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FORMATION OF 4',5'-DIDEHYDRO-5'-DEOXY-3'-*O*-METHYLURIDINE *VIA* REGIOSELECTIVE NUCLEOPHILIC ADDITION OF METHOXIDE ANION TO 2',3'-ANHYDRO-5'-DEHYDRO-5'-IODOURIDINE

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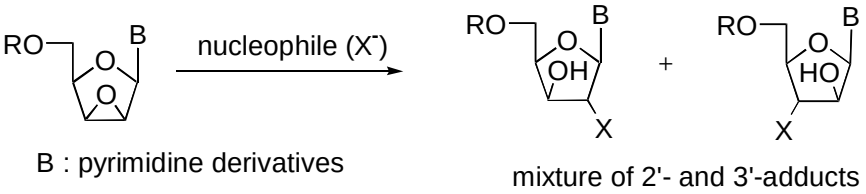
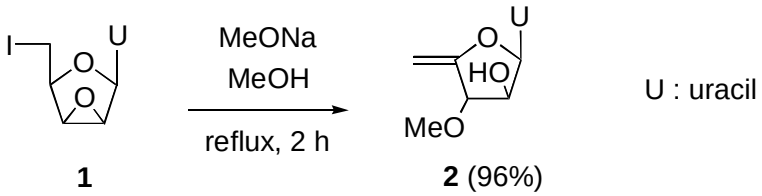
Abstract- Treatment of 2',3'-anhydro-5'-deoxy-5'-iodouracil (**1**) with sodium methoxide regioselectively provided 4',5'-didehydro-5'-deoxy-3'-*O*-methyl-uridine (**2**) as the sole product *via* 4',5'-didehydro-5'-deoxy-2',3'-epoxyuridine (**6**) as an intermediate.

The majority of therapeutic agents for the treatment of viral infections and cancers have been nucleoside derivatives[1]. Among the many nucleoside drugs, sugar-modified pyrimidine nucleosides, such as zalcitabine,[2] zidovudine,[2] lamivudine,[2] doxifluridine[3] and so on, have recently attracted much attention. Pyrimidine nucleosides modified in the sugar moiety can be synthesized either by modification of naturally occurring nucleosides[1,4] or by a sugar-base condensation reaction after the synthesis of the sugar moiety.[4] It is apparent that the former process is highly effective for the preparation of sugar-modified nucleosides since the low stereoselectivity of the sugar-base condensation reaction is a limitation of the latter method and separation of the α and β anomers is quite difficult.[4] Introduction of substituents to the 2'- or 3'-position of pyrimidine nucleosides can be accomplished by simple nucleophilic addition into 2',3'-anhydropyrimidine nucleosides[5] although these reactions are rather impractical because of there poor regioselectivity (Scheme 1).



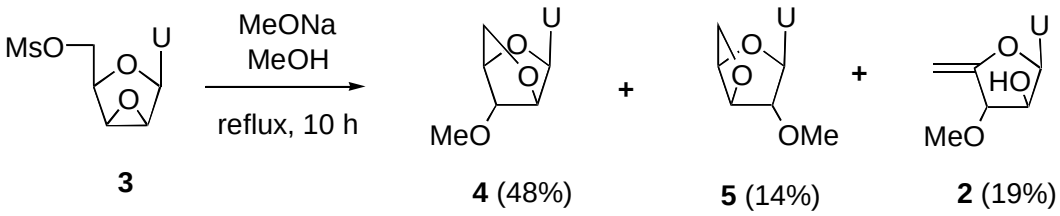
Scheme 1

In the course of our study on the modification of the sugar moiety using 2',3'-anhydrouridine, we found nucleophilic addition of sodium methoxide to 2',3'-anhydro-5'-deoxy-5'-iodouridine (**1**)[6] under reflux condition in MeOH proceeded regioselectively and, unexpectedly, provided 4',5'-didehydro-5'-deoxy-3'-*O*-methyluridine (**2**) as the sole product in 96% yield (Scheme 2).



