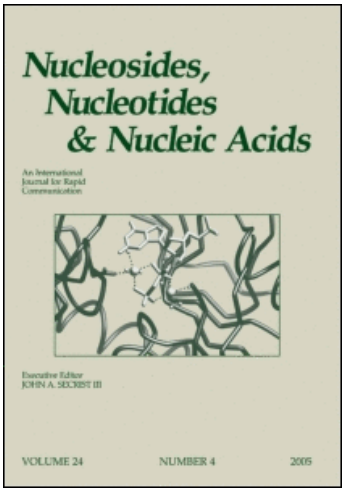


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Detailed Studies on Trimethylselyl Triflate Mediated Glycosylation *via* a 3,5-*O*-(l,l,3,3-Tetraisopropyl-Disiloxane-l,3-diyl)-2-*O*-methylribofuranos-l-yl Trichloroacetimidate Intermediate

Koh-ichiroh Shohda[a]; Takeshi Wada[a]; Mitsuo Sekine[a]
[a] Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, Yokohama, Japan

To cite this Article Shohda, Koh-ichiroh , Wada, Takeshi and Sekine, Mitsuo(1998) 'Detailed Studies on Trimethylselyl Triflate Mediated Glycosylation *via* a 3,5-*O*-(l,l,3,3-Tetraisopropyl-Disiloxane-l,3-diyl)-2-*O*-methylribofuranos-l-yl Trichloroacetimidate Intermediate', Nucleosides, Nucleotides and Nucleic Acids, 17: 12, 2199 — 2210
To link to this Article: DOI: 10.1080/07328319808004310
URL: http://dx.doi.org/10.1080/07328319808004310

NUCLEOSIDES & NUCLEOTIDES, 17(12), 2199-2210 (1998)

DETAILED STUDIES ON TRIMETHYLSILYL TRIFLATE MEDIATED GLYCOSYLATION *VIA* A 3,5-*O*-(1,1,3,3-TETRAISOPROPYL-DISILOXANE-1,3-DIYL)-2-*O*-METHYLRIBOFURANOS-1-YL TRICHLOROACETIMIDATE INTERMEDIATE

Koh-ichiroh Shohda, Takeshi Wada, and Mitsuo Sekine*

Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 226, Japan

ABSTRACT: The reaction of 3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methylribofuranos-1-yl trichloroacetimidate as the ribosyl donor with bis(trimethylsilyl)thymine was studied in detail. As the result, it was concluded that the main product is an α-glycoside derivative unlike the previous report. In connection with this glycosylation, several chemical properties of the byproduct obtained by the Chapman rearrangement are described.

Oligoribonucleotides containing 2'-*O*-methyl groups have been used for various studies involving antisense strategy, which has recently been studied extensively.[1-5] A number of 2'-*O*-methylribonucleosides have been synthesized *via* several approaches. Among them, regioselective synthesis of some 2'-*O*-methylribonucleoside derivatives has been realized by methylation of ribonucleosides with diazomethane in the presence of metal salts which can coordinate with the cis diol function.[6] However, these methods required tedious, time-consuming isolation procedures. Recently, several groups have developed methods for the 2'-*O*-methylation by using the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl group for the simultaneous protection of 5'- and 3'-OH,[7] and suitable protection of the nucleobase.[8-10] A new route to 2'-*O*-methylnucleosides from 2,2'-anhydrouridine derivatives by using displacement with metal methoxides was also reported.[11] In connection with these studies, more recently, a method for the synthesis of 2'-*O*-methyl-β-D-ribonucleosides has been reported.[12] This method involves the reaction between the 1-*O*-trichloroacetimidate (**2**) of 2-*O*-methyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranoside (**1**) and a silylated nucleobase in the presence of trimethylsilyl

Tel +81-45-924-5706, Fax +81-45-924-5772, email msekine@bio.titech.ac.jp

trifluoromethanesulfonate (TMSOTf) as a promoter. The stereoselectivity is reported to be more than 95% and the yields of the products were generally excellent. Therefore, we applied this method to the synthesis of some 2'-*O*-methyl-β-D-ribonucleosides involving 2'-*O*-methyl-2-thiouridine.[13] Extensive studies of the products derived from this type of reaction revealed that the α-selective glycosylation occurred predominantly under these conditions[12] with a concomitant Chapman-type rearrangement as a side reaction.[14-16] Here, we report the detailed studies of the structural determination of the product obtained by the glycosylation and several interesting chemical properties of the Chapman rearrangement product.

