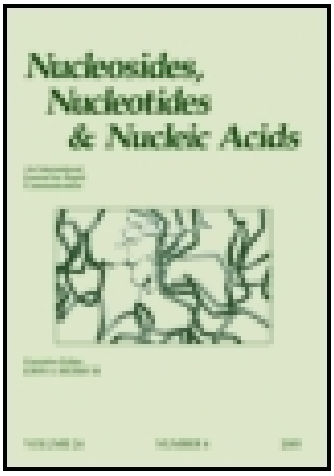

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Tandem Radical Cyclization-Oxygenation of 6-(2,2-Di-bromovinyl)-1-(2-deoxy-d-erytho-pent-1-enofuranosyl)-uracil: Synthesis of Anomeric Spiro Nucleosides Having Arabino and Ribo Configurations

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TANDEM RADICAL CYCLIZATION-OXYGENATION OF 6-(2,2-DIBROMOVINYL)-1-(2-DEOXY-D-*erythro*-PENT-1-ENOFURANOSYL)-URACIL: SYNTHESIS OF ANOMERIC SPIRO NUCLEOSIDES HAVING ARABINO AND RIBO CONFIGURATIONS

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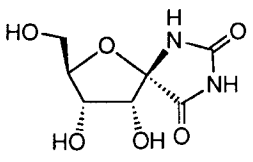
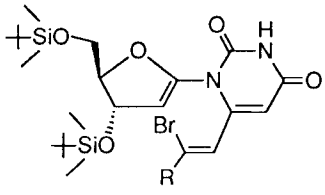
Abstract Radical-mediated 5-*exo-trig* cyclization of 6-(2,2-dibromovinyl)-1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)uracil, when carried out in the presence of oxygen, furnished an anomeric spiro nucleoside having arabino-configuration. The corresponding ribofuranosyl analogue was also synthesized *via* the 2'-keto derivative.

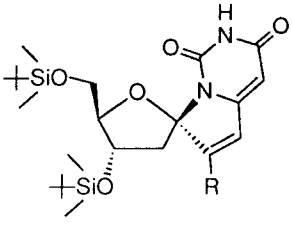
Hydantocidin (**1**) is a naturally-occurring nucleoside isolated from the culture broth of *Streptomyces hygroscopicus* SANK 63584.[1] Its unique anomeric spiro structure as well as herbicidal and plant-growth regulatory activities have stimulated the synthesis of a series of analogues.[2] As a result of these synthetic studies, it revealed that the presence of all three hydroxyl groups in the furanosyl moiety of **1** is essential for the herbicidal activity: none of the deoxy analogues (2'-, 3'-, 5'-deoxy, and 2',3'-dideoxy) was active.[3]



1



2 R= Br
3 R= CO_2Me



4 R= Br
5 R= CO_2Me

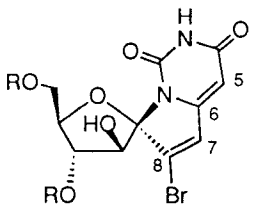
This paper is dedicated to Dr. Yoshihisa Mizuno, one of the founders of nucleic acids chemistry in Japan, on the occasion of his 75th birthday.

Recently, we reported a novel approach to the synthesis of anomeric spiro 2'-deoxy-nucleosides (**4** and **5**) from uridine, wherein 5-*exo-trig* cyclization of a radical generated from 6-substituted 1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)uracils (**2** and **3**) was used as a key reaction step.[4] To evaluate biological activities of this new class of nucleosides, it would be desirable to synthesize the derivatives having a 2'-hydroxyl group. This paper describes the synthesis of arabino- and ribofuranosyl derivatives of **4** from **2**.

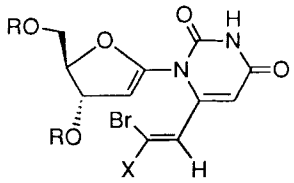
As a preliminary experiment, radical cyclization of **2** was carried out by using Bu_3SnD and AIBN in refluxing benzene to see face-selectivity of the reaction of the C-2' radical **B** which resulted from 5-*exo-trig* cyclization of the incipient vinyl radical **A** (Scheme 1). After HPLC separation of the reaction mixture,[5] **6** was isolated in 34.8% yield. The ^1H NMR spectrum of **6** clearly showed preferential deuterium incorporation into the β-face (β 84.6% *vs.* α 10.7%).[6]

An oxygen-initiated radical reaction of organic halides, which gives alcohols, has been reported.[7] When certain olefinic halides were employed as substrates, the reaction offers an efficient operation for tandem cyclization-oxygenation. Based on this precedent and the above experimental result in Scheme 1, we reasoned that trapping of the radical **B** with oxygen could give the arabinofuranosyl derivative **7**.

