable enough for further purification, the ^{1}H NMR spectrum warranted its sufficient purity and the NOE data[13] clearly supported the depicted "3′,4′-up" structure. In a similar manner, the epoxides **10** and **11** were prepared from **6** and **7**, respectively.



Reaction of the 3′,4′-Epoxides with Me_3Al. The above-prepared "3′,4′-up" epoxide **9** was reacted in CH_2Cl_2 with a commercially available hexane solution of Me_3Al that is free from ethereal solvents (Scheme 2). In Table 1 are summarized the results obtained by varying the amount of Me_3Al. There can be seen an apparent trend that formation of the anti-opened product 9-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)-4-*C*-methyl-β-D-xylofuranosyl]-N^6-pivaloyladenine (**12**)[14] becomes a favorable event upon increasing the amount of Me_3Al (entries 1−5). However, a dramatic change occurred in entry 6, where Me_3Al employed was prepared by reacting a THF solution of MeMgCl with $AlCl_3$. The observed exclusive formation in entry 6 of the syn-opened product 9-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)- 4-*C*-methyl- α-L-arabinofuranosyl]-N^6-pivaloyladenine (**13**)[15] was, therefore, assumed to be due to a complex formation between THF and Me_3Al during preparation of the reagent. In support of this assumption is the fact that the reaction of **9** with the commercially available Me_3Al (6 equiv), when carried out in THF, also gave **13** as the sole product, albeit in a lower yield (33%). The use of Et_2O as a reaction solvent led to essentially the same result (the yield of **13**, 25%). The highest yield of **13** (90%) was seen when the reaction was carried out in 1,4-dioxane at room temperature.

SCHEME 2

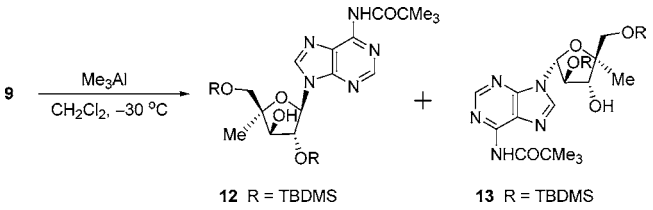


TABLE 1. Reaction of 9 with Me_3Al by Varing the Amount of Reagent[a]

entry	equiv of Me_3Al	combined yield (%) of **12** plus **13**	ratio of **12**/**13**[b]
1	1.0	69	2/1
2	3.0	76	2/1
3	4.0	80	3/1
4	6.0	90	5/1
5	10	93	6/1
6[c]	6.0	59	only **13**

[a] All reactions were carried out in CH_2Cl_2 at −30 °C for 4.5 h. [b] The ratios were determined by ^{1}H NMR spectroscopy. [c] The Me_3Al used in this entry was prepared by reacting a THF solution of MeMgCl with $AlCl_3$.

There have been several precedents for the reaction of Me_3Al with epoxides derived from cyclic enol ethers, 3,4-dihydro-2*H*-pyran,[16] and glycal[17,18] derivatives. In these instances, syn opening of the epoxide ring has been reported to be a dominant or exclusive reaction pathway. To see if the presence of the N^6-pivaloyladenine moiety in **9** has any influence on the reaction pathway, methyl 2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-*glycero*-pent-3-enofuranoside (**14**) was prepared from the known methyl 3,5-di-*O*-benzoyl-β-D-xylofuranoside[19] in 4 steps.[20] Upon DMDO oxidation of **14** and successive reaction with Me_3Al under the conditions in entry 4 in Table 1, there was formed solely the syn-opened product **15**[21] (90%) (Scheme 3).On the basis of the above experimental results, we assumed that the reaction mechanism between **9** and Me_3Al could be illustrated as shown in Scheme 4 (N^6-pivaloyladenine moiety is omitted for simplicity). Highly oxygenophilic Me_3Al would prefer coordination to the 3′,4′-epoxy structure of **9** to give **A**,

(8) Jain, T. C.; Jenkins, I. D.; Russell, A. F.; Verheyden J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 30.

(9) Oxidation of the base moiety of adenosine derivatives with dimethyldioxirane has been reported: Saladino, R.; Crestini, C.; Bernini, R.; Mincione, E.; Ciafrino, R. *Tetrahedron Lett.* **1995**, *36*, 2665.