Scheme 2

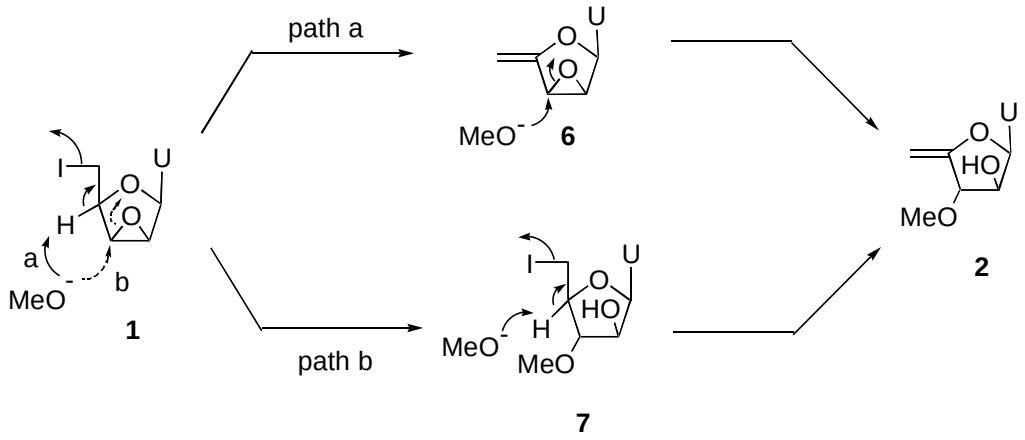
On the other hand, when 2',3'-anhydro-5'-*O*-mesyluridine (**3**) possessing an appropriate leaving group at 5'-position as well as **1** was used as a substrate under analogous conditions, 1-(2,5-anhydro-3-*O*-methyl-β-D-arabinofuranosyl)uracil (**4**, 48%) and 1-(3,5-anhydro-2-*O*-methyl-β-D-xylofuranosyl)uracil (**5**, 14%) were obtained together with expected **2** (19%) as a mixture[7] (Scheme 3). Consequently, the regioselective formation of **2** is a quite specific reaction for the 5'-iodo derivative (**1**).[8]



Scheme 3

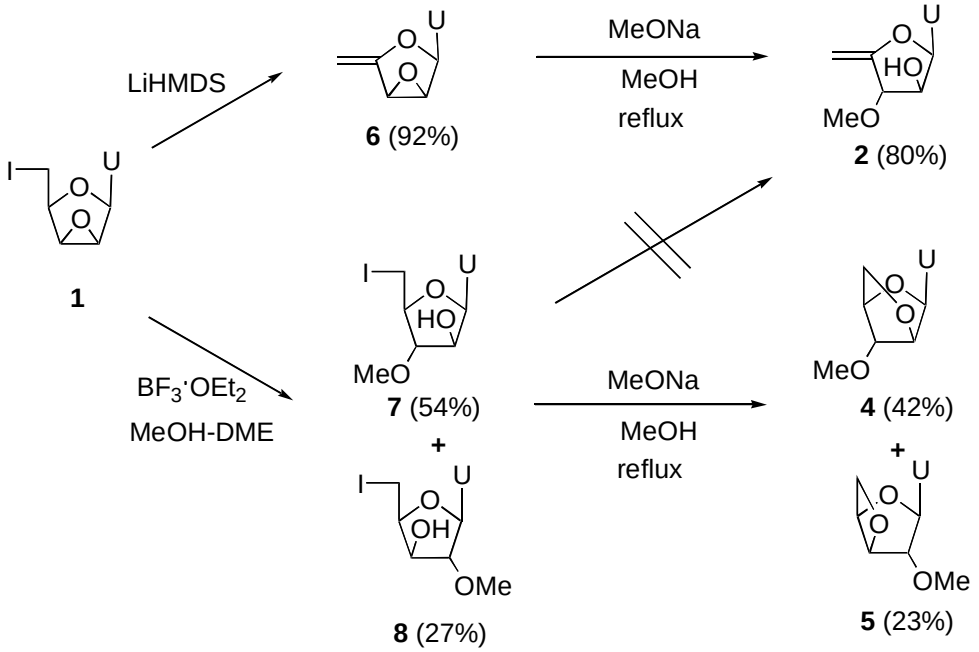
Alternate reaction sequences for the formation of **2** can be proposed as shown in Scheme 4.

4',5'-Didehydro-5'-deoxy-2',3'-epoxyuridine (**6**) produced by the elimination of HI by the attack of sodium methoxide to the 4'-hydrogen of **1** can be converted smoothly and regioselectively into the corresponding 3'-adduct (**2**) since the 3'-position of **6** is a highly activated allylic position[9] (path a). If the nucleophilic attack of methoxide anion occurred regioselectively at the 3'-position of **1** first, the corresponding ring-opening 3'-adduct (**7**) should be obtained. Subsequent elimination of HI can provide the 3'-adduct (**2**) (path b).



