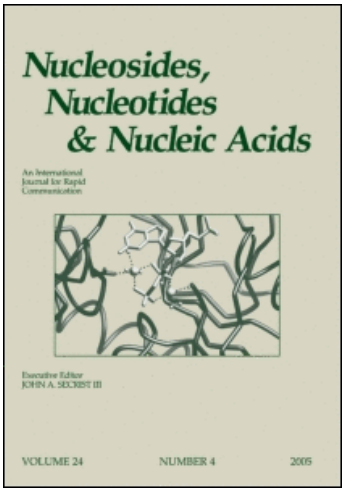

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SYNTHETIC USE OF EPOXY-SUGAR NUCLEOSIDES

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□ *Preparation of 1′,2′-, 3′,4′-, and 4′,5′-epoxy derivatives of nucleosides and their use for the stereoselective synthesis of 1′- and 4′-branched analogues are described.*

Keywords Unsaturated-sugar nucleoside; dimethyl dioxirane; epoxy-sugar nucleoside; organoaluminum reagent; ring opening; branched-sugar nucleoside; anti-HIV activity

INTRODUCTION

There have been several reports on the preparation and nucleophilic ring opening of nucleosides having an epoxy-sugar structure.[1] These are, however, limited to those of 2′,3′-epoxides. There are three other possible epoxides, 1′,2′-, 3′,4′-, and 4′,5′-, which are structurally unique in that the carbon bonded to the furanose oxygen is directly attached to the epoxide ring. These epoxides, therefore, are expected to readily undergo nucleophilic ring opening. By the same reason, the preparation of these epoxides from the corresponding unsaturated-sugar nucleosides has to be carried out under nonnucleophilic conditions. In our present studies, this was accomplished in acetone by employing dimethyl dioxirane (DMDO)[2] as an oxidizing reagent.

Although both organoaluminum reagents and organosilicon reagents/Lewis acid effects regio-defined and stereoselective ring opening of these 1′,2′-, 3′,4′-, and 4′,5′-epoxides to give either 1′-branched or 4′-branched nucleosides, focus is given to reactions with organoaluminum reagents in this proceeding, and mechanistic aspect of these reaction is principally described.

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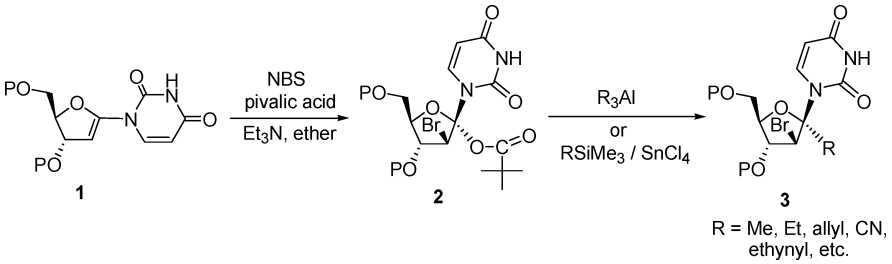


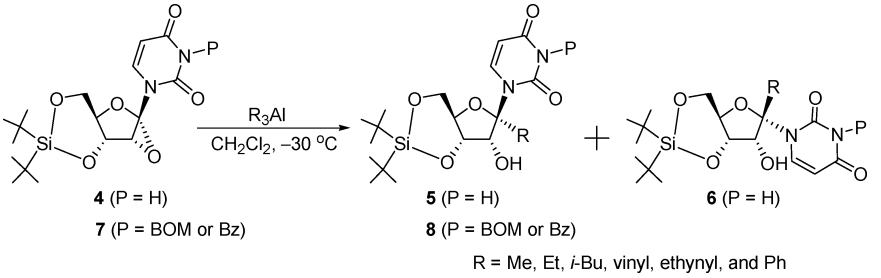
SCHEME 1 (P = TBDMS).

RESULTS AND DISCUSSION

Ring Opening of 1′,2′-Epoxy Nucleosides with R_3Al

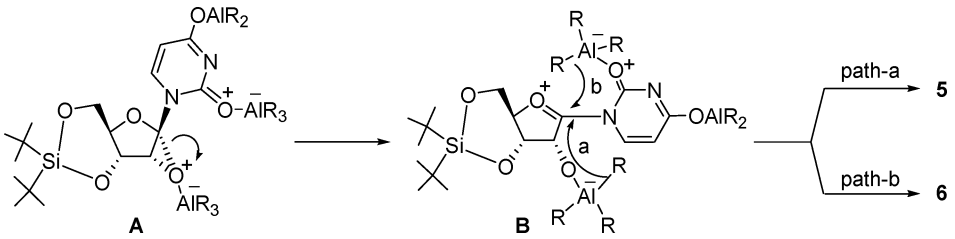
Our previous study,[3] directed toward the synthesis of 1′-branched uracil nucleosides, is shown in Scheme 1. This approach consists of two reactions: bromo-pivaloyloxylation of **1**, and subsequent stereospecific nucleophilic substitution of **2** with organoaluminum reagents or organosilicon reagents/$SnCl_4$. The resulting 1′-branched products **3** can be converted to 2′-deoxy as well as arabinofuranosyl derivatives by manipulating the 2′-bromine atom. However, transformation of **3** to ribofuranosyl derivatives remained problematic, which led us to investigate the present study.