(10) NOE data for **8**: H-1′/H-3′ (0.7%); H-2′/H-5′b (1.6%); H-2′/3′-OH (8.1%). Of the two protons at the 5′-position, the one that appears at a higher field is designated as H-5′a, and the other as H-5′b, throughout the text and the Experimental Section.

(11) For the preparation of dimethyldioxirane: Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber*. **1991**, *124*, 2377.

(12) For epoxidation of glycals with DMDO: Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(13) NOE data for **9**: H-3′/H-5′a (0.8%); H-3′/H-5′b (1.1%); H-3′/H-1′ (0.6%).

(14) The stereochemistry of **12** was confirmed based on the following NOE data: H-5′b/H-8 (0.9%); H-3′/H-1′ (1.9%); H-2′/3′-OH (4.1%); H-1′/H-3′ (1.7%); H-8/H-3′ (0.3%).

(15) The stereochemistry of **13** was confirmed based on the following NOE data: H-5′a/H-1′ (2.0%); H-5′a/H-3′ (2.0%); H-5′b/H-1′ (4.9%); H-5′b/H-3′ (6.0%); H-3′/H-1′ (1.0%).

(16) Bailey, J. M.; Craig, D.; Gallagher, P. T. *Synlett* **1999**, 132.

(17) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* **2000**, *2*, 231.

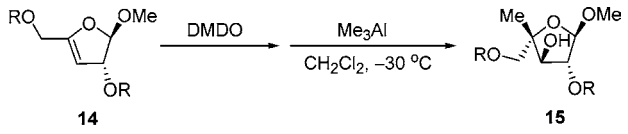
(18) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707.

(19) Collins, P. M.; Hurford, J. R.; Overend, W. G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2163.

(20) For the preparation of **14** from methyl 3,5-di-*O*-benzoyl-β-D-xylofuranoside, see the Supporting Information.

(21) NOE data for **15**: 4-Me/1-OMe (0.8%); 4-Me/H-2 (0.5%); 4-Me/3-OH (1.0%); H-3/H-1 (0.3%); H-5b/H-3 (3.9%); H-5b/H-1 (0.5%); 1-OMe/H-2 (0.1%).

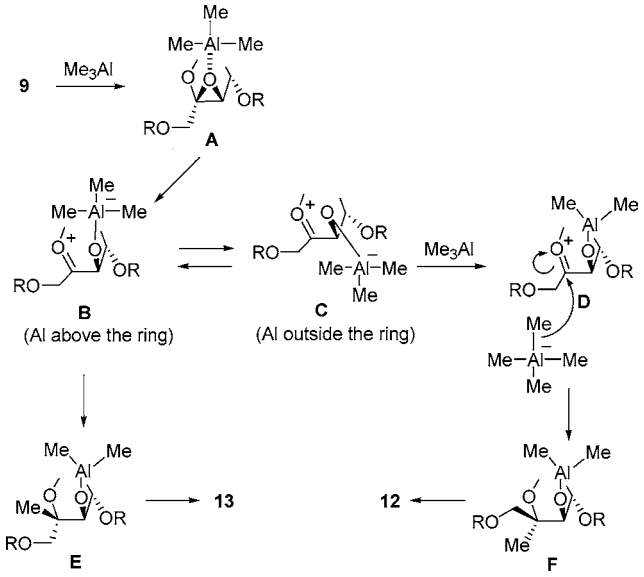
SCHEME 3 [a]



[a] R = TBDMS

[a] R = TBDMS

SCHEME 4 [a]



[a] R = TBDMS

which subsequently undergoes epoxide ring opening to form an oxonium ion that carries an alkoxyaluminate at the 3′-position. Two extreme conformers can be depicted for the oxionium ion through rotation of the 3′-O−Al bond: in one conformer **B**, Al is located above the furanose ring, and in the other conformer **C**, it is outside the ring avoiding either steric or electronic repulsion with the adenine base. In the case where the amount of the remaining Me_3Al is limited or it is complexed with an ethereal solvent, intramolecular attack of the methyl ligand from **B** (syn opening) would inevitably take place to give **E**, which is finally converted to **13**. On the other hand, when noncoordinated Me_3Al is sufficiently available in CH_2Cl_2, there is a good opportunity for **C** to transfer its methyl ligand to Me_3Al, yielding tetramethylaluminate and **D**.[22] Under such circumstances, the presence of the adenine base as well as the 3′-alkoxyaluminum substituent in **D** would render the stereochemical bias in favor of less hindered attack (anti opening) to lead to the dominant formation of **F**, which gives **12** after workup.