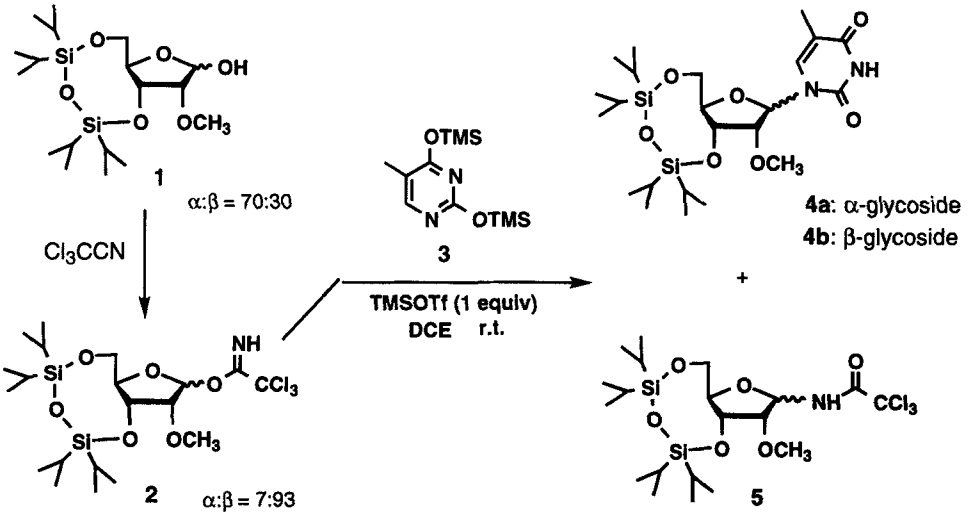
According to the original paper,[12] the reaction of the imidate **2** with 2,4-*O*-bis(trimethylsilyl)thymine **3**[17] in dichloroethane in the presence of 1 equiv of TMSOTf at room temperature completed within 1 min to give the β-glycoside **4b** as the main product.

To ascertain this procedure, we attempted the synthesis of the β-glycoside **4b** under the same conditions.[12] As a result, an 88:12 mixture of two products was obtained in 60% yield by silica gel column chromatography. However, the circular dichroism spectrum of this mixture showed the opposite Cotton effect[18-20] around 270 nm to that of the authentic compound[7,8,17,21] synthesized from β-ribothymidine as the starting material. The Cotton effect of the major product **4a** obtained by crystallization was negative at this region. These results suggested that the compound **4a** has an α-configuration at the anomeric position.

Robins *et al.* reported that the $J_{1'2'}$ coupling constants of 3', 5'-*O*-TIPDS-α-ribonucleosides and the β-counterparts were ca. 3.6 Hz and less than 0.5 Hz (singlet), respectively.[22] The $J_{1'2'}$ value of the main product was 3.6 Hz and the 1'-proton signal of the minor product was a singlet. These results strongly implied that the main product was not a β-glycoside but an α-glycoside. Moreover, Robins *et al.* showed that the resonance signal of the 1'-proton of 3', 5'-*O*-TIPDS-α-ribonucleosides appeared in lower magnetic field by 0.4-0.5 ppm than those of 3', 5'-*O*-TIPDS-β-ribonucleosides.[22,23] The chemical shifts of the 1'-protons of the main and minor products were 6.1 ppm and 5.7 ppm, respectively. This result also supported the predominant formation of the α-glycoside.

It is generally known that the 6-proton of pyrimidine-β-ribonucleosides correlates with the 2'- and/or 3'-protons in NOE measurements.[24] The correlation observed between the 6- and 4'-protons of this major product indicated similarly the same conclusion as described above.