Although DMDO-epoxidation of **1** or its 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-protected derivative took place preferentially at the β-face of the 1-enofuranosyl structure, employing the 3′,5′-*O*-di-*tert*-butylsilylene protection enabled us to prepared the desired 1′,2′-α-epoxide (**4**). Upon reacting **4** with a variety of organoaluminum reagents (R_3Al), the expected *syn*-ring-opened products (**5**) were always accompanied with the anti- ring-opened α-uridines (**6**), except for the reaction of Ph_3Al. On the other hand, the 1′,2′-α-epoxide prepared from N^6-pivaloyl-1′,2′-unsaturated adenosine in a similar manner gave exclusively the *syn*-ring-opened products. These results suggest that the observed formation of **6** may have something to do with the uracil base moiety. (See Scheme 2.)



SCHEME 2

We proposed a plausible mechanism for the reaction of **4** with R_3Al (Scheme 3).Dissociation of an acidic N^3-H of **4** with AlR_3 followed by its



SCHEME 3

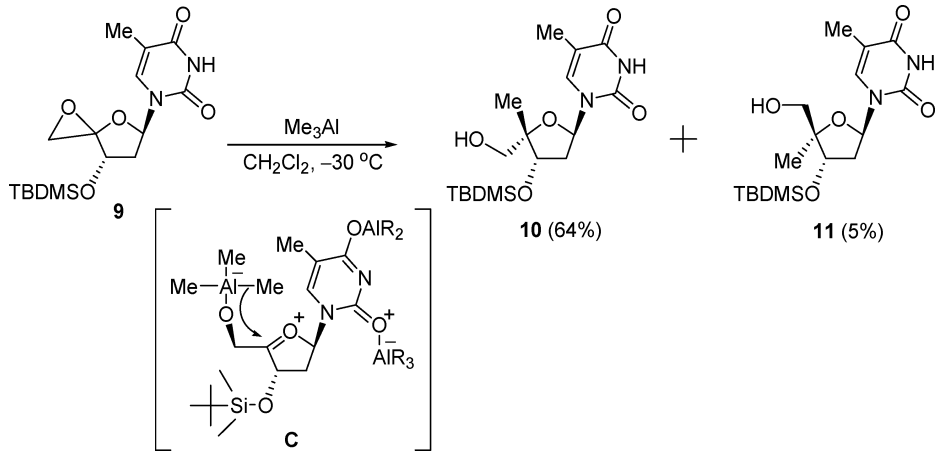
coordination to the oxygen atom of the epoxide ring as well as to that of the C^2-carbonyl would give **A**, which in turn forms the oxonium intermediate **B**. At this stage, if nucleophilic transfer of the aluminum ligand R takes place from the 2′-*O*-aluminate (path-a), **5** should be formed, whereas such attack from the base moiety (path-b) results in the formation of **6** or **5** depending on the conformation about the N^1-C^1 pivot bond. The observed sole formation of **5** in the reaction of Ph_3Al could be explicable in terms of inability of this bulky reagent to coordinate to the C^2-carbonyl oxygen.

Based on this mechanism, it would be reasonable to expect that the presence of a bulky protecting group at the N^3-position will prevent coordination of R_3Al to the C^2-carbonyl oxygen. Reactions carried out along this line by employing the N^3-protected substrate **7** uniformly gave the *syn*-ring-opened **8** as a sole product (Scheme 2).[4,5]

Ring Opening of 4′,5′-Epoxy Thymine Nucleosides with R_3Al: Finding of a Promising Anti-HIV-1 Agent 4′-Ethynylstavudine

This study was motivated by fairly recent reports that 4′-substituted nucleosides show significant inhibitory activity against HIV proliferation.[6] Since the most commonly utilized method for the synthesis of these compounds is manipulation of 4′-hydroxymethyl derivatives of nucleosides or sugars prepared via aldol-Cannizzaro reaction,[7] we intended to develop a new and general method based on nucleophilic ring opening of a suitable 4′,5′-epoxy structure.