If this mechanism is correct, the following two additional assumptions can be made: (1) formation of tetramethylaluminate (**C** → **D**) leading to anti-ring opening would be affected by the concentration of Me_3Al in the reaction medium, and (2) anti opening (**D** → **F**) would be encouraged by employing a less bulky 2′-*O*-protecting group. When the reaction in entry 4 in Table 1 (**12**/**13** = 5/1) was carried out in a 50-fold diluted medium (Me_3Al, 3.56 mM in the reaction medium), the ratio of **12**/**13** became 1.5/1, suggesting that intermolecular delivery

(22) Transfer of an ethyl group from the weaker acid M[Et_3AlOR] (M = K or Na) to the stronger acid Et_3Al is known to proceed quantitatively to give M[Et_4Al]: Lehmkuhl, H. *Angew. Chem., Int. Ed.* **1964**, *3*, 107.

TABLE 2. Reactions of 9−11 with Me_3Al [a]

entry	epoxide	products	combined yield (%) of the two isomers	ratio of β-D-isomer/α-L-isomer[b]
1	**9**	**12** and **13**	90	**12**/**13** = 5/1[c]
2	**10**	**16** and **17**	89	**16**/**17** = 10/1
3	**11**	**18** and **19**	94	**18**/**19** = 1/7

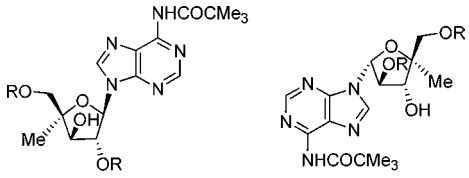
[a] All reactions were carried out in CH_2Cl_2 at −30 °C for 4.5 h by using Me_3Al (6.0 equiv). [b] The ratios were determined by ^1H NMR spectroscopy. [c] Data taken from Table 1

TABLE 3. Reaction of 9 with Me_3Al by Varying the Temperature [a]

entry	temp, °C	combined yield (%) of **12** plus **13**	ratio of **12**/**13**[b]
1	rt	92	0.7/1
2	0	98	1.4/1
3	−30	90	5/1[c]
4	−80	96	30/1

[a] All reactions were carried out in CH_2Cl_2 for 4.5 h by using Me_3Al (6.0 equiv). [b] The ratios were determined by ^1H NMR spectroscopy. [c] Data taken from Table 1.

of the methyl group from tetramethylaluminate had been suppressed. The influence of the 2′-*O*-silyl group was assessed by employing the 3′,4′-epoxides **9** (R = TBDMS), **10** (R = $SiEt_3$), and **11** (R = TBDPS) as substrates. The results are summarized in Table 2. Compared with the ratio previously observed in **9** (entry 1, **12**/**13** = 5/1), a significant increase of less hindered attack (anti opening) was seen by the use of **10** (entry 2, **16**/**17** = 10/1) having the less bulky triethylsilyl group. The fact that **11** containing the more bulky TBDPS group gave reversed stereoselectivity (entry 3, **18**/**19** = 1/7) exceeded our expectations. These experimental results may constitute further support to the proposed mechanism.



16 R = $SiEt_3$ **17** R = $SiEt_3$

18 R = TBDPS **19** R = TBDPS

Finally, the effect of the reaction temperature was examined. As shown in Table 3 from the reaction of **9**, it appeared that the lower the reaction temperature, the higher the selectivity for anti opening. This suggests that, at a lower temperature, the equilibrium between **B** and **C** (Scheme 4) had shifted toward **C**. Since stereoselectivity of the reaction of Me_3Al with the epoxide derived from **14**, lacking the nucleobase, was not affected by reaction temperature, forming the syn-opened product **15** exclusively at −80 °C (73%) as well as at room temperature (78%), the presence of the N^6-pivaloyladenine moiety may be crucial for this equilibrium shift. By combining two factors directing the stereoselectivity in combination, the reaction temperature and steric bulk of the 2′-*O*-silyl group, the highest selectivity of 50/1 for β-D-isomer/α-L-isomer was attained in the reaction of **10** (R = $SiEt_3$) at −80 °C (combined yield of **16** plus **17**: 90%).