We first carried out the reaction of **2** in toluene at room temperature, as reported in the literature,[7] while simultaneously bubbling dry air and adding a toluene solution of Bu_3SnH (3 equiv) over 40 h by a syringe pump to avoid reduction of the radical species **A** and/or **B**. The desired product **7** was obtained in 12.8% yield and its arabino configuration was confirmed by its NOESY spectrum: an NOE correlation was observed between 2'-OH and H-3'.[8] It was shown by ^1H NMR spectroscopy that the recovered **2** was contaminated with **8** which is assumed to have *Z*-configuration (J= 8.4 Hz). The yields of **2** and **8** were estimated to be 42.0 and 14.0%, respectively, by integrating H-7. A small amount of **4** (*ca.* 1%) was also formed in this reaction.

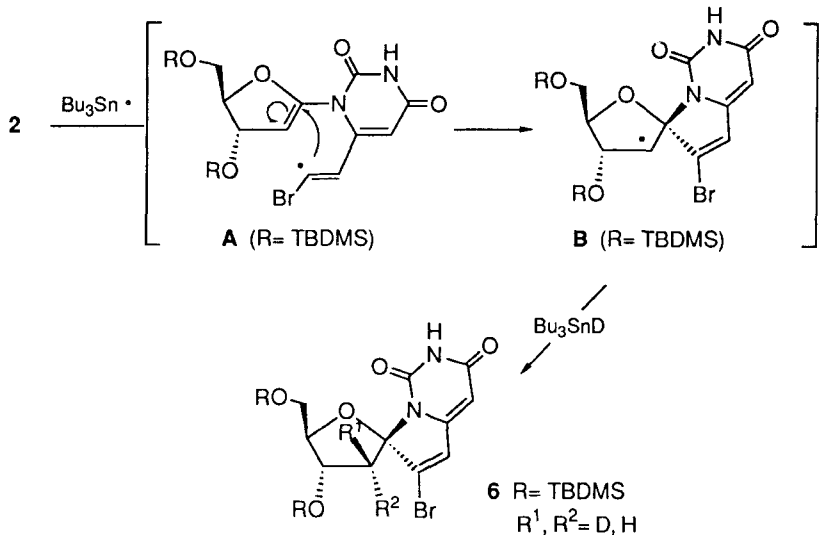


7 R= TBDMS



8 R= TBDMS, X= H
9 R= TBDMS, X= Ph

Although formation of **4** was not observed when oxygen, instead of dry air, was bubbled into the reaction mixture, the yield of **7** could not be improved even by increasing

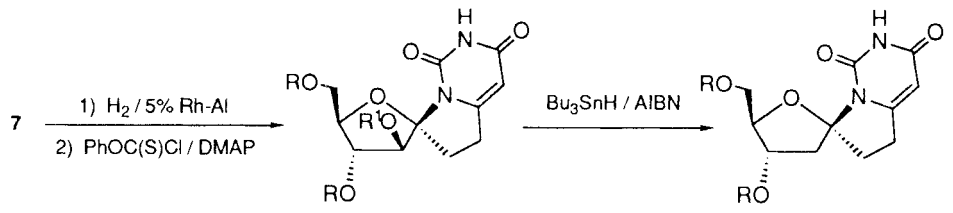


Scheme 1

the amount of Bu_3SnH (~6 equiv). When the tandem cyclization-oxygenation of **2** was carried out in refluxing benzene (O_2 bubbling, slow addition of 4 equiv of Bu_3SnH and 0.5 equiv of AIBN), the reaction time was reduced to 4 h and **7** was isolated in a slightly higher yield of 20.6%. In this case, ^1H NMR spectrum of the recovered **2** showed the presence of **8** as well as **9**[9] as contaminants (yields calculated from the integration of H-7: **2** 20.7%, **8** 6.8%, **9** 18.9%).