Ring opening of the epoxide **9** prepared from 4′,5′-unsaturated thymidine was first examined using Me_3Al (Scheme 4). As a result, dominant formation of the 4′-methyl-α-L-isomer **10** was observed, the desired β-D-isomer being formed only in 5% yield.[8] This unsatisfactory outcome is assumed to be due to conformational preference of the oxonium intermediate depicted as **C**, which can avoid the steric repulsion between the 5′-*O*-aluminate and the 3′-*O*-TBDMS group. In fact, the 4′,5′-epoxide (**12**) having the opposite 3′-configuration to **9** (Scheme 5), upon reacting with Me_3Al, gave solely the

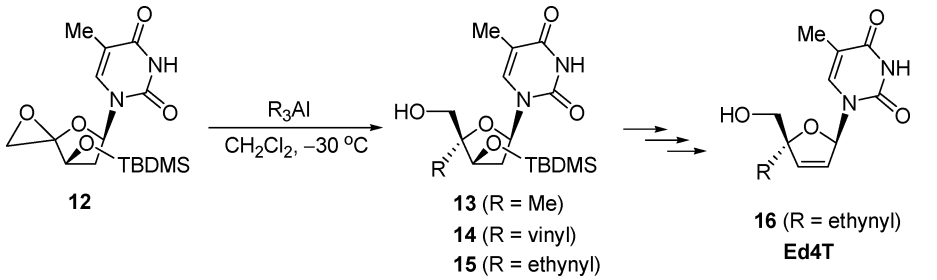


SCHEME 4

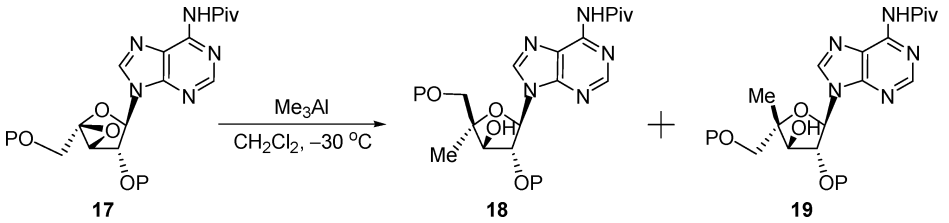
4′-methyl-β-D-isomer **13** (72%). By applying this method, the 4′-vinyl (**14**) and 4′-ethynyl (**15**) derivatives also were prepared. Attempts to effect inversion at the 3′-position of these 4′-branched products (**13–15**) by nucleophilic substitution gave mainly elimination products.

Among these elimination products, 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine (**16**: Ed4T) was found to be more inhibitory against HIV-1 than the parent compound stavudine (d4T), and much less toxic to various cells and also to mitochondrial DNA synthesis.[9–12] This compound has several additional advantages as a promising anti-HIV-1 agent: 1) it is a better substrate for human thymidine kinase than d4T;[10] 2) it is very much more resistant to catabolism by thymidine phosphorylase,[10] and 3) its activity enhances in the presence of a major mutation K103N,[11] a known resistant mutation for some non-nucleoside reverse transcriptase inhibitors.

Some structure-activity relationship studies of Ed4T (**16**) also were carried out.[13–15] For the analogues of **16** to be inhibitory against HIV-1, their 4′-carbon-substituent has to be sp-hybridized like ethynyl and cyano. Since methylation of the ethynyl group of **16** decreased the activity,[10] smaller size



SCHEME 5



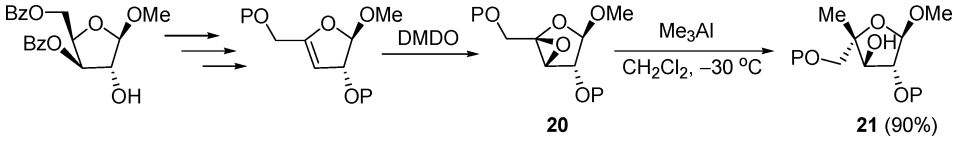
SCHEME 6 (P = TBDMS, Piv = pivaloyl).

could be an additional requirement for the 4′-substituent. Replacement of the furanose oxygen of **16** with sulfur[14] retains the activity, while that with methylene[15] resulted in total loss of the activity.