Conclusion

The "3′,4′-up" epoxides (**9**−**11**) of 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**1**), having a cyclic enol ether

structure, were efficiently prepared by oxidation with DMDO. Stereoselectivity of epoxide ring opening with Me_3Al, anti versus syn, was investigated by changing the amount of Me_3-Al, the solvent, the *O*-silyl protecting group, and the reaction temperature. Reaction of the 3′,5′-bis-*O*-TBDMS epoxide **9** carried out in CH_2Cl_2 in a range of 0 to −80 °C uniformly resulted in the preferential formation of the anti-ring-opened product **12**, which is in sharp contrast to the reported stereoselectivity for epoxides derived from 3,4-dihydro-2*H*-pyran and glycal derivatives.

The fact that **14** lacking the adenine base, upon reacting in CH_2Cl_2 at −30 °C, gave solely the syn-opened product **15** suggests an important role of the nucleobase for the observed anti-selectivity. By employing **9**, it was also possible to change stereochemical bias toward exclusive formation of the syn-opened product **13**, simply by carrying out the reaction in an ethereal solvent, such as THF, Et_2O, and 1,4-dioxane. These results led us to propose a reaction mechanism depicted in Scheme 4. Based on this mechanism, the highest anti-selectivity (anti/syn = 50/1) was accomplished by reacting the 2′-*O*-$SiEt_3$ epoxide **10** in CH_2Cl_2 at −80 °C.

Since 9-(β-D-xylofuranosyl)adenine has long been known as a biologically active nucleoside analogue[23] and since nucleosides having a carbon substituent at the 4′-position constitute a promising class of antiviral agents,[24,25] we believe that the present study may be useful for the development of new biologically active nucleoside analogues.

Experimental Section

9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-*glycero*-pent-3-enofuranosyl]adenine (2). To a pyridine (20 mL) solution of **1** (2.0 g, 8.06 mmol) was added TBDMSCl (3.6 g, 24.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min and then at room temperature for 24 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated aq $NaHCO_3$. Evaporation of the organic layer followed by column chromatography ($CHCl_3$/MeOH = 60/1) gave **2** (foam, 3.69 g, 96%): UV (MeOH) λ_{max} 260 nm (ϵ 15 200), λ_{min} 231 nm (ϵ 4 100); ^{1}H NMR ($CDCl_3$) δ 0.06, 0.09, 0.10, and 0.11 (12H, each as s), 0.89 and 0.92 (18H, each as s), 4.26 and 4.30 (2H, each as d, J = 14.6 Hz), 5.18 (1H, d, J = 1.3 Hz), 5.25 (1H, dd, J = 1.8 and 1.3 Hz), 5.58 (2H, br), 6.41 (1H, d, J = 1.8 Hz), 7.85 (1H, s), 8.39 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.40, −5.38, −4.54, −4.51, 18.1, 18.3, 25.7, 25.8, 58.6, 80.1, 91.9, 99.8, 119.5, 137.7, 149.7, 153.4, 155.4, 161.8; FAB-MS (*m*/*z*) 478 (M^+ + H). Anal. Calcd for $C_{22}H_{39}N_5O_3Si_2$: C, 55.31; H, 8.23; N, 14.66. Found: C, 55.27; H, 8.36; N, 14.62.

