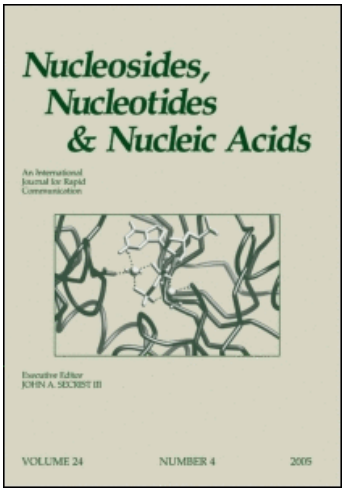

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Efficient Synthesis of 2'-Bromo-2'-Deoxy-3',5'-*O*-TPDS-pyrimidine Nucleosides by Boron Trifluoride Catalyzed Reaction of O^2,2'-Anhydro-(1-β-D-Arabinofuran0Syl)pyrimidine Nucleosides with Lithium Bromide

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NOTE

EFFICIENT SYNTHESIS OF 2'-BROMO-2'-DEOXY-3',5'-*O*-TPDS-PYRIMIDINE NUCLEOSIDES BY BORON TRIFLUORIDE CATALYZED REACTION OF O^2,2'-ANHYDRO-(1-β-D-ARABINO-FURANOSYL)PYRIMIDINE NUCLEOSIDES WITH LITHIUM BROMIDE[#,1]

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ABSTRACT: Efficient syntheses of 2'-bromo-2'-deoxy-3',5'-*O*-TPDS-uridine (**5a**) and 1-(2-bromo-3,5-*O*-TPDS-β-D-ribofuranosyl)thymine (**5b**) from uridine and 1-(β-D-ribofuranosyl)thymine are described, respectively. The key step is a treatment of 3',5'-*O*-TPDS-O^2,2'-anhydro-1-(β-D-arabinofuranosyl)uracil (**4a**) and -thymine (**4b**) with LiBr in the presence of BF_3-OEt_2 in 1,4-dioxane at 60 °C to give **5a** and **5b** in 98%, and 96% yield, respectively.

The incorporation of a halogeno group in the sugar moiety of a nucleoside, particularly in the 2' and 3' position, provides a versatile intermediate for the synthesis of a variety of chemically modified nucleosides, which are of great interest from the biochemical, medicinal, and chemical viewpoints. The synthesis of 2'-deoxyuridine has been fulfilled in term of the reduction reaction of intermediates bearing halogeno or thioether function at their 2' position. Hanessian *et al.*[2-3] reported the synthesis of 2'-bromo-2'-deoxyuridine derivatives by the reaction of 2',3'-*O*-benzylideneuridine with *N*-bromosuccinimide (NBS), which gave not only 2'-bromo-2'-deoxyuridine derivative, but also 3'-*O*-benzoyl-2',5-dibromouridine. Chemical conversion of O^2,2'-anhydro-1-(β-D-arabinofuranosyl)uracil into the corresponding 2'-deoxy-2'-halogeno derivative has been performed by treatment with an anhydrous hydrogen halide at 0°C in a sealed stainless vessel for a long period,[4-6] a quasiphosphonium halide,[7-9] tetrachlorosilane,[10] or a reagent prepared from a hydrogen halide and

[#] This paper is dedicated to Dr. Yoshihisa Mizuno, an Emeritus Professor of Hokkaido University, on the occasion of his 75th birthday.

DMF.[11] Alternatively, uridine (**1a**) and/or O^2,2'-anhydro-1-(β-D-arabinofuranosyl)-uracil (**2a**)[12] were converted to 3',5'-di-*O*-acyl-2'-halogeno-2'-deoxyuridine by treatment with an acyl halide[13-15] instead of hydrogen halide.