Schmidt *et al.* reported the stereo-controlled synthesis of 1-*O*-trichloroacetimidate derivatives at the anomeric position and achieved the SN-2 type of reactions with nucleophiles to give glycosylated products with the reverse configuration.[25-27] Generally, the β-stereoisomers can be synthesized from the corresponding α-1-*O*-



SCHEME 1

trichloroacetimidates and, similarly, the α-stereoisomers can be produced from the β-imidates. The starting material **2** used in this study was synthesized from the 1-unprotected riboside **1** by the usual Schmidt procedure.[28,29] The reaction of **1** with 4 equiv of trichloroacetonitrile in dichloroethane in the presence of 1 equiv of DBU gave a mixture of the α- and β-imidates in 77% yield. The ^{1}H NMR of **2** showed that the β-stereoisomer was predominantly obtained over the α-isomer with a ratio of 93:7, although the ratio of the α- and β-stereoisomers in the compound **1** was determined to be 70:30.

In attempts to enhance the ratio of the α- to β-imidate intermediates, several experiments were conducted. The reaction of **1** with 4 equiv of trichloroacetonitrile in the presence of 1 equiv of K_2CO_3 as a base resulted in a mixture with 93:7, but the yield decreased to 71%. Interestingly, when a strong base such as sodium hydride was used in place of K_2CO_3, the β-stereoisomer with purity of more than 99% was predominantly obtained in 39% yield. These results indicated that the β-imidate is kinetically and thermodynamically more stable than the α-isomer.

In this nucleoside synthesis, a byproduct was also obtained. As described below, this product was assigned as a Chapman rearrangement product **5**.[14-16] The characterization of **5** was performed by the ^{1}H-NMR analysis and 1D-differential NOE experiments.[30]

A clear-cut coupling between the 1'-proton and NH proton indicates direct evidence for the connection of the nitrogen atom to the anomeric carbon. In addition, the

TABLE 1. The reaction of **2** with silylated bases in the presence of TMSOTf

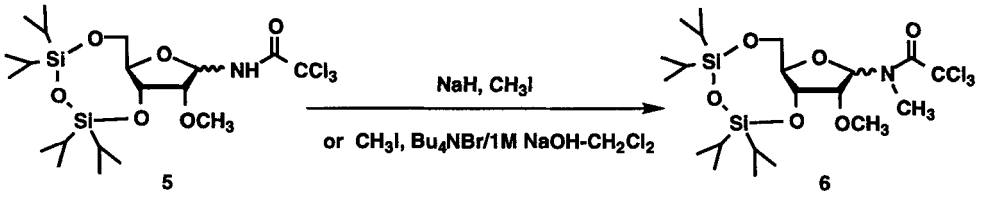
entry	nucleobase	TMSOTf (equiv)	temp.	time	yield of nucleoside (%)	ratio of α:β	5 (%)
1	2-thiouracil	1.0	rt	<1 min	71	98:2	-
2	5-(phthalimido-methyl)uracil	1.0	rt	<1 min	62	95:5	-
3	5-(azidomethyl)-uracil	1.0	rt	<1 min	61	93:7	-
4	T	1.0	rt	<1 min	60	88:12	36
5	T	0.2	rt	6 h	85	82:18	12
6	T	0.04	rt	18 h	93	80:20	6
7	T	0.04	0 °C	72 h	77	78:22	15
8	none	1.0	rt	<1 min	-	-	82
9	none	0.04	rt	15 min	-	-	91

observation of NOE with the 4'-proton and the 2'-*O*-methyl proton, when the NH proton of the main isomer was irradiated, demonstrated that the α-anomer is predominant in compound **5**.

It has been reported that the Chapman rearrangement, which is an imidate-amide rearrangement, occurred at higher temperatures[14] and/or in the presence of Lewis acids like BF_3.[15,16] The yield of **5** was 36% under the conditions previously reported.[12] To clarify the present reaction, we examined several experiments as summarized in Table 1.

With a lesser amount of TMSOTf, formation of the nucleoside **4** was increased although the selectivity of the α- and β-isomers **4a** and **4b** was somewhat deminished. More interestingly, the Chapman rearrangement product was obtained in a high yield of 91% when **3** was not added and 0.04 equiv of TMSOTf was employed.

