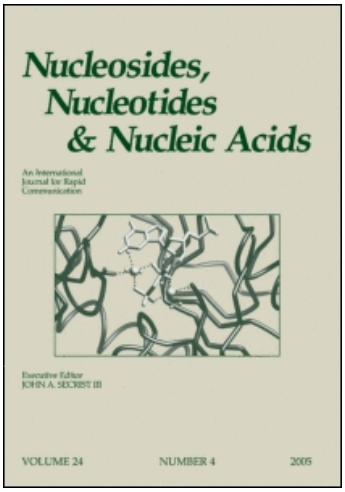


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A New Approach to the Synthesis of 4'-Carbon-Substituted Nucleosides: Development of a Highly Active Anti-HIV Agent 2', 3'-Didehydro-3'-Deoxy-4'-Ethynylthymidine

Kazuhiro Haraguchi[a]; Shingo Takeda[a]; Masanori Sumino[a]; Hiromichi Tanaka[a]; Ginger E. Dutschman[b]; Yung-Chi Cheng[b]; Takao Nitanda[c]; Masanori Baba[c]
[a] School of Pharmaceutical Sciences, Showa University, Tokyo, Japan [b] Department of Pharmacology, School of Medicine, Yale University, New Haven, Connecticut, USA [c] Center for Chronic Viral Diseases, Division of Antiviral Chemotherapy, Faculty of Medicine, Kagoshima University, Kagoshima, Japan

To cite this Article Haraguchi, Kazuhiro , Takeda, Shingo , Sumino, Masanori , Tanaka, Hiromichi , Dutschman, Ginger E. , Cheng, Yung-Chi , Nitanda, Takao and Baba, Masanori(2005) 'A New Approach to the Synthesis of 4'-Carbon-Substituted Nucleosides: Development of a Highly Active Anti-HIV Agent 2', 3'-Didehydro-3'-Deoxy-4'-Ethynylthymidine', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 343 — 347
To link to this Article: DOI: 10.1081/NCN-200059774
URL: http://dx.doi.org/10.1081/NCN-200059774

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):343–347, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200059774

Taylor & Francis
Taylor & Francis Group

A NEW APPROACH TO THE SYNTHESIS OF 4′-CARBON-SUBSTITUTED NUCLEOSIDES: DEVELOPMENT OF A HIGHLY ACTIVE ANTI-HIV AGENT 2′, 3′-DIDEHYDRO-3′-DEOXY-4′-ETHYNYLTHYMIDINE

Kazuhiro Haraguchi, Shingo Takeda, Masanori Sumino, and Hiromichi Tanaka
▫ *School of Pharmaceutical Sciences, Showa University, Tokyo, Japan*

Ginger E. Dutschman and Yung-Chi Cheng ▫ *Department of Pharmacology, School of Medicine, Yale University, New Haven, Connecticut, USA*

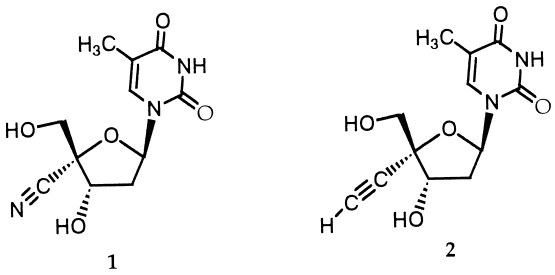
Takao Nitanda and Masanori Baba ▫ *Center for Chronic Viral Diseases, Division of Antiviral Chemotherapy, Faculty of Medicine, Kagoshima University, Kagoshima, Japan*

▫ *Oxidation of 3′-O-TBDMS-4′,5′-unsaturated thymidine* ***3*** *with dimethyldioxirane (DMDO) allowed the isolation of the epoxide* ***4****. Upon reacting with organosilicon reagents in the presence of* $SnCl_4$*,* ***4*** *underwent stereoselective ring opening to give 4′-α-allyl (****6****), 4′-α-(2-bromoallyl) (****7****), 4′-α-(cyclopenten-3-yl) (****8****), and 4′-α-cyano (****9****) derivatives of thymidine. Reactions of the 3′-epimer* ***12*** *with organoaluminum reagents gave 4′-α-methyl (****13****), 4′-α-vinyl (****14****), and 4′-α-ethynyl (****15****) analogues. Compounds* ***13–15*** *were transformed into corresponding 2′,3′-didehydro-3′-deoxy derivatives. Evaluation of their ability to inhibit the replication of HIV in cell culture showed that 4′-ethynyl-d4T (****19****) is more potent and less toxic than the parent compound d4T.*