Scheme 4

In order to clarify the reaction sequence, preparation of both plausible intermediates (**6** and **7**) was attempted. Treatment of 2',3'-anhydro-5'-deoxy-5'-iodouridine (**1**) with $BF_3 \cdot OEt_2$ under reflux conditions in MeOH-DME gave 3'- and 2'-adducts as a mixture (**7** and **8**, 54% and 27%, respectively). When the mixture of **7** and **8** was treated with sodium methoxide under reflux conditions in MeOH, only 2',5'- and 3',5'-anhydro derivatives (**4** and **5**, 42% and 23%, respectively) were acquired without the formation of **2**. On the other hand, the unsaturated epoxide (**6**), obtained by the reaction of **1** with LiHMDS,[9] with sodium methoxide gave the corresponding **2** as the sole product (80%) *via* regioselective nucleophilic attack of the methoxide anion at the highly activated allylic 3'-position of **6** (Scheme 5).[9] These results clearly indicate that **6** is an obvious intermediate for the formation of the 3'-adduct (**2**) starting from **1**.



Scheme 5

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All column chromatography was carried out with silica gel (230–400 mesh, Wakogel C-300). All reactions were monitored by TLC performed on glass-backed silica gel 60 F_{254}, 0.2 mm plates (MERCK), and compounds were visualized under UV light (254 nm). Melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer or a JEOL GX 270 spectrometer (^{1}H: 400 or 270 MHz, ^{13}C: 100 MHz). Chemical shifts (δ) are given in ppm relative to residual solvent or tetramethylsilane as an internal standard. UV spectra were obtained from EtOH solutions on a Shimadzu UV-260 spectrophotometer. Low and high-resolution MS spectra were taken on a JEOL JMS-SX 102 or JMS-D300 machine. Microanalyses were carried out at the Microanalytical Laboratory of our University. Compounds known in the literature were characterized by comparison of their ^{1}H NMR spectral data with the previously reported data.

Reaction of 1-(2,3-anhydro-5-deoxy-5-iodo-β-D-lyxofuranosyl)uracil (1)[6] with MeONa.

To a stirred solution of **1** (168 mg, 0.5 mmol) in dry MeOH (10 mL) was added 28% MeOH solution of sodium methoxide (0.48 mL, 2.5 mmol) at rt under argon atmosphere. The reaction mixture was refluxed for 2 h and the mixture was neutralized with saturated methanolic NH_4Cl solution and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$: MeOH = 20 : 1) to give 1-(5-deoxy-3-*O*-methyl-β-D-*threo*-pent-4-enofuranosyl)uracil (**2**)[9] (115 mg, 96%).

2: mp 166-167 °C (MeOH); UV (EtOH) λ_{max}: 260.8 nm, 210.4 nm; MS *m/z* (relative intensity): 240 (M^+, 1%), 111 (B^+, 100%); ^{1}H NMR (DMSO-d_6) δ: 11.47 (1H, br s, N^3-H), 7.41 (1H, d, *J*=8.0 Hz, 6-H), 6.29

(1H, d, *J*=3.4 Hz, 1'-H), 6.07 (1H, d, *J*=2.9 Hz, 2'-OH), 5.74 (1H, d, *J*=8.0 Hz, 5-H), 4.67 (1H, s, 5'-Ha), 4.43 (1H, s, 5'-Hb), 4.21 (1H, br s, 2'-H), 4.13 (1H, br s, 3'-H), 3.42 (3H, s, 3'-OCH_3); ^{13}C NMR (DMSO-d_6) δ: 163.16 (4-C), 157.49 (4'-C), 150.31 (2-C), 141.60 (6-C), 100.62 (5-C), 88.07 (5'-C), 86.70 (1'-C), 83.96 (3'-C), 72.15 (2'-C), 55.76 (3'-OCH_3); Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.07; H, 5.04; N, 11.52.

Reaction of 1-(2,3-anhydro-5-*O*-mesyl-β-D-lyxofuranosyl)uracil (3)[6] with MeONa.