The β-anomeric stereochemistry of **7** was ascertained by the reaction sequence shown in Scheme 2, since the initial attempt to convert **7** to **4** by radical deoxygenation of the corresponding 2'-*O*-phenoxythiocarbonyl derivative failed, forming an intractable mixture of products. Thus, **7** was first subjected to catalytic hydrogenation to give the 6,1'-(ethano)spongouridine **10** (quantitative yield). The 2'-hydroxyl group of **10** was thiocarbonylated to yield **11** (27.3%),[10] the radical deoxygenation of which led to the previously prepared **12**.[4]

Synthesis of the ribofuranosyl analogue was carried out by oxidation of **7** with DMSO-$(CF_3CO)_2O$[11] and subsequent hydride reduction.[12,13] The choice of this oxidizing reagent was motivated by the fact that the 2'-hydroxyl group in **7** is sterically hindered, as shown in the above low-yield preparation of **11**, and thus competing acylation would be highly unfavored.[14] Oxidation of **7** with this reagent in CH_2Cl_2 at –78 °C gave the 2'-keto derivative **13** in 72.1% yield. When **13** was treated with $NaBH_4$ in MeOH at

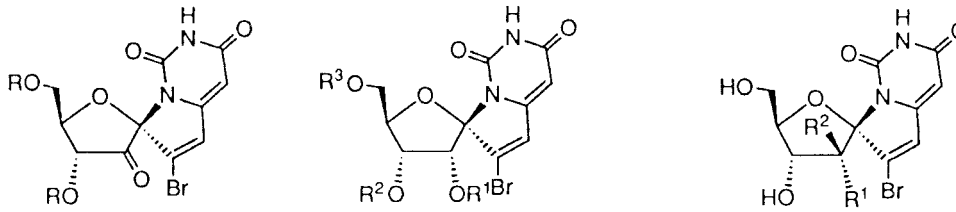


10 R= TBDMS, R^1= H
11 R= TBDMS, R^1= C(S)OPh

12 R= TBDMS

Scheme 2

room temperature, **14** (27.7%) and **15** (34.2%) were obtained along with **7** (34.7%). That one *tert*-butyldimethylsilyl group in **15** is located in the 2'-*O*-position, as the result of a base-catalyzed migration in a vicinal-diol system,[15] was verified by ^{1}H-^{1}H decoupling and deuterium exchange NMR experiments.[16]



13 R= TBDMS

14 R^1= H, R^2= R^3= TBDMS
15 R^1= R^3= TBDMS, R^2= H

16 R^1= H, R^2= OH
17 R^1= OH, R^2= H

Finally, desilylation of **7** and **14** (or **15**) was carried out in a conventional manner (Bu_4NF and AcOH in THF) to give the corresponding free anomeric spiro nucleosides **16** and **17**. Compound **16** was analyzed by X-ray crystallography.[17] Its ORTEP drawing is depicted in Fig. 1 and the atomic coordinates are summarized in Table 1.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 23 °C (internal standard, Me_4Si) with a JEOL JNM-GX 400 spectrometer. Mass spectra (MS) were taken on a JEOL SX-102A spectrometer in FAB mode (*m*-nitrobenzyl alcohol as a matrix). Ultraviolet spectra (UV) were recorded on a JASCO Ubest-55 spectrophotometer. Column chromatography was

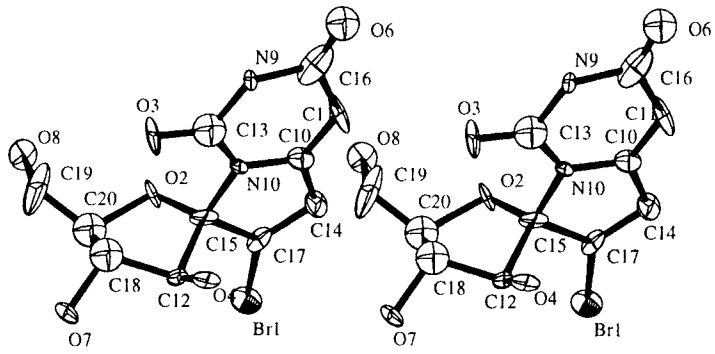


FIG. 1. ORTEP Stereoview of **16**.

TABLE 1. Atomic Coordinates and B_{iso}/B_{eq} of Non-hydrogen Atoms Used for Crystallographic Analysis of **16**.