Finally, several properties of the Chapman rearrangement product **5** are described below. The reaction of **5** with methyl iodide in the presence of NaH gave the *N*-methylated product **6** in 61% yield. The compound **6** was also obtained in 53% yield by the phase-transfer conditions[31] using CH_3I-CH_2Cl_2/1M NaOH in the presence of a catalytic amount of Bu_4NBr.[21,32] On the other hand, acetylation and sulfonation of **5** failed under the usual conditions using acetic anhydride and tosyl chloride or triflic anhydride. Several attempts to activate compound **6** by use of TMSOTf and other Lewis acids such as $SnCl_4$[33] and $TiCl_4$ also failed.



SCHEME 2

In conclusion, it was disclosed that the reaction of **2** with the silylated thymine derivative **3** gave the α-glycoside **4a** predominantly. In other words, this reaction might be useful for the synthesis of 2'-*O*-methyl-α-ribonucleoside derivatives since the stereoselectivity of the α-isomer is high.[34,35]

EXPERIMENTAL

General. CD spectra were recorded by a JASCO J-500 spectrometer. $CDCl_3$ was used as a solvent in all NMR experiments. ^1H NMR spectra were measured at 270 MHz with Me_4Si as an internal reference, and ^{13}C NMR spectra were obtained at 67.8 MHz with Me_4Si or $CDCl_3$ (δ = 77.0 ppm) as an internal standard. 1,2-Dichloroethane, toluene, and xylene were distilled from CaH_2 after being refluxed for several hours and stored over molecular sieves 4A. Pyridine was distilled after being refluxed over *p*-toluenesulfonyl chloride for several hours, redistilled from CaH_2, and stored over molecular sieves 4A. TLC was performed on precoated glass plates of Merk Kieselgel 60 F_{254} (Merck, No. 5715). Column chromatography was carried out with silica gel C-200 purchased from Wako Co., Ltd. D-ribose was purchased from Tokyo Kasei Co., Ltd. Elemental analyses were performed by Microanalytical Laboratory, Tokyo Institute of Technology, at Nagatsuta.

3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methylribofuranos-1-yl trichloroacetimidate (2). Method A.[12] Compound **1** (133 mg, 0.327 mmol) was dried by repeated coevaporation with dry pyridine, followed by dry toluene and finally dissolved in dry 1,2-dichloroethane (3.3 ml). To the solution was added trichloroacetonitrile (131 μl, 1.31 mmol) and 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU) (49 μl, 0.329 mmol). The resulting mixture was stirred for 20 min at room temperature and then extracted by the use of chloroform/sodium phosphate buffer (pH 7.0). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with

hexane-ethyl acetate (98:2, v/v) containing 0.5% pyridine to give **2** (138 mg, 77%, α:β = 7:93). ^{1}H NMR δ 0.96-1.13 (28H, m, *i*-Pr of TIPDS), 3.54 and 3.63 (3H, 2s, diastereomeric 2-*O*-CH_3), 3.80-4.16 (4H, m, 2-H, 4-H, 5-H, and 5'-H), 4.29-4.60 (1H, m, and dd, $J_{2H\text{-}3H}$ = 4.3 Hz, $J_{3H\text{-}4H}$ = 8.3 Hz, diastereomeric 3-H), 6.18 and 6.26 (1H, d, $J_{1H\text{-}2H}$ = 4.3 Hz, and s, diastereomeric 1-H), 8.49 (1H, brs, N-H).

Method B. Compound **1** (239 mg, 0.587 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine, dry toluene and finally dissolved in dry 1,2-dichloroethane (5.9 ml). To the solution was added trichloroacetonitrile (236 μl, 2.35 mmol) and potassium carbonate (81 mg, 0.587 mmol). The mixture was stirred for 2 h at room temperature and then extracted by the use of chloroform/water. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel, and eluted with hexane-ethyl acetate (98:2, v/v) containing 0.5% pyridine to give **2** (229 mg, 71%, α:β = 7:93).