9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-*glycero*-pent-3-enofuransyl]-N^6-pivaloyladenine (5). To a CH_2Cl_2 (20 mL) solution of **2** (5.8 g, 12.1 mmol) was added *i*-Pr_2NEt (3.2 mL, 18.2 mmol) and pivaloyl chloride (1.8 mL, 14.6 mmol) under positive pressure of dry Ar at 0 °C. After being stirred for 2 h at 0 °C, the reaction mixture was partitioned between CH_2Cl_2 and saturated aq $NaHCO_3$. Evaporation of the organic layer followed by column chromatography (hexane/EtOAc = 5/1) gave **5** (foam, 5.85 g, 86%): UV (MeOH) λ_{max} 272 nm (ϵ 17 800), λ_{min} 236 nm (ϵ 6 000); ^{1}H NMR ($CDCl_3$) δ 0.05, 0.08, 0.10, and 0.11 (12H, each as s), 0.89 and 0.92 (18H, each as s), 1.41 (9H, s), 4.26 and 4.31 (2H, each as d, J = 14.6 Hz), 5.17 (1H, d, J = 1.3 Hz), 5.26 (1H, dd, J = 1.8 and 1.3 Hz), 6.47 (1H, d, J = 1.8 Hz), 8.02 (1H, s), 8.48 (1H, br), 8.77 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.42, −5.39, −4.6, 18.0, 18.3, 25.7, 25.8, 27.4, 40.4, 58.5, 80.2, 92.1, 99.9, 122.8, 139.9, 149.5, 151.4, 152.4, 161.8, 175.7; FAB-MS (*m*/*z*) 562 (M^+ + H). Anal. Calcd for $C_{27}H_{47}N_5O_4Si_2$: C, 57.72; H, 8.43; N, 12.46. Found: C, 57.70; H, 8.61; N, 12.47.

9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-4-(3-chlorobenzoyloxy)-β-D-xylofuranosyl]-N^6-pivaloyladenine (8). To a CH_2Cl_2 (5 mL) solution of **5** (200 mg, 0.36 mmol) was added a CH_2Cl_2 (20 mL) solution of *m*-CPBA (purity minimum 65%, 280 mg, 1.07 mmol). After being stirred for 1.5 h at room temperature, the reaction mixture was treated with Et_3N (0.15 mL) and partitioned between CH_2Cl_2 and H_2O. Evaporation of the organic layer followed by column chromatography (hexane/EtOAc = 2/1) gave **8** (foam, 42.9 mg, 16%): UV (MeOH) λ_{max} 272 nm (ϵ 21 200), λ_{min} 248 nm (ϵ 12 800); ^{1}H NMR ($CDCl_3$) −0.14, −0.02, 0.05, and 0.07 (12H, each as s), 0.72 and 0.86 (18H, each as s), 1.42 (9H, s), 4.34 and 4.38 (2H, each as d, J = 11.1 Hz), 4.69 (1H, dd, J = 3.1 and 7.3 Hz), 4.73 (1H, dd, J = 3.1 and 3.8 Hz), 5.59 (1H, d, J = 7.3 Hz), 6.25 (1H, d, J = 3.8 Hz), 7.38−7.42, 7.55−7.58, 7.94−7.96, and 8.03−8.04 (4H, m), 8.23 (1H, s), 8.59 (1H, br), 8.77 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.1, −4.8, 17.8, 18.4, 25.5, 25.9, 27.5, 40.7, 62.0, 80.4, 81.9, 91.2, 112.6, 123.5, 128.1, 129.8, 129.9, 131.9, 133.5, 134.6, 142.2, 150.2, 150.7, 152.6, 163.9, 175.7; FAB-MS (*m*/*z*) 734 (M^+ + H). Anal. Calcd for $C_{34}H_{52}ClN_5O_7Si_2$: C, 55.60; H, 7.14; N, 9.54. Found: C, 55.55; H, 7.25; N, 9.46.

The Epoxide 9 Formed by DMDO Oxidation of 5. This compound was not fully characterized due to its instability. Spectral data of this compound are as follows: ^{1}H NMR ($CDCl_3$) δ 0.09, 0.11, and 0.13 (12H, each as s), 0.92 (18H, s), 1.41 (9H, s), 3.72 (1H, s), 4.17 and 4.27 (2H, each as d, J = 12.3 Hz), 4.63 (1H, s), 6.54 (1H, s), 8.38 (1H, s), 8.56 (1H, br), 8.73 (1H, s); FAB-MS (*m*/*z*) 578 (M^+ + H).