To a stirred solution of **3** (608 mg, 2.0 mmol) in dry MeOH (15 mL) was added 28% MeOH solution of sodium methoxide (1.93 mL, 10.0 mmol) at rt under argon atmosphere. The reaction mixture was refluxed for 10 h and the mixture was neutralized with saturated methanolic NH_4Cl solution and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$: MeOH = 100 : 1) to give 1-(3,5-anhydro-2-*O*-methyl-β-D-xylo-furanosyl)uracil (**5**) (69 mg, 14%) as the first fraction, 1-(2,5-anhydro-3-*O*-methyl-β-D-arabinofuranosyl) uracil (**4**) (231 mg, 48%) as the second fraction and **2** (85 mg, 19%) as the third fraction.

4: mp 201-202 °C (Et_2O); UV (EtOH) λ_{max}: 264.2 nm, 210.0 nm; MS *m/z* (relative intensity): 129 (S^+, 2%), 112 (B^++1, 4%), 69 (100%); ^{1}H NMR (DMSO-d_6) δ: 11.48 (1H, br s, N^3-H), 7.90 (1H, d, *J*=8.3 Hz, 6-H), 6.06 (1H, br s, 1'-H), 5.67 (1H, d, *J*=8.3 Hz, 5-H), 4.84 (1H, br s, 4'-H), 4.45 (1H, d, *J*=2.4 Hz, 2'-H), 4.37 (1H, d, *J*=2.4 Hz, 3'-H), 4.15 (1H, d, *J*=9.3 Hz, 5'-Ha), 4.03 (1H, d, *J*=9.3 Hz, 5'-Hb), 3.50 (3H, s, 3'-OCH_3); ^{13}C NMR (DMSO-d_6) δ: 163.18 (4-C), 150.47 (2-C), 140.96 (6-C), 100.40 (5-C), 89.34 (1'-C), 83.36 (3'-C), 77.81 (4'-C), 74.25 (2'-C), 72.16 (3'-C), 57.31 (3'-OCH_3); Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.25; H, 5.11; N, 11.39.

5: MS *m/z* (relative intensity): 240 (M^+, 2%), 129 (S^+, 62%), 112 (B^++1, 7%), 41 (100%); ^{1}H NMR ($CDCl_3$) δ: 9.39 (1H, br s, N^3-H), 7.94 (1H, d, *J*=8.3 Hz, 6-H), 6.45 (1H, d, *J*=2.0 Hz, 1'-H), 5.85 (1H, d, *J*=8.3 Hz, 5-H), 5.30 (1H, d, *J*=3.4 Hz, 3'-H), 5.08 (1H, dd, *J*=3.4 and 3.4 Hz, 4'-H), 4.84 (1H, dd, *J*=3.4 and 8.3 Hz, 5'-Ha), 4.24 (1H, d, *J*=8.3 Hz, 5'-Hb), 4.16 (1H, d, *J*=2.0 Hz, 2'-H), 3.45 (3H, s, 3'-OCH_3); ^{13}C NMR ($CDCl_3$) δ: 163.72 (4-C), 151.09 (2-C), 140.62 (6-C), 103.68 (5-C), 94.39 (1'-C), 89.03 (3'-C), 88.56 (2'-C), 81.10 (4'-C), 77.33 (5'-C), 58.73 (3'-OCH_3); HRMS *m/z* Calcd for $C_{10}H_{12}N_2O_5$: 240.0746. Found: 240.0760.

1-(5-Deoxy-5-iodo-3-*O*-methyl-β-D-arabinofuranosyl)uracil (7) and 1-(5-deoxy-5-iodo-2-*O*-methyl-β-D-xylofuranosyl)uracil (8).

To a stirred solution of **1** (67 mg, 0.2 mmol) in dry MeOH (5 mL) and ethyleneglycol dimethyl ether (5 mL) was added BF_3·OEt_2 (0.15 mL, 1.2 mmol) at 0 °C under argon atmosphere. The reaction mixture was refluxed for 24 h and was concentrated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$: MeOH = 100 : 1) to afford 1-(5-deoxy-5-iodo-3-*O*-methyl-β-D-arabinofuranosyl)uracil (**7**) (39 mg, 53 %) and 1-(5-deoxy-5-iodo-2-*O*-methyl-β-D-xylofuranosyl)uracil (**8**) (20 mg, 27 %) as a mixture. Yields were estimated by the integration ratios of the ^{1}H NMR spectra of the mixture.