Atom	X	Y	Z	*Beq* (Å^2)
Br (1)	0.1718 (5)	0.2002 (4)	0.1370 (2)	2.85 (8)
O (2)	0.403 (3)	0.379 (2)	0.254 (1)	1.8 (5)
O (3)	0.857 (4)	0.419 (3)	0.285 (1)	3.8 (7)
O (4)	0.774 (3)	0.147 (2)	0.233 (1)	1.6 (5)
O (6)	1.102 (4)	0.582 (2)	0.068 (1)	3.9 (7)
O (7)	0.516 (4)	0.136 (2)	0.380 (1)	2.6 (5)
O (8)	0.237 (5)	0.496 (2)	0.388 (1)	3.4 (6)
N (9)	0.974 (5)	0.503 (2)	0.173 (1)	2.2 (7)
N (10)	0.698 (4)	0.377 (2)	0.174 (1)	1.5 (6)
C (10)	0.691 (6)	0.388 (3)	0.099 (2)	2.1 (8)
C (11)	0.832 (6)	0.451 (4)	0.060 (2)	2.9 (8)
C (12)	0.577 (5)	0.186 (3)	0.250 (2)	1.8 (7)
C (13)	0.839 (6)	0.429 (3)	0.216 (2)	2.3 (8)
C (14)	0.506 (5)	0.327 (3)	0.071 (2)	2.5 (8)
C (15)	0.526 (5)	0.308 (3)	0.207 (2)	1.9 (7)
C (16)	0.987 (7)	0.524 (4)	0.095 (2)	4 (1)
C (17)	0.412 (4)	0.278 (3)	0.135 (2)	1.8 (6)
C (18)	0.557 (7)	0.239 (4)	0.329 (2)	4 (1)
C (19)	0.411 (7)	0.398 (5)	0.391 (2)	6 (1)
C (20)	0.401 (6)	0.315 (2)	0.333 (2)	2.8 (8)

carried out on silica gel (Silica Gel 60, Merck). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck). HPLC was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H)·KIT column (2 x 25 cm).

Tandem radical cyclization-oxygenation of 2. Formation of 8-bromo-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-6,1'-(etheno)spongouridine (7). To a refluxing benzene (31 mL) solution of **2** (312 mg, 0.489 mmol), a mixture of Bu_3SnH (0.53 mL, 1.96 mmol) and AIBN (40.2 mg, 0.245 mmol) in benzene (4.55 mL) was added over 4 h by a syringe pump, while bubbling O_2 into the reaction mixture from a balloon. The reaction mixture was purified first by silica gel column chromatography (17-50% EtOAc in hexane) and then by preparative TLC (33% EtOAc in hexane). This gave **7** (58 mg, 20.6%) and a mixture of **2**, **8**, and **9** (142 mg). Compound **7** was crystallized from EtOAc-hexane: mp 208-208.5 °C; UV (MeOH) λ_{max} 298 nm (ε 15200), $\lambda_{shoulder}$ 350 nm (ε 5600), 308 nm (ε 13400), and 287.5 nm (ε 12800); ^{1}H NMR ($CDCl_3$) δ 0.05, 0.12, and 0.15 (12H, each as s, SiMe), 0.89 and 0.91 (18H, each as s, SiBu-*t*), 2.78 (1H, d, D_2O exchangeable, $J_{2',OH}$= 10.8 Hz, 2'-OH), 3.85 (1H, dd, J_{gem}= 11.7, $J_{4',5'}$= 2.9 Hz, H-5'a), 3.89 (1H, dd, $J_{4',5'}$= 6.6 Hz, H-5'b), 4.02 (1H, ddd, $J_{3',4'}$= 8.4 Hz, H-4'), 4.52 (1H, dd, $J_{2',3'}$= 7.3 Hz, H-2'), 4.66 (1H, dd, H-3'), 5.68 (1H, d, $J_{5,NH}$= 2.2 Hz, H-5), 6.56 (1H, s, H-7), 8.76 (1H, br, D_2O exchangeable, NH); FAB-MS *m/z* 577 and 575 (M^++H), 561 and 559 (M^+−Me), 519 and 517 (M^+−Bu-*t*). Anal. Calcd for $C_{23}H_{39}BrN_2O_6Si_2$: C, 47.99; H, 6.83; N, 4.87. Found: C, 47.73; H, 6.98; N, 4.86.