Method C. Compound **1** (242 mg, 0.596 mmol) was dried by repeated coevaporation with dry pyridine, dry toluene and finally dissolved in dry 1,2-dichloroethane (6 ml). To the solution were added trichloroacetonitrile (239 μl, 2.38 mmol) and 55% sodium hydride (26 mg, 0.596 mmol). After being stirred at room temperature for 48 h, the mixture was quenched by addition of sodium phosphate buffer (pH 7.0), and extracted with chloroform/water. The usual workup followed by silica gel column chromatography eluted with hexane-ethyl acetate (98:2, v/v) containing 0.5% pyridine gave **2** (127 mg, 39%, α:β = 1:99).

Silylation of Nucleobases.[17] An appropriate nucleobase (0.5 mmol) was dissolved in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (2.0 ml) and pyridine (0.5 ml). After the mixure was refluxed for 1 h, the solvent was removed under reduced pressure, and coevaporation was performed repeatedly by dry xylene. The residue was dissolved in 1,2-dichloroethane, and the solution was added to dried starting material **2**.

Glycosylation *via* the Known Method (TABLE 1, Entries 1-4).[12]

2-Thio-1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methyl-α(and β)-D-ribofuranos-1-yl]uracil (Entry 1). 3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methylribofuranos-1-yl trichloroacetimidate (**2**) (284 mg, 0.516 mmol) was dried by repeated coevaporation with dry pyridine, dry toluene and dry 1,2-dichloroethane, and finally dissolved in dry 1,2-dichloroethane (2.2 ml). To the solution was added bis(trimethylsilyl)-2-thiouracil (155 mg, 0.568 mmol) in 1,2-dichloroethane (3 ml) and then TMSOTf (100 μl, 0.516 mmol) was added to the mixture. The mixture was stirred at room temprature for 5 min. After being cooled to 0 °C and quenched by an excess of triethylamine (173 μl), the mixture was extracted with chloroform/5% $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and

evaporated under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with hexane-ethyl acetate (4:1, v/v) to give the 2- thiouridine derivative (190 mg, 71%, α:β = 98:2, determined by ^{1}H NMR): UV(CH_3CN) λmax 287 nm, λmin250 nm; ^{1}H NMR δ 0.98-1.11 (28H, m, *i*-Pr of TIPDS), 3.62 and 3.69 (3H, 2s, 2'-*O*-CH_3), 3.96-4.09 (4H, m, 2'-H, 4'-H, 5'-H, and 5"-H), 4.33 (1H, dd, $J_{2'H\text{-}3'H}$ = 4.6 Hz, $J_{3'H\text{-}4'H}$ = 8.6 Hz, 3'-H), 5.75 and 6.61 (1H, s and d, respectively, $J_{1'H\text{-}2'H}$ = 5.0 Hz, diastereomeric 1'-H), 6.06 and 6.22 (1H, 2d, $J_{5H\text{-}6H}$ = 6.9 Hz and 6.6 Hz, respectively, diastereomeric 5-H), 7.85 and 8.01 (1H, 2d, $J_{5H\text{-}6H}$ = 6.6 Hz and 6.9 Hz, respectively, diastereomeric 6-H), 12.29 (1H, br, NH); ^{13}C NMR δ 12.69, 12.72, 12.98, 13.44, 16.88, 16.97, 17.13, 17.24, 17.34, 59.95, 60.58, 72.01, 80.47, 80.92, 87.24, 111.63, 154.65, 161.40, 163.94. Anal. Calcd. for $C_{22}H_{40}N_2O_6SSi_2 \cdot 0.2\ H_2O$: C, 50.78; H, 7.82; N, 5.38; S, 6.16. Found: C, 50.59; H, 7.72; N, 5.14; S, 5.90.

