

Ring Opening of 4',5'-Epoxy nucleosides: A Novel Stereoselective Entry to 4'-C-Branched Nucleosides

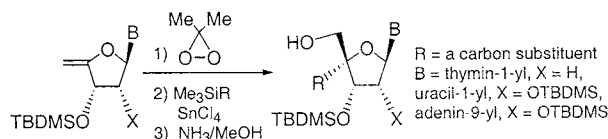
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ABSTRACT



Stereoselective synthesis of 4'- α -carbon-substituted nucleosides has been accomplished through epoxidation of 4',5'-unsaturated nucleosides with dimethyldioxirane (DMDO) and successive SnCl₄-promoted ring opening of the resulting 4',5'-epoxy nucleosides with organosilicon reagents.

Nucleoside analogues are recognized as an important class of biologically active compounds, especially as antiviral and antitumor agents.¹ Recently, 4'-substituted nucleosides have attracted much attention because of the discovery of the potent anti-HIV agents 4'-azido- (**1**) and 4'-cyanothymidine (**2**).² Although incorporation of heteroatoms into the 4'-position of nucleosides can be carried out by the simple electrophilic addition to 4',5'-unsaturated nucleosides,^{2,3} this method is not suitable for carbon substituents.

The most commonly utilized method for the preparation of 4'-branched analogues is manipulation of 4'-hydroxymethyl derivatives of nucleosides or sugars prepared via an aldol-Cannizzaro reaction of the corresponding aldehyde.^{4,5} Other recently reported methods include intramolecular

radical cyclization of a 3'-O-silicon-tethered nucleoside C4'-radical⁶ and electrophilic substitution of nucleoside 5'-esters.⁷

Although ring opening of epoxides with carbon nucleophiles constitutes a powerful synthetic operation for C–C bond-forming reactions,⁸ little attention has been paid for its application to the synthesis of branched sugar-nucleosides.⁹ In this paper, we wish to describe a novel method for the stereoselective synthesis of 4'- α -carbon-substituted nucleosides based on epoxidation of 4',5'-unsaturated nucleosides followed by SnCl₄-assisted ring opening with organosilicon reagents.

One would readily anticipate from their enol ether structure that 4',5'-unsaturated nucleosides would be highly susceptible to nucleophilic attack under acidic conditions. In fact, it has

(1) For a review, see: *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993.

(2) Prisbe, E. J.; Maag, H.; Verheyden, J. P. H.; Ryzdewski, R. M. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993; pp 101–113.

(3) (a) Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 3346–3357. (b) Owen, G. R.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 3010–3017. (c) Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4386–4395. (d) Sasaki, T.; Minamoto, K.; Kuroyanagi, S.; Hattori, K. *Tetrahedron Lett.* **1973**, *14*, 2731–2733. (e) Sasaki, T.; Minamoto, K.; Hattori, K. *J. Am. Chem. Soc.* **1973**, *95*, 1350–1351.

(4) (a) Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. *J. Med. Chem.* **1999**, *42*, 2901–2908. (b) Ohru, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. *J. Med. Chem.* **2000**, *43*, 4516–4525.

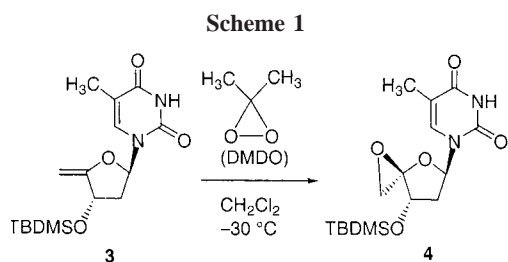
(5) Other synthetic methods: (a) Secrist, J. A., III; Winter, W. J., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2554–2555. (b) Haraguchi, K.; Tanaka, H.; Itoh, Y.; Yamaguchi, K.; Miyasaka, T. *J. Org. Chem.* **1996**, *61*, 851–858. (6) Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 7153–7157.

(7) Jung, M. E.; Toyota, A. *J. Org. Chem.* **2001**, *66*, 2624–2635.

(8) For a review, see: Smith, J. G. *Synthesis* **1984**, 629–656.