^{1}H NMR and MS data of **8** are as follows: ^{1}H NMR ($CDCl_3$) δ 0.07, 0.08, and 0.09 (12H, each as s, SiMe), 0.88 and 0.90 (18H, each as s, SiBu-*t*), 3.64 (1H, dd, $J_{4',5'}$= 7.0, J_{gem}= 10.6 Hz, H-5'), 3.79 (1H, dd, $J_{4',5'}$= 5.5 Hz, H-5'), 4.43 (1H, ddd, $J_{3',4'}$= 2.6 Hz, H-4'), 4.98 (1H, t, $J_{2',3'}$= $J_{3',4'}$= 2.6 Hz, H-3'), 5.15 (1H, d, H-2'), 6.21 (1H, d, $J_{5,NH}$= 1.8 Hz, H-5), 6.78 (1H, d, $J_{7,8}$= 8.4 Hz, H-8), 6.81 (1H, dd, $J_{5,7}$= 0.7 Hz, H-7), 8.56 (1H, br, NH); FAB-MS *m/z* 583 and 581 (M^++Na), 561 and 559 (M^++H), 545 and 543 (M^+−Me), 503 and 501 (M^+−Bu-*t*).

Selected ^{1}H NMR and MS data of **9** are as follows: ^{1}H NMR ($CDCl_3$) δ 4.95 (1H, dd, $J_{2',3'}$= 2.9 Hz, H-3'), 5.22 (1H, d, H-2'), 6.19 (1H, t, $J_{5,7}$= $J_{5,NH}$= 1.1 Hz, H-5), 6.84 (1H, d, H-7), 7.37-7.39 (3H, m, Ph), 7.59-7.62 (2H, m, Ph), 8.43 (1H, br, NH); FAB-MS *m/z* 637 and 635 (M^++H), 579 and 577 (M^+−Bu-*t*).

Transformation of 7 to 12. A mixture of **7** (34.6 mg, 0.0542 mmol), Et_3N (7.6 μL, 0.0542 mmol), and 5% Rh-Al (8 mg) in MeOH (1.5 mL) was vigorously stirred at room temperature for 2 h under H_2 atmosphere. After removal of the catalyst, the reaction mixture was chromatographed on a silica gel column (33% EtOAc in hexane). This gave

10 (27 mg, quantitative) as a colorless oil. ^{1}H NMR and MS data of **10** are as follows: ^{1}H NMR ($CDCl_3$) δ 0.00, 0.02, 0.11, and 0.16 (12H, each as s, SiMe), 0.86 and 0.90 (18H, each as s, SiBu-*t*), 2.23 (1H, dd, J= 6.6, J_{gem}= 13.2 Hz, H-8), 2.34 (1H, ddd, J= 8.4 and 8.8 Hz, H-8), 2.84 (1H, dd, J= 8.4, J_{gem}= 17.6 Hz, H-7), 3.04 (1H, ddd, J= 6.6 and 8.8 Hz, H-7), 3.63 (1H, ddd, $J_{3',4'}$= 7.7, $J_{4',5'}$= 2.2 and 5.9 Hz, H-4'), 3.70 (1H, dd, $J_{4',5'}$= 5.9, J_{gem}= 11.7 Hz, H-5'), 3.80 (1H, dd, $J_{4',5'}$= 2.2 Hz, H-5'), 3.86 (1H, d, $J_{2',OH}$= 12.5 Hz, 2'-OH), 4.17 (1H, dd, $J_{2',3'}$= 7.3 Hz, H-2'), 4.59 (1H, dd, $J_{3',4'}$= 7.7 Hz, H-3'), 5.64 (1H, s, H-5), 9.37 (1H, br, NH); FAB-MS *m/z* 521 (M^++Na), 499 (M^++H), 483 (M^+–Me), 441 (M^+–Bu-*t*), 505 and 503 (M^+–$OSiMe_2$Bu-*t*).