There has been, however, no report on the synthesis of 2'-bromo-2'-deoxyribonucleoside derivatives using 1,1,3,3-tetraisopropyldisiloxan-1,3-diyl (TPDS) protecting group for the 3'- and 5'-hydroxyl groups.[16] Therefore, we set out to investigate such a synthetic approach to 2'-bromo-2'-deoxy-3',5'-*O*-TPDS-pyrimidine nucleosides by way of O^2,2'-anhydro-3',5'-*O*-TPDS-1-(β-D-arabinofuranosyl)uracil (**4a**), prepared by introduction of the TPDS protecting group to **2a** which was obtained by the reaction of **1a** with ethylene carbonate, and/or -thymine (**4b**), prepared by the reaction of 1-(3,5-*O*-TPDS-β-D-ribofuranosyl)thymine (**3b**) with trifluoromethane-sulfonyl chloride (TfCl) and DMAP in dichloromethane (CH_2Cl_2) at room temperature. Subsequently, bromination reactions of **4a** and **4b** were respectively attempted under various conditions. Both **4a** and **4b** were not susceptible to bromination reaction with lithium bromide (LiBr) at all. In order to facilitate their bromination reaction, there might be an idea to use rather naked bromide ion such as tetrabutylammonium bromide, but such a kind of salts is practically difficult to separate from the objective compounds in chromatography due to its phase transfer catalystic property ; this assumption led us to avoid this approach to bromination.

As an alternative approach, the reaction with a bromide involving acid catalysis was performed with respect to **4a** and **4b**; the acid catalyst such as boron trifluoride diethyl etherate (BF_3-OEt_2) should be subjected to coordination by the carbonyl oxygen at 4-position and, thus, exert significant electron withdrawing effect toward 2' position through the heterocylic and anhydro bond system, i.e., enhance the δ^+ character of C-2' which might make the nucleophilic reaction with LiBr significantly facilitated (FIG.1).

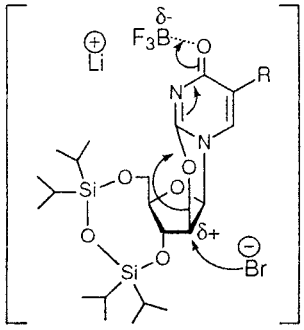


FIG. 1 Transition State

Consequently, bromination reactions of **4a** by use of LiBr in the presence of BF_3 were performed to elaborate the reaction conditions looking at the effect of temperature; the results obtained are summarized in TABLE 1.

In the presence of BF_3 (1.1 mol. equiv. to **4a**), the reaction was performed at room temperature (ENTRY 1), 40 °C (ENTRY 2), 60 °C (ENTRY 3), and 80 °C (ENTRY 4), to give **5a** (78%, 94%, 98%, and 98% yield, respectively), and it was thus proved to give a quantitative yield of **5a** sufficiently at 60 °C. The use of 0.5 mol. equiv. of BF_3 gave 61% yield of **5a** (ENTRY 5) under the same conditions, but

TABLE 1

ENTRY	mol. equiv. of BF_3	Temp. (℃)	**5a** Yield (%)
1	1.1	rt	78
2	1.1	40	94
3	1.1	60	98
4	1.1	80	98
5	0.5	60	61
6	0	60	N.R.

the reaction without the catalyst no product (ENTRY 6); the latter result demonstrate the significance of the acid catalysis in the bromination expectedly.

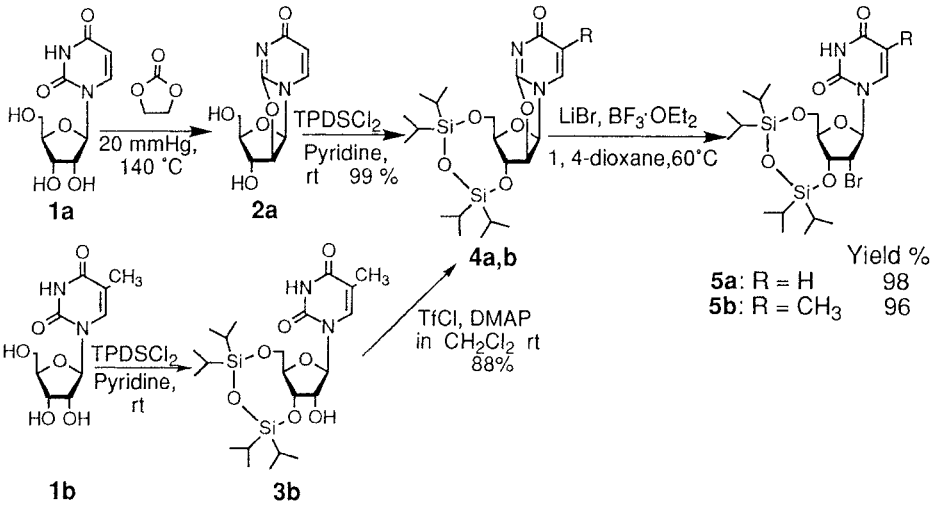
The reaction of **4b** under the same conditions gave **5b** in a quantitative yield (96% yield) (SCHEME 1).