Keywords Anti-HIV, 4′-Substituted Nucleosides, Didehydro-3′-Deoxythymidine, Dimethyldioxirane, Epoxidation, Organosilicon Reagents, Lewis Acids, Organoaluminum Reagents

This work was financially supported in part by grants from the Japan Health Sciences Foundation (SA14718 to H. T.), Japan Society for the Promotion of Science (KAKENHI No. 15590100 to K. H. and No. 15590020 to H. T.), the Research Foundation of Pharmaceutical Sciences (to K. H.), and NIH USA (RO1 AI 38204 to Y.-C. Cheng).

Address correspondence to Dr. Kazuhiro Haraguchi, School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan; Fax: 81-3-3784-8252; E-mail: harakazu@pharm.showa-u.ac.jp



1 2

FIGURE 1 4′-Cyano- and 4′-ethynylthymidines.

INTRODUCTION

Nucleoside analogues are an important class of biologically active compounds, especially as antiviral and antitumor agents.* Recently, 4′-substituted nucleosides have attracted much attention because of the discovery of the potent anti-HIV agents 4′-cyano (**1**) and 4′-ethynyl (**2**) analogues of thymidine (Figure 1).[2,3] The most frequently utilized method for the preparation of these analogues is manipulation of 4′-hydroxymethyl derivatives of nucleosides or sugars prepared via an aldol-Cannizzaro reaction of the corresponding aldehyde.[4,5]

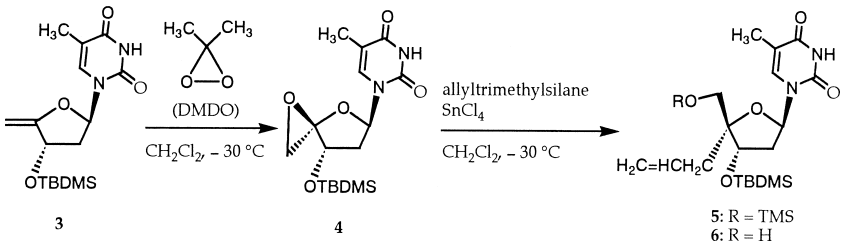
Although ring opening of epoxides with carbon nucleophiles constitutes a powerful synthetic operation for C–C bond-forming reactions,† little attention has been paid for its application to the synthesis of branched sugar-nucleosides.[7] In this article, we describe a novel method for the stereoselective synthesis of 4′-α-carbon-substituted nucleosides based on epoxidation of 4′,5′-unsaturated nucleosides followed by ring opening with organosilicon reagents or organoaluminum reagents. Results of the anti-HIV evaluation of the synthesized compounds are also reported.

RESULTS AND DISCUSSION

Ring Opening of 4′,5′-Epoxythymidine Derivative 4 with Organosilicon Reagents

When 3′-*O*-TBDMS-4′,5′-unsaturated thymidine **3** was treated with an acetone solution of dimethyldioxirane (DMDO) in CH_2Cl_2 at −30°C, the reaction went to completion within 0.5 h, and 4′,5′-epoxythymidine derivative **4** was formed in a single diastereomer (Scheme 1).[8] Subsequent reaction of **4** with allyltrimethylsilane in the presence of $SnCl_4$ gave two products. Their ^1H NMR spectra showed that the more polar product was the expected 4′-α-allylthymidine (**6**) whereas the less polar one was its 5′-*O*-trimethylsilyl derivative (**5**). Thus, simple extractive

*For a review, see Ref. [1].
†For a review, see Ref. [6].