7: ^{1}H NMR ($CDCl_3$) δ: 11.11 (1H, br s, N_3-H), 7.70 (1H, d, *J*=8.3 Hz, 6-H), 6.12 (1H, d, *J*=3.4 Hz, 1'-H), 5.56 (1H, d, *J*=8.3 Hz, 5-H), 4.81-4.85 (1H, m, 2'-H), 4.15-4.20 (1H, m, 4'-H), 3.83-3.86 (1H, m, 3'-H),

3.50 (3H, s, 3'-OCH_3), 3.41-3.55 (2H, m, 5'-H x 2).

8: ^{1}H NMR ($CDCl_3$) δ: 10.27 (1H, br s, N_3-H), 7.61 (1H, d, *J*=8.3 Hz, 6-H), 5.80 (1H, br s, 1'-H), 5.54 (1H, d, *J*=8.3 Hz, 5-H), 4.49-4.57 (1H, m, 4'-H), 4.30-4.33 (1H, m, 3'-H), 4.13 (1H, br s, 2'-H), 3.57 (3H, s, 3'-OCH_3), 3.41-3.55 (2H, m, 5'-H x 2).

(**7**)+ (**8**) MS *m/z* (relative intensity): 368 (M^+, 1%), 113 (B^++2, 13%), 71 (S^+, 100%)

Reaction of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (7) and 1-(5-deoxy-5-iodo-2-*O*-methyl-β-D-xylofuranosyl)uracil (8) with MeONa.

To a stirred solution of **7** and **8** (total 40 mg, 0.11 mmol) in dry MeOH (5 mL) was added 28% MeOH solution of sodium methoxide (0.08 mL, 0.44 mmol) at rt under argon atmosphere. The reaction mixture was refluxed for 12 h and the mixture was neutralized with saturated methanolic NH_4Cl solution and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$: MeOH = 100 : 1) to give **5** (6 mg, 23%) as the first fraction and **4** (11 mg, 42%) as the second fraction.

Reaction of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (6)[6] with MeONa.[9]

To a stirred solution of **6** (13 mg, 0.06 mmol) in dry MeOH (5 mL) was added 28% MeOH solution of sodium methoxide (0.06 mL, 0.3 mmol) at rt under argon atmosphere. The reaction mixture was refluxed for 6 h and the mixture was neutralized with saturated methanolic NH_4Cl solution and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography ($CHCl_3$: MeOH = 20 : 1) to give **2** (12 mg, 80%).

REFERENCES AND NOTES

1. L. R. Townsend, *Chemistry of Nucleosides and Nucleotides;* Plenum, New York, 1998; A. Matsuda, *J. Synth. Org. Chem. Jpn.*, 1990, **48**, 907; C. Perigaud, G. Gosselin, and J.-L. Imbach, *Nucleosides Nucleotides*, 1992, **11**, 903; H. Maag, R. M. Rydzewski, M. J. McRoberts, D. Crawford-Ruth, J. P. H. Verheyden, and E. J. Prisbe, *J. Med. Chem.*, 1992, **35,** 1440; M.-J. Camarasa, M.-J. Perez-Perez, A. San-Felix, J. Balzarini, and E. De Clercq, *J. Med. Chem.*, 1992, **35**, 2721; M.-J. Perez-Perez, A. San-Felix, J. Balzarini, E. De Clercq, and M. -J. Camarasa, *J. Med. Chem.*, 1992, **35**, 2988.
2. E. De Clercq, *Med. Chem. Res.*, 2004, **13**, 439.
3. P. Schoeffski, *Anti-Cancer Drugs*, 2004, **15**, 85.
4. Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, and R. K. Robins, *J. Am. Chem. Soc.*, 1984, **106**, 6379; H. Aoyama, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2073; T. Okauchi, H. Kubota, and K. Narasaka, *Chem. Lett*., 1989, 801.
5. I. L. Doerr, J. F. Codington and, J. J. Fox, *J. Org. Chem.*, 1965, **30**, 467; J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, *J. Org. Chem.*, 1966, **31**, 205; T. Sasaki, K. Minamoto, and K. Hattori, *Tetrahedron*, 1974, **30**, 2689; G. Kowollik and P. Langen, *Z. Chem.*, 1975, **15**, 147; U. Reichman, D. H. Hollenberg, C. K. Chu, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*,