A mixture of **10** (27 mg, 0.0542 mmol), phenyl chlorothionoformate (11.2 μL, 0.0813 mmol), and DMAP (19.9 mg, 0.0163 mmol) in CH_3CN (2 mL) was stirred overnight at room temperature. The reaction mixture was evaporated to dryness and the residue was partitioned between EtOAc (30 mL) and water (5 mL). Preparative TLC (20% EtOAc in hexane) of the organic layer gave **11** (9.4 mg, a colorless oil, 27.3%) and **10** (14.4 mg, 53.3%). MS and ^{1}H NMR data of **11** are as follows: ^{1}H NMR ($CDCl_3$) δ 0.07, 0.13, and 0.15 (12H, each as s, SiMe), 0.90 and 0.91 (18H, each as s, SiBu-*t*), 2.45-2.52 and 2.83-2.93 (1H and 3H, each as m, H-7 and H-8), 3.88 (1H, dd, $J_{4',5'}$= 6.8, J_{gem}= 15.9 Hz, H-5'), 3.95-4.03 (2H, m, H-5' and H-4'), 4.99 (1H, t, $J_{2',3'}$= 7.0 Hz, H-3'), 5.59 (1H, d, $J_{5,NH}$= 1.5 Hz, H-5), 6.09 (1H, d, $J_{2',3'}$= 7.0 Hz, H-2'), 6.96 (2H, d, J= 7.7 Hz, Ph), 7.30 (1H, t, J= 7.7 Hz, Ph), 7.40 (2H, t, J= 7.7 Hz, Ph), 8.06 (1H, br, NH); FAB-MS *m/z* 657 (M^++Na), 635 (M^++H), 619 (M^+–Me), 577 (M^+–Bu-*t*).

A mixture of **11** (9.4 mg, 0.0148 mmol), Bu_3SnH (8.0 μL, 0.0296 mmol), and AIBN (2.4 mg, 0.0148 mmol) in benzene (1.5 mL) was refluxed for 3 h under positive pressure of Ar. Preparative TLC (33% EtOAc in hexane) of the reaction mixture gave **12** (1.3 mg, a white solid, 18.2%), **11** (3.8 mg, 40.4%), and **10** (0.7 mg, 9.5%). For physical data of **12**, see reference 4.

8-Bromo-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-keto-6,1'-(etheno)-uridine (13). To a mixture of DMSO (0.11 mL, 1.55 mmol) and CH_2Cl_2 (10 mL), $(CF_3CO)_2O$ (0.34 mL, 2.41 mmol) was added at –78 °C under positive pressure of dry Ar. After 25 min, **7** (307 mg, 0.533 mmol) in CH_2Cl_2 (5.3 mL) was added dropwise to the above solution, while maintaining the temperature below –70 °C. The reaction mixture was stirred for 1 h below –70 °C, quenched by adding Et_3N (0.71 mL, 5.06 mmol), and then partitioned between CH_2Cl_2 and ice-water. Silica gel column chromatography (20-33% EtOAc in hexane) of the organic layer gave **13** (221 mg, 72.1%) as a pale yellow foam, which was crystallized from EtOAc-hexane to give an analytically pure sample: mp 193.5-194.2 °C; UV (MeOH) λ_{max} 300.6 nm (ε 14400) and 246.2 nm (ε 8800), λ_{min} 268.2 nm

(ε 7900); ^{1}H NMR ($CDCl_3$) δ 0.08, 0.14, and 0.19 (12H, each as s, SiMe), 0.91 (18H, s, SiBu-*t*), 3.99 (1H, dd, J_{gem}= 11.7, $J_{4',5'}$= 5.9 Hz, H-5'a), 4.05 (1H, dd, $J_{4',5'}$= 2.9 Hz, H-5'b), 4.44 (1H, ddd, $J_{3',4'}$= 8.4 Hz, H-4'), 4.88 (1H, d, H-3'), 5.70 (1H, s, H-5), 6.68 (1H, s, H-7), 8.81 (1H, br, NH); FAB-MS *m/z* 597 and 595 (M^++Na), 575 and 573 (M^++H), 559 and 557 (M^+–Me), 517 and 515 (M^+–Bu-*t*), 443 and 441 (M^+–$OSiMe_2$Bu-*t*). Anal. Calcd for $C_{23}H_{37}BrN_2O_6Si_2$: C, 48.16; H, 6.50; N, 4.88. Found: C, 48.31; H, 6.55; N, 4.79.

Reduction of 13 with $NaBH_4$ to yield 14 and 15. To a solution of **13** (202 mg, 0.353 mmol) in MeOH (16 mL), $NaBH_4$ (26.4 mg, 0.689 mmol) was added at room temperature. After stirring for 40 min, the mixture was further treated with $NaBH_4$ (26.4 mg) to ensure disappearence of the starting material. The reaction mixture was quenched with AcOH (81 μL, 1.41 mmol) and evaporated to dryness. The resulting residue was partitioned between EtOAc (50 mL) and water (10 mL). Silica gel column chromatography (10-50% EtOAc in hexane) of the organic layer gave **14** (56.2 mg, 27.7%, a white solid), **15** (69.4 mg, 34.2%, a white solid), and **7** (70.4 mg, 34.7%).