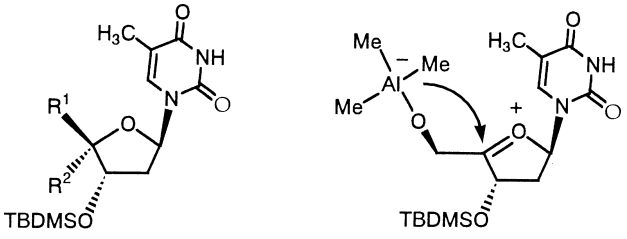
SCHEME 1 Epoxidation of **3** with DMDO and subsequent ring opening of 4′,5′-epoxythymidine derivative **4** with allyltrimethylsilane.

workup of the reaction mixture followed by treatment with NH_3/MeOH allowed the isolation of **6** in 80% yield.

4′-α-(2-Bromoallyl)-(**7**) (47%) and 4′-α-(cyclopenten-3-yl)-thymidine derivative (**8**) (32%) were also synthesized as a single isomer by reacting **4** with (2-bromoallyl)-trimethylsilane and (cyclopentenyl)trimethylsilane, respectively. 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 **9** (45%).

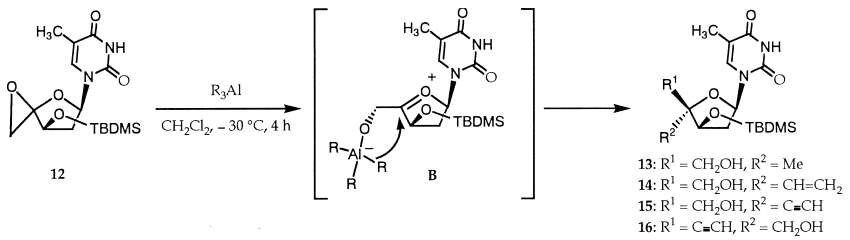
Ring Opening of the 4′,5′-Epoxide 12 with Organoaluminum Reagents

Reaction of **4** with Me_3Al resulted in the dominant formation of **10** (64%), the desired product **11** being isolated only in 5% yield (Figure 2).[9] This stereochemical outcome was assumed to be a reflection of conformational preference of the oxonium intermediate: conformer **A** can avoid the steric repulsion between the 5′-*O*-aluminate and the 3′-*O*-TBDMS group. To see if our assumption is reasonable, the 4′,5′-epoxide **12** having the opposite 3′-configuration to **4** was prepared from the corresponding 4′,5′-unsaturated derivative by DMDO oxidation. When **12** was reacted with Me_3Al under the conditions shown in Scheme 2 (a possible intermediate is depicted as **B**), exclusive formation of **13** (72%) having the expected 4′-configuration was observed. This was also the case for $(CH_2 = CH)_3Al$, although



10: R^1 = Me, R^2 = CH_2OH
11: R^1 = CH_2OH, R^2 = Me

FIGURE 2 Ring opening of 4′,5′-epoxide **4** with Me_3Al.



SCHEME 2 Ring opening of the 4′,5′-epoxide **12** with organoaluminum reagents.

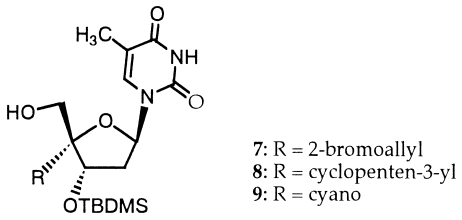


FIGURE 3 4′-Carbon-substituted thymidine derivatives.

the yield of **14** (27%) was rather low. In contrast to these two reactions, both the 4′-α-(**15**: 57%) and 4′-β-(**16**: 31%) substituted products were isolated upon reacting **12** with $(HC \equiv C)_3Al$ (Figure 3).

Transformation of **13–15** to the respective 4′-substituted analogue of d4T was carried out by sequential conventional reactions: acetylation of the 5′-hydroxyl group, desilylation (TBAF/THF), 3′-*O*-mesylation, elimination of MsOH (DBN/CH_3CN), and deacetylation (NH_3/MeOH). Compounds **17–19** were obtained in good overall yields (Figure 4).