1976, **41**, 2042; D. H. Hollenberg, K. A. Watanabe, and J. J. Fox, *J. Med. Chem.*, 1977, **20**, 113; C. F. Hummel and R. P. Carty, *Nucleosides Nucleotides*, 1983, **2**, 249; H. K. Misra, W. P. Gati, E. E. Knaus, and L. I. Wiebe, *J. Heterocycl. Chem.*, 1984, **21**, 773; A. Mete, J. B. Hobbs, D. I. C. Scopes, and R. F. Newton, *Tetrahedron Lett*., 1985, **26**, 97; M. Ashwell, A. S. Jones, and R. T. Walker, *Nucleic Acids Res*., 1987, **15**, 2157; D. Häbich and W. Barth, *Synthesis*, 1988, 943; J.-C. Wu, T. Pathak, W. Tong, J.-M. Vial, G. Remaud, and J. Chattopadhyaya, *Tetrahedron*, 1988, **44**, 6705; T. R. Webb, H. Mitsuya, and S. Broder, *J. Med. Chem.*, 1988, **31**, 1475; A, Matsuda, M. Satoh, H. Nakashima, N. Yamamoto, and T. Ueda, *Heterocycles*, 1988, **27**, 2545; P. Herdewijn, J. Balzarini, M. Baba, R. Pauwels, A. Van Aerschot, G. Janssen, and E. De Clercq, *J. Med. Chem.*, 1988, **31**, 2040; J.-C. Wu and J. Chattopadhyaya, *Tetrahedron*, 1989, **45**, 4507; P. Herdewijn, A. Van Aerschot, and L. Kerremans, *Nucleosides Nucleotides*, 1989, **8**, 65; M. E. Perlman and K. A. Watanabe, *Nucleosides Nucleotides*, 1989, **8**, 145; P. Wigerinck, A. Van Aerschot, G. Janssen, P. Claes, J. Balzarini, E. De Clercq, and P. Herdewijn, *J. Med. Chem*., 1990, **33**, 868; K. Haraguchi, H. Tanaka, H. Maeda, Y. Itoh, S. Saito, and T. Miyasaka, *J. Org. Chem*., 1991, **56**, 5401; J.-T. Haung, L.-C. Chen, L. Wang, M.-H. Kim, J. A. Warshaw, D. Armstrong, Q.-Y. Zhu, T.-C. Chou, K. A. Watanabe, J. Matulic-Adamic, T.-L. Su, J. J. Fox, B. Polsky, P. A. Baron, J. W. M. Gold, W. D. Hardy, and E. Zuckerman, *J. Med. Chem.*, 1991, **34**, 1640; Z. Xi, P. Agback, J. Plavec, A. Sandström, and J. Chattopadhyaya, *Tetrahedron*, 1992, **48**, 349; K. Minamoto, Y. Hamano, Y. Matsuoka, K. Watanabe, T. Hirota, and S. Eguchi, *Nucleosides Nucleotides*, 1992, **11**, 457; X. Ariza, J. Garces, and J. Vilarrasa, *Tetrahedron Lett*., 1992, **33**, 4069; K. Watanabe, K. Yanagihara, K. Minamoto, and H. Iwasaki, *Nucleosides Nucleotides*, 1993, **12**, 1061; R. Johnson, B. V. Joshi and, C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1994, 133; S. Bera, T. Pathak, and G. J. Langley, *Tetrahedron*, 1995, **51**, 1459; C. D. Roussev, M. F. Simeonov, and D. D. Petkov, *J. Org. Chem*., 1997, **62**, 5238; B.-C. Chen, S. L. Quinlan, J. G. Reid, and R. H. Spector, *Tetrahedron Lett*., 1998, **39**, 729; X. Liu and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2227; K. Haraguchi, Y. Itoh, S. Takeda, Y. Honma, H. Tanaka, T. Nitanda, M. Baba, G. E. Dutschman, and Y.-C. Cheng, *Nucleosides, Nucleotides & Nucleic Acids*, 2004, **23**, 647.

6. J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem*., 1962, **27**, 163.
7. The reaction of 2',3'-anhyrdo-5'-*O*-mesyluridine (**3**) and $AlMe_3$ as an nucleophile also provided similar 2',5'-anhyrdo and 3',5'-anhyrdo derivatives as a mixture. See, K. Hirota, H. Takasu, and H. Sajiki, *Heterocycles*, 2000, **52**, 1329.
8. The present method is not applicable to the nucleophilic reaction with $AlMe_3$, less basic nucleophiles.[7]
9. K. Hirota, H. Takasu, Y. Tsuji, and H. Sajiki, *Chem. Commun.*, 1999, 1827; H. Takasu, Y. Tsuji, H. Sajiki, and K. Hirota, *Tetrahedron* in press.