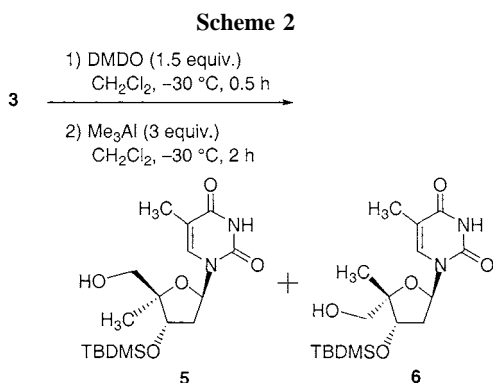
(9) Ashwell, M.; Jones, A. S.; Walker, R. T. *Nucleic Acids Res.* **1987**, *15*, 2157–2166.

been reported that *m*-CPBA-oxidation of 4',5'-unsaturated thymidine (4',5'-didehydro-5'-deoxythymidine) in MeOH resulted in the formation of 4'-methoxythymidine as a mixture of 4'-epimers.^{2,10} We, therefore, examined dimethyldioxirane (DMDO), which can be used under neutral conditions in aprotic solvents.¹¹ When 3'-*O*-TBDMS-4',5'-unsaturated thymidine (**3**) was treated with an acetone solution of DMDO (1.5 equiv) in CH₂Cl₂ at -30 °C, the reaction went to completion within 0.5 h and 4',5'-epoxythymidine **4** (a single isomer, evidenced by ¹H NMR) was obtained simply by removal of the solvents (Scheme 1). The



depicted stereochemistry of **4** came from the observed nOe correlation between H-5'/Si-*t*-Bu (0.9%) as well as the assumption that the α -face of the 4',5'-double bond would be shielded by the TBDMS group. Although DMDO has been known to oxidize the pyrimidine base of nucleosides,¹² no such side reaction was observed in the epoxidation of **3**.

The initial attempt to ring-open **4** was carried out with Me₃Al (3 equiv) as shown in Scheme 2. Although exclusive

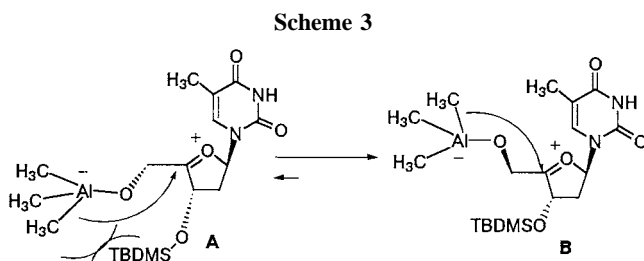


cleavage of the oxirane ring at the 4'-position was seen, the stereochemical outcome of this reaction was discouraging, forming the 4'- β -methyl isomer **6** (64%) as the major product together with **5** (5%). The stereochemistry of these products

(10) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440–1451.

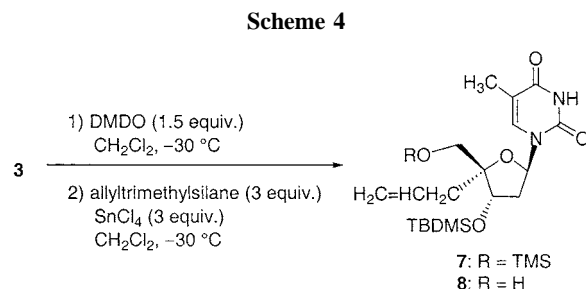
(11) (a) Adam, W.; Hadjjarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227–232. (b) Adam, W.; Bialas, J.; Hadjjarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(12) Example of oxidative modification of pyrimidine base with DMDO: Saladino, R.; Bernini, R.; Crestini, C.; Minocione, E.; Bergamini, A.; Marini, S.; Palamara, A. T. *Tetrahedron* **1995**, *51*, 7561–7578.



was determined by nOe experiment: **5** H-1'/Me-4' (4%), **6** H-3'/Me-4' (9%), and H-6/Me-4' (3%). As shown in Scheme 3, the result can be rationalized by assuming that the oxonium intermediate is in equilibrium as the conformers **A** and **B**, and that "intramolecular" methyl transfer to the 4'-position had occurred predominantly from **B** due to the steric repulsion associated with **A**. This assumption led us to examine Lewis acid-mediated intermolecular ring opening of **4** with organosilicon reagents.

Reaction of **4** with allyltrimethylsilane (3 equiv) using SnCl₄ (3 equiv) gave two products (Scheme 4). Their ¹H



NMR spectra showed that the more polar product was the expected 4'- α -allylthymidine **8** [nOe data: H-5'/H-3' (5.3%) and H-1'/CH₂=CHCH₂-4' (0.8%)] while the less polar one was its 5'-*O*-trimethylsilyl derivative (**7**). Thus, simple extractive workup of the reaction mixture followed by treatment with NH₃/MeOH enabled the isolation of **8** in 80% yield. The use of other Lewis acids, such as TiCl₄ or EtAlCl₂, gave mainly thymine, and **8** was obtained only in very low yields (5–7%).