Consequently, the reaction of **4** with LiBr catalyzed by BF_3 was confirmed to be efficient enough for bringing about 1-(2-bromo-2-deoxy-β-D-ribofuranosyl)-pyrimidines (**5**) quantitatively.

EXPERIMENTAL

General Procedures. Melting points were determined with a Yanagimoto micro-melting-point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were determined with a Bruker AM-400 spectrometer at 400 MHz and at 100 MHz, respectively. Chemical shifts were recorded in δ scale relative to an internal reference of chloroform (7.26 ppm for ^{1}H-NMR and 77.0 ppm for ^{13}C-NMR spectra), unless otherwise noted. Dimethyl sulfoxide-d_6 (DMSO-d_6) (2.50 ppm for ^{1}H spectra) was occasionally used as an internal reference. Signal peaks of ^{13}C-NMR spectra were assigned by the DEPT experiment, respectively. Mass spectra (MS) were measured with a VG instrument at 70 eV. Elemental analyses were achieved with a Perkin Elmer 240-002 analyzer. TLC was performed on aluminum plates precoated with Merck silica gel 60 F_{254}, and spots were detected with a UV lamp (253.7 nm), and column chromatography on Wakogel C-300 (Wako Pure Chemicals Co., Ltd.) and Kieselgel 60 (Merck Co., Ltd.).

***O*^{2},2'-Anhydro-3',5'-*O*-TPDS-1-(β-D-arabinofuranosyl)uracil (4a) from 2a.** The mixture of dried **2a**[12] (2.262g, 10 mmol) and $TPDSCl_2$ (3.2 mL, 10 mmol) in pyridine (100 mL) was stirred at room temperature. After stirring for 24 hr, the



SCHEME 1

solvent was evaporated and the residue was extracted with ethyl acetate (400 mL). The extract was successively washed with H_2O (200 mL), cold aqueous 1 M HCl (200 mL), H_2O (200 mL), an aqueous saturated solution of Na_2CO_3 (200 mL), and brine (200 mL). The organic layer was then dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated, and the residue was chromatographed on a column of silica gel employing $CHCl_3$ - MeOH system followed by recrystallization to gave **4a** (3.56 g, 76% yield), mp 179-180 °C (from diethyl ether), ^{1}H-NMR ($CDCl_3$): δ 7.3 (1H, d, $J_{6,5}$ = 7.51 Hz, H-6), 6.1 (1H, d, $J_{5,6}$ = 7.51 Hz, H-5), 5.98 (1H, d, $J_{1',2'}$ = 6.15 Hz, H-1'), 5.3 (1H, dd, $J_{2',1'}$ = 6.15 Hz, $J_{2',3'}$ = 3.92 Hz, H-2'), 4.5 (1H, dd, $J_{3',2'}$ = 3.92 Hz, $J_{3',4'}$ = 7.40 Hz, H-3'), 3.8-4.1(3H, m, H-4', H-5'a, H-5'b), 0.6-1.3 (28H, m, isoPr x 4). *Anal.* Calcd for $C_{21}H_{36}N_2O_6Si_2 \cdot 2/3H_2O$: C, 52.80; H, 7.81; N, 5.86. Found: C, 53.02; H, 7.64; N, 5.90.

O^2,2'-Anhydro-3',5'-*O*-TPDS-1-(β-D-arabinofuranosyl)thymine(4b) from 3b. A solution of dried **3b** (268 mg, 0.53 mmol) and DMAP (260 mg, 212 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature. After stirring for 30 min, to the resultant solution was added TfCl (0.19 mL, 1.06 mmol) at 4° C with stirring. After stirring for 3 hr at 4°C, the reaction was quenched with H_2O, and extracted with CH_2Cl_2 (400 mL). The extract was successively washed with an aqueous saturated solution of Na_2CO_3 (200 mL) and brine (200 mL), and the organic layer was then dried over anhydrous Na_2SO_4. The filtrate, obtained by filtration, was evaporated,