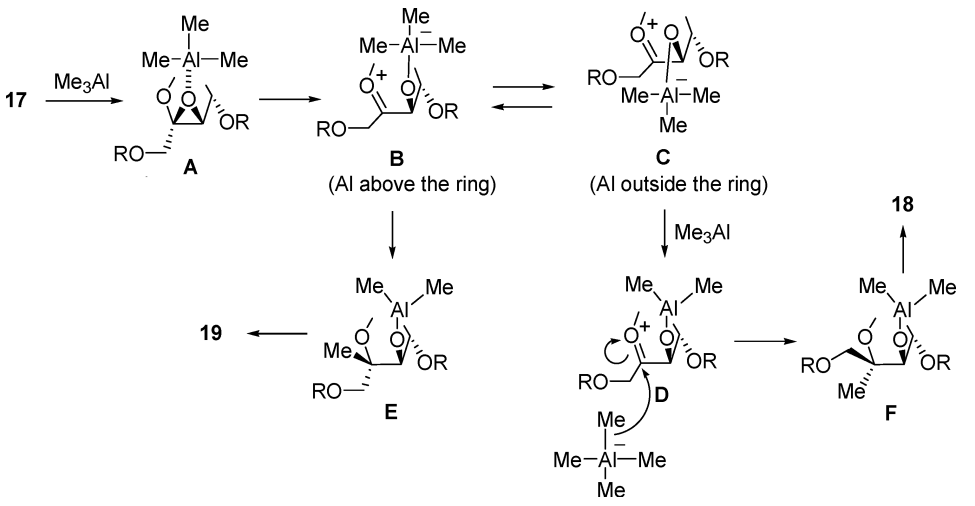
Factors Controlling the Stereoselectivity of Epoxide Ring Opening (*anti* vs. *syn*) with Me_3Al: Study on a 3′,4′-Epoxy Adenine Nucleoside

Simple epoxides are known to react with Me_3Al in a manner of *anti*-ring-opening, but no clear explanation is available for this stereochemical outcome. On the other hand, the epoxides derived from glycals, cyclic enol ethers, and 3,4-dihydro-2*H*-pyran give *syn*-opened products.[16] As shown in Scheme 6, by employing **17**, we investigated factors governing the stereoselectivity of its epoxide ring-opening (*anti*- vs. *syn*-opening) with Me_3Al.[17]

Although **17** is a kind of glycal-derived epoxide, preferential formation of the *anti*-opened **18** was observed when the reaction was carried out in CH_2Cl_2. Also, it was found that the ratio of **18** (*anti*-opened)/**19** (*syn*-opened) varies significantly (from 2/1 to 6/1) by increasing the amount of Me_3Al (from 1.0 equiv. to 10 equiv). In contrast to this, the same reaction carried out in THF, Et_2O, or 1,4-dioxane by using 6.0 equiv. of Me_3Al uniformly led to the exclusive formation of the *syn*-opened product **19**. To see if the presence of the N^6-pivaloyladenine base has any influence on the stereochemistry, the corresponding sugar epoxide **20** was prepared and reacted with Me_3Al (6.0 equiv). As shown in Scheme 7, although this reaction was carried out in CH_2Cl_2, the sole formation of the *syn*-opened product **21** was observed.



SCHEME 7 (P = TBDMS).



SCHEME 8 (R = TBDMS).

These experimental results enabled us to propose a possible reaction mechanism between **17** and Me_3Al depicted in Scheme 8 (N^6-pivaloyladenine moiety is omitted for simplicity). Highly oxygenophilic Me_3Al would prefer coordination to the 3′,4′-epoxy structure of **17** to give **A**, 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 oxonium ion as a result of 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.

When the amount of remaining Me_3Al is limited or it is complexed with an ethereal solvent, intramolecular attack of the methyl ligand from **B** would inevitably take place to give **E** (*syn*-opening), which is finally converted to **19**. On the other hand, in the case where noncoordinated M_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[18] and **D**. 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 to lead to the dominant formation of **F** (*anti*-opening), which gives **18** after work up.

Such transfer of the methyl ligand from **B** to Me_3Al would also be affected by the concentration of Me_3Al in the reaction medium. The reaction which gave the ratio of **18**/**19** = 5/1 (6 equiv. of Me_3Al), when carried out in a 50-fold diluted medium, the ratio became 1.5/1.

One would imagine that the stereochemical outcome of this reaction also would be affected by the bulkiness of the 2′-*O*-silyl group. The

ratio of **18/19** = 5/1 observed for **17** (TBDMS-protected epoxide) became 10/1 when the corresponding TES (triethylsilyl)-protected epoxide was employed. It was beyond our expectation that the TBDPS (di-*tert*-butyldiphenylsilyl)-protected epoxide gave the reverse stereoselectivity (**18/19** = 1/7).

A significant change of the ratio was also observed by varying the reaction temperature. At a higher temperature, almost equal amounts of **18** and **19** were formed (at 0°C, 1.4/1; at room temperature 0.7/1). At a lower temperature of −80°C, the ratio was inverted and became 30/1. By combining the experimental results obtained thus far, the highest stereoselectivity (**18/19** = 50/1, combined yield 90%) was attained by carrying out the reaction at −80°C in CH_2Cl_2 employing the TES-protected epoxide.

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