5-Phthalimidomethyl-1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methyl-α(and β)-D-ribofuranos-1-yl]uracil (Entry 2). The trichloroacetimidate **2** (138 mg, 0.250 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine, dry toluene and dry 1,2-dichloroethane, and finally dissolved in dry 1,2-dichloroethane (1 ml). To the solution was added a solution of bis(trimethylsilyl)-5-(phthalimidomethyl)uracil (115 mg, 0.275 mmol) in 1,2-dichloroethane (1.5 ml). TMSOTf (48.3 μl, 0.250 mmol) was added and the resulting mixture was stirred at room temprature for 5 min, cooled to 0 °C, quenched by addition of triethylamine (83 μl), and extracted with chloroform/5% $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with hexane-ethyl acetate (3:2, v/v) to give the desired nucleoside (103 mg, 62%, α:β = 95:5, determined from ^{1}H NMR): ^{1}H NMR δ 1.01-1.13 (28H, m, *i*-Pr of TIPDS), 3.48 and 3.64 (3H, 2s, 2'-*O*-CH_3), 3.93-4.16 (4H, m, 2'-H, 4'-H, 5'-H, and 5"-H), 4.32-4.43 (1H, m, and dd, $J_{2'H\text{-}3'H}$ = 4.0 Hz, $J_{3'H\text{-}4'H}$ = 9.2 Hz, diastereomeric 3'-H), 4.58 and 4.66 (2H, 2d, $J_{5Ha\text{-}5Hb}$ = 14.9 Hz, 5-Ha and 5-Hb), 5.69 and 6.08 (1H, s and d, respectively, $J_{1'H\text{-}2'H}$ = 3.5 Hz, diastereomeric 1'-H), 7.63 and 7.91 (1H, 2s, diastereomeric 6-H), 7.68-7.87 (4H, m, Ar-H), 8.74 (1H, s, NH); ^{13}C NMR δ 12.67, 12.99, 13.41, 16.91, 16.98, 17.13, 17.24, 17.36, 34.34, 59.91, 60.38, 71.84, 79.64, 81.51, 85.10, 107.51, 123.32, 132.04, 133.93, 141.53, 149.99, 162.10, 167.69. Anal. Calcd. for $C_{31}H_{45}N_3O_9Si_2 \cdot H_2O$: C, 54.93; H, 6.99; N, 6.20. Found: C, 55.05; H, 6.70; N, 6.16.

5-Azidomethyl-1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methyl-α(and β)-D-ribofuranos-1-yl]uracil (Entry 3). The trichloroacetimidate **2** (134 mg, 0.243 mmol) was dried by repeated coevaporation with dry pyridine, dry toluene and dry 1,2-dichloroethane, and finally dissolved in dry 1,2-

dichloroethane (1 ml). To the mixture was added a solution of bis(trimethylsilyl)-5-(azidomethyl)uracil (82.1 mg, 0.267 mmol) in 1,2-dichloroethane (1.4 ml) and then TMSOTf (47.0 μl, 0.243 mmol) was added, and stirred at room temprature for 5 min. After being cooled to 0 °C and quenched by excess of triethylamine, the mixture was extracted with chloroform/5% $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure, and the residue was purified by silica gel column chromatography, and eluted with hexane-ethyl acetate (7:3, v/v) to give the desired nucleoside (82.5 mg, 61%, α:β = 93:7, determined from ^1H NMR): ^1H NMR δ 0.96-1.09 (28H, m, *i*-Pr of TIPDS), 3.52 and 3.67 (3H, 2s, 2'-*O*-CH_3), 3.94-4.18 (6H, m, 2'-H, 4'-H, 5'-H, 5"-H, 5-Ha, and 5-Hb), 4.43-4.64 (1H, m, and dd, $J_{2'H\text{-}3'H}$ = 3.6 Hz, $J_{3'H\text{-}4'H}$ = 9.2 Hz, diastereomeric 3'-H), 5.73 and 6.14 (1H, s and d, respectively, $J_{1'H\text{-}2'H}$ = 3.6 Hz, diastereomeric 1'-H), 7.46 and 7.81 (1H, 2s, diastereomeric 6-H), 9.66 (1H, brs, NH); ^{13}C NMR δ 12.96, 13.01, 13.21, 13.39, 13.61, 16.89, 16.97, 17.04, 17.11, 17.22, 17.25, 17.33, 47.23, 59.91, 60.43, 71.83, 79.64, 81.71, 85.21, 107.71, 140.49, 149.99, 163.02, 163.90. MS (FAB+) calcd for $C_{23}H_{42}O_7N_5Si_2$ [M + H^+] 556.2625, found 556.2610.