Reaction of Me_3Al with 9 Listed in Entry 4 of Table 1 as a Typical Procedure: Formation of 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-4-*C*-methyl-β-D-xylofuranosyl]-N^6-pivaloyladenine (12) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-4-*C*-methyl-α-L-arabinofuranosyl]-N^6-pivaloyladenine (13). To a CH_2Cl_2 (12 mL) solution of **5** (200 mg, 0.36 mmol) was added an acetone solution of DMDO (ca. 0.04M, 13.2 mL, 0.53 mmol) under positive pressure of dry Ar at −30 °C. After the mixture was stirred for 0.5 h at −30 °C, the solution containing **9** was evaporated and dried under diminished pressure. Compound **9** thus prepared was dissolved in CH_2Cl_2 (12 mL) and cooled to −30 °C. To this was added Me_3Al (1.03 M hexane solution, 2.12 mL, 2.14 mmol). The reaction mixture was stirred for 4.5 h at −30 °C, quenched by adding saturated aq NH_4Cl, and filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave a mixture of **12** and **13** (foam, 190.1 mg, 90%, **12**/**13** = 5/1). HPLC (hexane/EtOAc = 1/1) separation of the mixture gave analytical pure **12** (foam, t_R 10.9 min) and **13** (foam, t_R 13.0 min).

Physical date for 12: UV (MeOH) λ_{max} 272 nm (ϵ 18 100), λ_{min} 235 nm (ϵ 4 300); ^{1}H NMR ($CDCl_3$) δ −0.08, 0.04, 0.09, and 0.10 (12H, each as s), 0.85 and 0.92 (18H, each as s), 1.41 (9H, s), 1.43 (3H, s), 3.77 and 3.88 (2H, each as d, J = 10.6 Hz), 4.04 (1H, d, J = 1.8 Hz), 4.60 (1H, dd, J = 3.5 and 1.8 Hz), 4.93 (1H, br), 6.04 (1H, d, J = 3.5 Hz), 8.29 (1H, s), 8.59 (1H, br), 8.76 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −5.0, −4.8, 17.9, 18.3, 21.5, 25.6, 26.0, 27.5, 40.6, 67.3, 83.0, 84.3, 87.1, 90.2, 123.3, 142.2, 149.8, 151.1, 152.5, 175.7; FAB-MS (*m*/*z*) 594 (M^+ + H). Anal. Calcd for $C_{28}H_{51}N_5O_5Si_2$: C, 56.63; H, 8.66; N, 11.79. Found: C, 56.53; H, 8.84; N, 11.76.

Physical data for 13: UV (MeOH) λ_{max} 272 nm (ϵ 18 300), λ_{min} 237 nm (ϵ 6 300). ^{1}H NMR ($CDCl_3$) δ −0.04, 0.06, and 0.08 (12H, each as s), 0.87 and 0.92 (18H, each as s), 1.39 (3H, s), 1.41 (9H, s), 3.62 and 3.81 (2H, each as d, J = 9.7 Hz), 4.15 (1H, d, J = 1.4 Hz), 4.72 (1H, dd, J = 2.4 and 1.4 Hz), 5.72 (1H, br), 5.80 (1H, d, J = 2.4 Hz), 8.07 (1H, s), 8.55 (1H, br), 8.77 (1H, s); ^{13}C

(23) For an example, see: Ellis, D. B.; LePage, G. A. *Mol. Pharmacol.* **1965**, *1*, 231.

(24) For an excellent review, see: Hayakawa, H.; Kohgo, S.; Kitano, K.; Ashida, N.; Kodama, E.; Mitsuya, H.; Ohrui, H. *Antiviral Chem. Chemother*. **2004**, *15*, 169.

(25) For a recent example, see: Tanaka, H.; Haraguchi, K.; Kumamoto, H.; Baba, M.; Cheng, Y.-C. *Antiviral Chem. Chemother*. **2005**, *16*, 217.

NMR ($CDCl_3$) δ −5.5, −5.4, −5.0, −4.8, 17.8, 18.2, 25.6, 25.8, 27.4, 40.5, 66.4, 79.2, 85.0, 89.7, 92.7, 124.0, 142.6, 150.1, 152.1, 175.6; FAB-MS (*m*/*z*) 594 ($M^+ + H$). Anal. Calcd for $C_{28}H_{51}N_5O_5Si_2$: C, 56.63; H, 8.66; N, 11.79. Found: C, 56.43; H, 8.83; N, 11.68.

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Supporting Information Available: General Experimental Section, scheme, and procedures for the preparation of **14**, characterization data for compounds **3**, **4**, **6**, **7**, **10**, **11**, **14**−**16**, **17**−**19**, and ^{13}C NMR spectra of compounds **14**, **15**, and those involved in the preparation of **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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