Anti-HIV Activity of 4′-Carbon-Substituted d4T

The anti-HIV-1 III_B activity of **17–19** was evaluated and the results were summarized in Table 1.[10] Interestingly, 4′-ethynyl-d4T **19** was found to be more potent and less toxic to host cells than d4T.

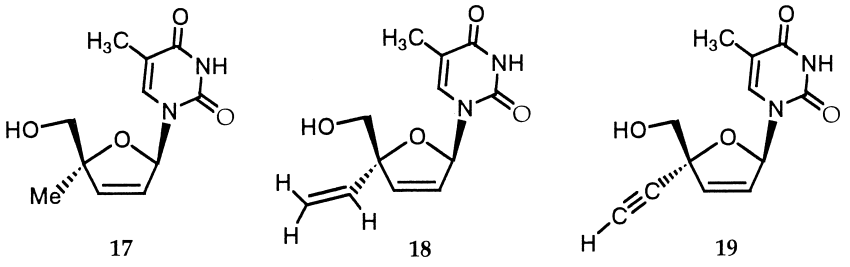


FIGURE 4 4′-Substituted d4T.

TABLE 1 Anti-HIV 1 IIIB Activity of **17–19** in MT-2 Cells

Compd	IC_{50} (μM)[a]	CC_{50} (μM)[b]
17	>100	>100
18	>100	>100
19	0.20	>100
Stavudine	2.8	100

[a]Inhibitory concentration required to achieve 50% protection of MT-2 cells against the cytopathic effect of HIV-1 III_B.

[b]Cytotoxic concentration required to reduce the viability of mock-infected MT-2 cells by 50%.

REFERENCES

1. *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C.K., Baker, D.C., Eds.; Plenum Press: New York, 1993.
2. O-Yang, C.; Wu, H.Y.; Fraser-Smith, E.B.; Walker, K.A.M. Synthesis of 4′-*C*-cyanothymidine and analogs as potent inhibitors of HIV. Tetrahedron Lett. **1992**, *33*, 37.
3. Kodama, E.; Kohgo, S.; Kitano, K.; Machida, H.; Gatanda, H.; Shigeta, S.; Matsuoka, M.; Ohrui, H.; Mitsuya, H. 4′-Ethynyl nucleoside analogues: potent inhibitors of multidrug-resistant human immunodeficiency virus variant in vitro. Antimicrob. Agents Chemother. **2001**, *45*, 1539.
4. Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. Synthesis and biological activities of 4′α-*C*-branched-chain sugar pyrimidine nucleosides. J. Med. Chem. **1999**, *42*, 2901.
5. Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. Synthesis of 4′-*C*-ethynyl-β-arabino- and 4′-*C*-ethynyl-2′-deoxy-β-D-ribo-pentofuranosylpyrimidines and -purines and evaluation of their anti-HIV activity. J. Med. Chem. **2000**, *43*, 4516.
6. Smith, J.G. Synthetically useful reactions of epoxides. Synthesis **1987**, *15*, 2157.
7. Ashwell, M.; Jones, A.S.; Walker, R.T. The synthesis of some branched-chain-sugar nucleoside analogues. Nucleic Acids Res. **1987**, *15*, 2157.
8. Haraguchi, K.; Takeda, S.; Tanaka, H. Ring opening of 4′,5′-epoxynucleosides: a novel stereoselective entry to 4′-*C*-branched nucleosides. Org. Lett. **2003**, *5*, 1399.
9. Haraguchi, K.; Takeda, S.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G.E.; Cheng, Y.-C. Synthesis of a highly active new anti-HIV agent 2′,3′-didehydro-3′-deoxy-4′-ethynylthymidine. Bioorg. Med. Chem. Lett. **2003**, *13*, 3775.
10. Dutschman, G.E.; Grill, S.P.; Gullen, E.A.; Haraguchi, K.; Takeda, S.; Tanaka, H.; Baba, M.; Cheng, Y.-C. Novel 4′-substituted stavudine analog with improved anti-human immunodeficiency virus activity and decreased cytotoxicity. Antimicrob. Agents Chemother. **2004**, *48*, 1640.