The above SnCl₄-assisted stereoselective allylation also worked with 4',5'-epoxides derived from **9** and **13** (Figure

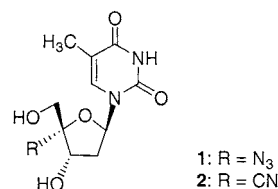


Figure 1.

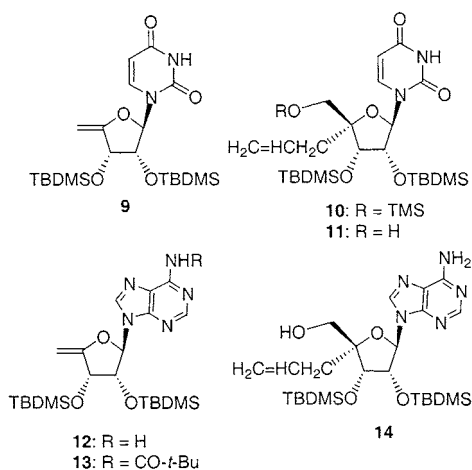
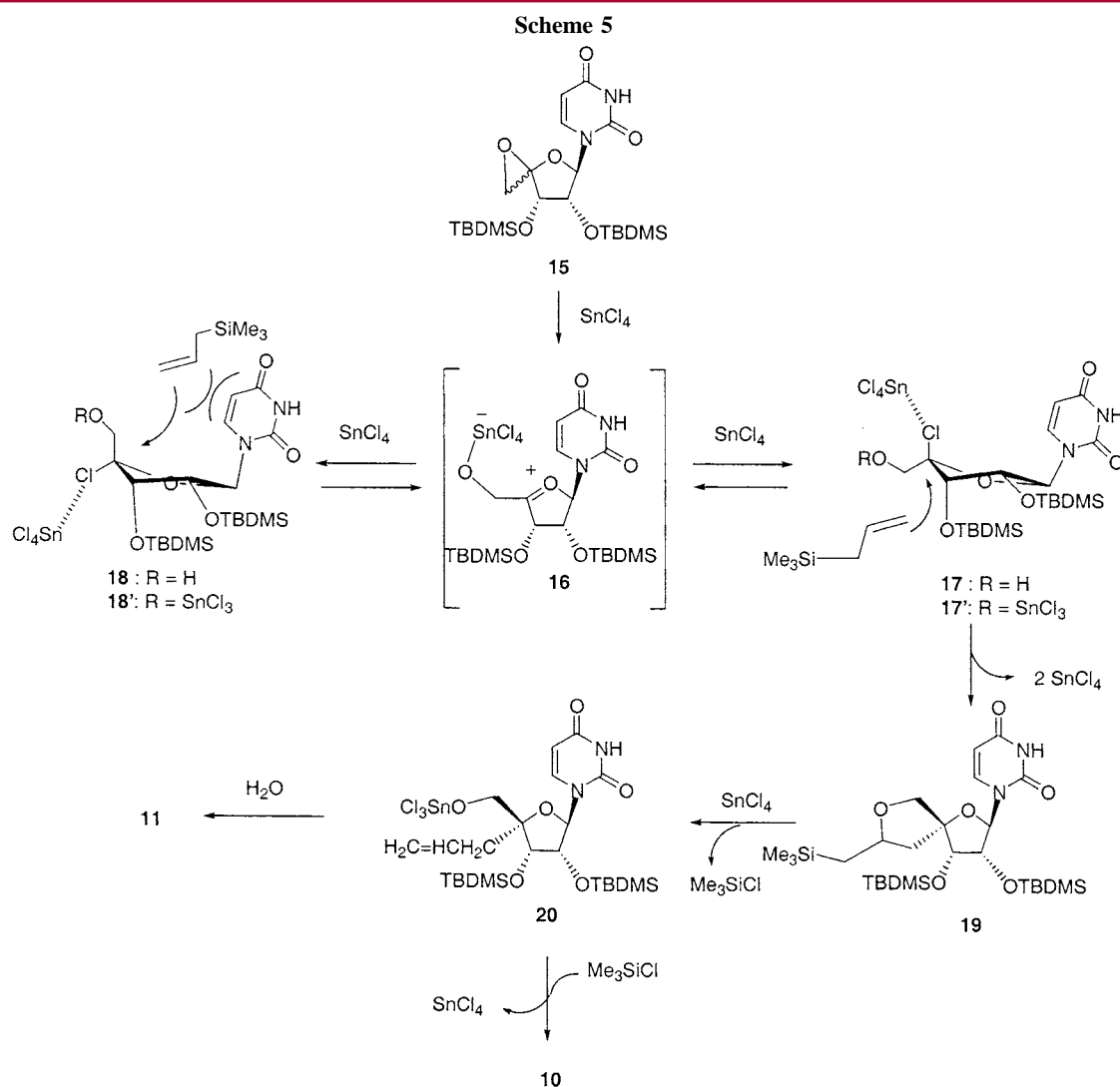


Figure 2.