and the residue was chromatographed on a column of silica gel employing 1:1 toluene - ethyl acetate and 30:1 CH_2Cl_2 - MeOH, then recrystallized to give **4b** (243 mg, 88%), mp 179 - 180 °C (from diethyl ether), ^{1}H-NMR ($CDCl_3$): δ 7.2 (1H, d, $^4J_{6,5Me}$ = 1.25 Hz, H-6), 5.98 (1H, d, $J_{1',2'}$ = 6.19 Hz, H-1'), 5.3 (1H, dd, $J_{2',1'}$ = 6.19 Hz, $J_{2',3'}$ = 3.99 Hz, H-2'), 4.5 (1H, dd, $J_{3',2'}$ = 3.99 Hz, $J_{3',4'}$ = 7.40 Hz, H-3'), 3.8-4.1(3H, m, H-4', H-5'a, H-5'b), 1.95(3H, d, $^4J_{5Me,6}$ = 1.25 Hz, Me-5), 0.6-1.3 (28H, m, isoPr x 4). *Anal.* Calcd for $C_{22}H_{38}N_2O_6Si_2$: C, 54.74; H, 7.93; N, 5.80. Found: C, 54.78; H, 7.95; N, 5.84.

2'-Bromo-2'-deoxy-3',5'-*O*-TPDS-uridine (5a) from 4a. To a mixture of **4a** (0.234 g, 0.5 mmol) and LiBr (56 mg, 0.75 mmol) in dry dioxane (5 mL) was added BF_3-OEt_2 (0.076 mL, 0.6 mmol) with stirring at 60 °C under argon atmosphere. After stirring for 6 h (the spot of **4a** on TLC disappeared), the solvent was concentrated in *vacuo*, and the resulting residue was, after the addition of brine (5 mL), extracted with CH_2Cl_2 (20 mL x 3) and combined CH_2Cl_2 layer was washed with brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated in *vacuo*, and the residue was chromatographed on a column of silica gel employing toluene-ethyl acetate system to give **5a** (0.267 g, 98 % yield). ^{1}H-NMR ($CDCl_3$): δ 8.30 (1H, bs, H-3), 7.88 (1H, d, $J_{6,5}$ = 8.2 Hz, H-6), 6.11 (1H, s, H-1'), 5.67(1H, dd, $^4J_{5,NH}$ = 1.9 Hz, $J_{5,6}$ = 8.2 Hz, H-5), 4.37(1H, d, $J_{2',3'}$ = 4.7 Hz, H-2'), 4.18 - 4.49 (3H, m, H-3', H-4', H-5'a), 4.01(1H, dd, $J_{5'b,4'}$ = 2.3 Hz, $J_{5'a,5'b}$ = 13.7 Hz, H-5'b), 0.78-1.3 (28H, m, isoPr x 4). *Anal.* Calcd for $C_{21}H_{37}BrN_2O_6Si_2$: C, 45.89; H, 6.79; N, 5.10. Found: C, 45.88; H, 6.61; N, 5.09.

1-(2-bromo-3,5-*O*-TPDS-β-D-ribofuranosyl)thymine (5b) form 4b. To the mixture of **4b** (3.1g, 6.4 mmol) and LiBr (660 mg, 7.6 mmol) in refined dioxane (65 mL) was added BF_3-OEt_2 (0.89 mL, 7.6 mmol) with stirring at 60 °C for 2 h under argon atmosphere, and a work-up in a similar manner as above gave a foam of **5b** (3.462g, 96%), . ^{1}H-NMR ($CDCl_3$) : δ 8.21(1H, bs, H-3), 7.56(1H, d, $^4J_{6,5\text{-Me}}$ = 1.2 Hz, H-6), 5.98 (1H, s, H-1'), 4.39 (1H, d, $J_{2',3'}$ = 5.4 Hz, H-2'), 4.1 - 4.4(3H, m, H-3', H-4', H-5'a), 4.01 (1H, dd, $J_{5'b,4'}$ = 2.7 Hz, $J_{5'a,5'b}$ = 13.6 Hz, H-5'b), 1.92 (3H, d, $^4J_{5\text{-Me},6}$ = 1.2 Hz, 5-Me), 1.25 - 0.8 (28H, m, *iso*Pr x 4). *Anal.* Calcd for $C_{21}H_{37}BrN_2O_6Si_2$: C, 46.88; H, 6.97; N, 4.97. Found: C, 46.83; H, 6.82; N, 4.86.

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