Physical data of **14** are as follows: mp 235.5- 236 °C (EtOAc-hexane); UV (MeOH) λ_{max} 298 nm (ε 15700), $\lambda_{shoulder}$ 310 nm (ε 13500), λ_{min} 230 nm (ε 6400); ^{1}H NMR ($CDCl_3$) δ 0.08, 0.17, and 0.20 (12H, each as s, SiMe), 0.91 and 0.95 (18H, each as s, SiBu-*t*), 3.22 (1H, d, $J_{2',OH}$= 7.3 Hz, 2'-OH), 3.82 (1H, dd, $J_{4',5'}$= 5.9, J_{gem}= 11.0 Hz, H-5'), 3.97 (1H, dd, $J_{4',5'}$= 5.9 Hz, H-5'), 4.35 (1H, dt, $J_{3',4'}$= 4.4, $J_{4',5'}$= 5.9 Hz, H-4'), 4.59 (1H, dd, $J_{2',3'}$= 7.3, $J_{3',4'}$= 4.4 Hz, H-3'), 5.04 (1H, t, $J_{2',3'}$= 7.3, H-2'), 5.63 (1H, d, $J_{5,NH}$= 2.2 Hz, H-5), 6.62 (1H, s, H-7), 7.84 (1H, br, NH); FAB-MS *m/z* 599 and 597 (M^++Na), 577 and 575 (M^++H), 561 and 559 (M^+–Me), 519 and 517 (M^+–Bu-*t*). Anal. Calcd for $C_{23}H_{39}BrN_2O_6Si_2$: C, 47.99; H, 6.83; N, 4.87. Found: C, 48.00; H, 6.85; N, 4.74.

^{1}H NMR and MS data of **15** are as follows: ^{1}H NMR ($CDCl_3$) δ –0.03, 0.07, and 0.08 (12H, each as s, SiMe), 0.88 and 0.91 (18H, each as s, SiBu-*t*), 2.77 (1H, d, $J_{3',OH}$= 5.5 Hz, 3'-OH), 3.85 (1H, dd, $J_{4',5'}$= 6.6, J_{gem}= 11.0 Hz, H-5'), 3.93 (1H, dd, $J_{4',5'}$= 6.6 Hz, H-5'), 4.24 (1H, ddd, $J_{2',3'}$= 7.3, $J_{3',4'}$= 3.7 Hz, H-3'), 4.47 (1H, dt, $J_{3',4'}$= 3.7, $J_{4',5'}$= 6.6 Hz, H-4'), 5.34 (1H, d, $J_{2',3'}$= 7.3 Hz, H-2'), 5.65 (1H, d, $J_{5,NH}$= 1.8 Hz, H-5), 6.59 (1H, s, H-7), 8.17 (1H, br, NH); FAB-MS *m/z* 599 and 597 (M^++Na), 577 and 575 (M^++H), 561 and 559 (M^+–Me), 519 and 517 (M^+–Bu-*t*).

8-Bromo-6,1'-(etheno)spongouridine (16). A mixture of **7** (69.6 mg, 0.121 mmol), Bu_4NF (84 mg, 0.266 mmol), and AcOH (21 μL, 0.367 mmol) in THF (3.5 mL) was stirred overnight at room temperature. The mixture was separated by preparative TLC

(10% MeOH in $CHCl_3$) to give **7** (32.2 mg, 76.7%), which was crystallized from EtOH: mp 259-260.5 °C (dec.); UV (MeOH) λ_{max} 297 nm (ε 15300), $\lambda_{shoulder}$ 322.5 nm (ε 6400), 308 nm (ε 13600), and 264 nm (ε 12200); ^{1}H NMR (DMSO-d_6) δ 3.59 (1H, ddd, $J_{4',5'}$= 2.2, J_{gem}= 11.7, $J_{5',OH}$= 5.5 Hz, H-5'a), 3.68 (1H, ddd, $J_{4',5'}$= 7.9 Hz, H-5'b), 3.81 (1H, dt, $J_{3',4'}$= 7.9 Hz, H-4'), 4.27 (1H, dd, $J_{2',3'}$= 7.9, $J_{2',OH}$= 5.9 Hz, H-2'), 4.41 (1H, dt, $J_{3',OH}$= 5.5 Hz, H-3'), 4.70 (1H, t, 5'-OH), 5.58 (1H, d, 3'-OH), 5.66 (1H, s, H-5), 6.02 (1H, d, 2'-OH), 7.06 (1H, s, H-7), 11.06 (1H, br, NH); FAB-MS *m/z* 371 and 369 (M^++Na), 349 and 347 (M^++H). Anal. Calcd for $C_{11}H_{11}BrN_2O_6 \cdot 1/3H_2O$: C, 37.41; H, 3.33; N, 7.93. Found: C, 37.53; H, 3.02; N, 7.81.