2). Thus, allylation of the epoxide prepared from **9** gave a mixture of **10** and **11**. After NH_3/MeOH treatment of the

mixture, 4'- α -allyluridine **11** was isolated in 90% overall yield from **9**. In the case of **12**, to avoid N^1 -oxidation with DMDO, it was necessary to acylate the 6- NH_2 group. By using the N^6 -pivaloyl derivative **13**, 4'- α -allyl-adenosine **14** was obtained in 52% overall yield.

To elucidate the mechanism of the present allylation, the above-mentioned reactions of **9** were studied in some detail. Epoxidation of **9** with DMDO gave a 4',5'-epoxide **15** as a single isomer, although its stereochemistry could not be determined with an nOe experiment. When this epoxide was reacted solely with SnCl_4 in CH_2Cl_2 , two 4'-chlorinated products (**17** and **18**) were isolated. The stereochemistry was established on the basis of an nOe experiment. Analysis of their $J_{1',2'}$ and $J_{2',3'}$ values suggested that **17** and **18** would take the conformations as shown in Scheme 5, respectively. Independent treatment of **17** and **18** again with SnCl_4 resulted in isomerization, forming both compounds. Although no reaction took place by adding allyltrimethylsilane to a CH_2Cl_2 solution of **17**, addition of a catalytic amount of SnCl_4 (0.5 equiv) to this mixture caused an instantaneous reaction to give the spiro intermediate **19** (a mixture of two



diastereomers) that was isolated by HPLC and fully characterized. In the reaction medium, **19** was found to be converted slowly to **10** and **11**. Compound **18** behaved exactly in the same manner as **17**. These observations led us to propose the reaction mechanism in Scheme 5. The 4'- β - (**17'**) and 4'- α -chloro (**18'**) derivatives exist in equilibrium, and are interconvertible through the oxonium ion **16**. For the SnCl_4 -assisted reaction with allyltrimethylsilane, **18'** would be kinetically less favored because of the pseudoequatorial orientation of the chlorine atom,¹³ and presumably also due to steric hindrance exerted by the base moiety. On the other hand, the pseudoaxial chlorine atom in **17'** as well as the sterically less encumbered α -face permit its ready $\text{S}_{\text{N}}2$ reaction with allyltrimethylsilane to lead to the intermediate **19**. The β -effect of the silicon atom ensures regioselective opening of the spiro ring to yield **20**. Trapping of **20** with TMSCl gives rise to **10**, whereas quenching with H_2O furnishes **11**.

Finally, the scope of the present reaction was briefly examined by reacting 4',5'-epoxythymidine derivative **4** with other organosilicon reagents (Figure 3). Compounds **21** (47%) and **22** (32%) were synthesized as a single isomer by using (2-bromoallyl)trimethylsilane and (cyclopentenyl)-trimethylsilane, respectively, in CH_2Cl_2 in the presence of SnCl_4 (3 equiv). It would be worthy to mention that the present method provides an access to a potent anti-HIV agent, 4'- α -cyanothymidine, since a cyano group can be introduced into the 4'-position by using cyanotrimethylsilane to yield **23** (45%).

(13) Eliel, E. L.; Ro, R. S. *Chem. Ind.* **1956**, 251–252.

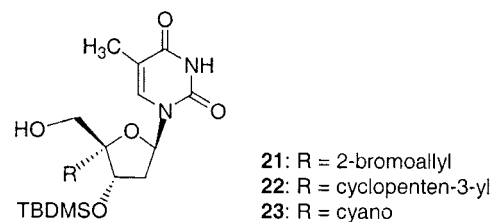


Figure 3.

In conclusion, a novel method for the stereoselective synthesis of 4'- α -carbon-substituted nucleoside analogues has been disclosed, using the SnCl_4 -assisted ring opening of 4',5'-epoxynucleosides with organosilicon reagents. The evidence-based reaction mechanism of 4'- α -selective allylation has also been proposed through the present study.

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Supporting Information Available: Experimental procedures and full characterization for compounds **3**, **5**, **6**, **8–14**, **17–19**, and **21–23**; ^1H NMR and MS spectrum of compound **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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