1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methyl-α(and β)-D-ribofuranos-1-yl]thymine (Entry 4). 3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methylribofuranos-1-yl trichloroacetimidate (**2**) (160 mg, 0.290 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine (1 ml x 3), dry toluene (1 ml x 3), and dry 1,2-dichloroethane (1 ml x 2) and finally dissolved dry 1,2-dichloroethane (1 ml). To the solution was added bis(trimethylsilyl)thymine (**3**) (86.3 mg, 0.319 mmol) in 1,2-dichloroethane (1.9 ml) and then to the mixture was added TMSOTf (56 μl, 0.290 mmol), and stirred at room temperature for 5 min. After being cooled to 0 °C and quenched by triethylamine (500 μl), extraction was performed with chloroform/5% $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with hexane-ethyl acetate (3:1, v/v) to give the desired nucleosides (89 mg, 60%, **4a**:**4b** = 88:12, determined from ^1H NMR), and Chapman rearrangement product (**5**) (58 mg, 36%). The mixture of **4a** and **4b** obtained was recrystallized from hexane-ethyl acetate to give **4a** as pure white crystals (53 mg): mp 186-187 °C; ^1H NMR δ 0.99-1.09 (28H, m, *i*-Pr of TIPDS), 1.93 (3H, s, 5-CH_3), 3.50 (3H, s, 2'-*O*-CH_3), 3.95-4.14 (4H, m, 2'-H, 4'-H, 5'-H, and 5"-H), 4.43 (1H, dd, $J_{2'H\text{-}3'H}$ = 4.0 Hz, $J_{3'H\text{-}4'H}$ = 9.2 Hz, 3'-H), 6.14 (1H, d, $J_{1'H\text{-}2'H}$ = 3.6 Hz, 1'-H), 7.21 (1H, s, 6-H), 8.11(1H, brs, N-H); ^{13}C NMR δ 12.55, 12.67, 12.99, 13.43, 16.91, 16.98, 17.13, 17.24, 17.27, 17.36, 60.09, 60.49, 71.79, 79.91, 81.60, 85.01, 109.06, 137.20, 150.35, 163.99. Anal. Calcd. for $C_{23}H_{42}N_2O_7Si_2$: C, 53.67; H, 8.22; N, 5.44. Found:

C, 53.33; H, 7.96; N, 5.54. **4b**: ^{1}H NMR δ 0.96-1.12 (28H, m, *i*-Pr of TIPDS), 1.92 (3H, s, 5-CH_3), 3.67 (3H, s, 2'-*O*-CH_3), 3.73 (1H, d, $J_{2'H\text{-}3'H}$ = 4.6 Hz, 2'-H), 3.95-4.28 (4H, m, 3'-H, 4'-H, 5'-H and 5"-H), 5.75 (1H, s, 1'-H), 7.62 (1H, s, 6-H), 10.04 (1H, brs, N-H). ^{13}C NMR δ 12.29, 12.62, 12.83, 13.35, 16.77, 16.88, 16.95, 17.07, 17.20, 17.31, 17.38, 59.14, 59.26, 68.21, 81.47, 83.85, 88.63, 110.14, 135.06, 150.21, 164.49. The ^{1}H NMR assignment of **4b** was done by the remaining peaks after elimination of the signals of **4a** from the ^{1}H NMR spectrum of a ca. 2:1 mixture of **4a** and **4b**, which was recovered as the filtrate after the above mentioned crystalization of **4a**.

1D-Differential NOE Measurements of Nucleosides (4a, 4b) and of Chapman Rearrangement Product (5). The 1D-differential NOE spectrum of each compound was recorded in a NOEDIF mode of the spectrometer by irradiation of the 6-H or NH proton). The intensity of NOE was estimated by comparison with the inverted signal of the irradiated proton.

Chapman Rearrangement of 3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methylribofuranos-1-yl trichloroacetimidate (2).