8-Bromo-6,1'-(etheno)uridine (17). This compound was prepared in almost quantitative yield either from **14** or **15** by the same procedure as described for the preparation of **16**. Crystallization from EtOH gave an analytically pure sample: mp >300 °C; UV (MeOH) λ_{max} 297.4 nm (ε 15600), $\lambda_{shoulder}$ 307 nm (ε 13500) and 283 nm (ε 12800); ^{1}H NMR (DMSO-d_6) δ 3.53 (1H, ddd, $J_{4',5'}$= 6.6, J_{gem}= 11.9, $J_{5',OH}$= 5.5 Hz, H-5'a), 3.66 (1H, ddd, $J_{4',5'}$= 3.3 Hz, H-5'b), 4.19 (1H, dt, $J_{3',4'}$= 6.6 Hz, H-4'), 4.26 (1H, ddd, $J_{2',3'}$= 7.0, $J_{3',OH}$= 6.2 Hz, H-3'), 4.71 (1H, dd, $J_{2',OH}$= 5.5 Hz, H-2'), 4.72 (1H, t, 5'-OH), 5.05 (1H, d, 3'-OH), 5.41 (1H, d, 2'-OH), 5.68 (1H, s, H-5), 7.03 (1H, s, H-7), 11.15 (1H, br, NH); FAB-MS *m/z* 349 and 347 (M^++H). Anal. Calcd for $C_{11}H_{11}BrN_2O_6$: C, 38.06; H, 3.19; N, 8.07. Found: C, 38.29; H, 3.14; N, 7.85.

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5) In addition to **6**, the α-anomer [yield 6.0%, deuterium content (%) at the C-2': β/α = 69.8/20.8] and the 6-*endo* cyclized product (yield 7.0%, single isomer, deuterium content at the anomeric position: 96.7%) were also isolated. The stereochemistry of the latter product about C-2' position is not known at the present time.

6) Due to anisotropic effect of the fixed C-2 carbonyl group in **4**, H-2'β appears at lower field of δ 2.78 ppm as compared to H-2'α (δ 2.46 ppm). The assignment of these protons was confirmed by the presence of an NOE correlation between H-2'α and H-4'.

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9) Although **9** can be assumed to be a single isomer, its olefinic configuration is not known.

10) A significant amount (53.3%) of the starting material (**10**) was recovered.

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12) When the Mitsunobu reaction of **7** was carried out (diethyl azodicarboxylate, PPh_3, benzoic acid, 3 equiv each, in THF, room temperature, overnight), no reaction took place. Further addition of the same amounts of reagents resulted in the formation of a complex mixture of products, from which only **7** (43.9%) was isolated by preparative TLC (6% hexane in Et_2O).

13) Hydride reduction of 1'-*C*-branched 2'-ketouridines has been reported to yield the ribofuranosyl product predominantly: Yoshimura, Y.; Otter, B. A.; Ueda, T.; Matsuda, A. *Chem. Pharm. Bull.* **1992**, *40*, 1761-1769.

14) Oxidation of **7** with PDC in CH_2Cl_2 gave a complex mixture of products, from which only **7** was isolated in 46.6% recovery.

15) Base-catalyzed interconversion of 2'- and 3'-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl nucleosides in MeOH has been reported: Jones, S. S.; Reese C. B. *J. Chem. Soc. Perkin I* **1979**, 2762-2764.

16) The H-2' (δ 5.34 ppm) in **15** is readily assignable, because of significant down field shift due to anisotropic effect of the base moiety (*cf.* H-3': δ 4.24 ppm).

17) Crystal data of **16** are as follows: space group $P2_12_12_1$ (orthorhombic), Z= 4, a= 6.691(10), b= 11.022(9), c= 18.022(9) Å, *V*= 1329(1) Å^3, *Dc*= 1.735 gcm^{-3}.