Compound **2** (158 mg, 0.286 mmol, α:β = 7:93) was dried by repeated coevaporation with dry pyridine, dry toluene and dry 1,2-dichloroethane, and finally dissolved in dry 1,2-dichloroethane (2.9 ml). To the solution was added TMSOTf (55 µl, 0.286 mmol), and stirred at room temperature for 5 min. After being cooled to 0 °C and quenched by triethylamine (500 µl), the mixture was extracted with chloroform/5% $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure, and the residue was purified by silica gel column chromatography, and eluted with hexane-ethyl acetate (95:5, v/v) to give the Chapman rearrangement product **5** (129 mg, 82%, α:β = 96:4): ^{1}H NMR δ 0.97-1.14 (28H, m, *i*-Pr of TIPDS), 3.64 and 3.65 (3H, 2s, diastereomeric 2-*O*-CH_3), 3.73-4.06 (4H, m, 2-H, 4-H, 5-H, and 5'-H), 4.33-4.40 (1H, m, and dd, $J_{2H\text{-}3H}$ = 4.6 Hz, $J_{3H\text{-}4H}$ = 7.9 Hz, diastereomeric 3-H), 5.42 and 5.75 (1H, d, $J_{1H\text{-}2H}$ = 5.3 Hz, and dd, $J_{1H\text{-}2H}$ = 4.6 Hz, $J_{1H\text{-}NH}$ = 8.6 Hz, diastereomeric 1-H). 7.93 (1H, d, $J_{1H\text{-}NH}$ = 8.6 Hz, N-H); ^{13}C NMR δ 12.72, 12.85, 13.16, 13.41, 13.50, 16.95, 17.04, 17.13, 17.18, 17.29, 17.41, 60.24, 61.13, 72.44, 79.44, 80.02, 81.37, 92.51, 161.67. Anal. Calcd. for $C_{20}H_{38}NO_6Si_2Cl_3$: C, 43.59; H, 6.95; N, 2.54; Cl, 19.30. Found: C, 43.91; H, 6.83; N, 2.38; Cl, 19.02.

3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*O*-methylribofuranos-1-yl-*N*-methyltrichloroacetamide (6). Method A. Compound **5** (317 mg, 0.576 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and dry dimethylformamide, and dissolved in dry dimethylformamide (5.8 ml). To the solution were added methyl iodide (178 µl, 2.88 mmol) and 55% sodium hydride (50.3 mg, 1.15 mmol). After being stirred at room temperature for 20 min, the mixture was

treated successively with sodium phosphate buffer (pH 7.0) and chloroform. The quenched mixture was extracted, and the organic layer was dried over Na_2SO_4, filtered, and then evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with hexane-ethyl acetate (98:2, v/v) to give **6** (197 mg, 61%): ^1H NMR δ 1.02-1.11(28H, m, *i*-Pr of TIPDS), 3.29 and 3.36 (3H, 2brs, diastereomeric N-CH_3), 3.93-4.12 (4H, m, 2-H, 4-H, 5-H, and 5'-H), 4.20-4.34 (1H, m, and dd, $J_{2H\text{-}3H}$ = 4.3 Hz, $J_{3H\text{-}4H}$ = 9.2 Hz, diastereomeric 3-H), 5.81 (1H, brs, 1-H); ^{13}C NMR δ 12.64, 12.98, 13.37, 16.89, 16.97, 17.09, 17.18, 17.31, 32.80, 59.88, 60.52, 70.96, 80.85, 80.90, 81.24, 87.89, 93.08, 159.57. Anal. Calcd. for $C_{21}H_{40}NO_6Si_2Cl_3$: C, 44.64; H, 7.13; N, 2.48; Cl, 18.82. Found: C, 44.75; H, 7.09; N, 2.51; Cl, 18.61.

Method B. Compound **5** (125 mg, 0.226 mmol) was dissolved in dichloromethane-methyl iodide (3:1, v/v, 6 ml). To the solution was added 1M NaOH (9 ml) and tetrabutylammonium bromide (7.3 mg, 0.023 mmol) as phase transfer catalyst. The mixture was vigorously stirred at room temperature for 40 h. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluted with hexane-ethyl acetate (98:2, v/v) to give **6** (68 mg, 53%).

ACKNOWLEDGEMENTS. This work was supported by a Grant from "Research for the Future" Program of the Japan Society for the Promotion of Science (JSPS-RFTF97I00301) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

REFERENCES

1. Lesnik, E. A.; Guinosso, C. J.; Kawasaki, A. M.; Sasmor, H.; Zounes, M.; Cummins, L. L.;Ecker, D. J.; Cook, P. D.; Freier, S. M. *Biochemistry* **1993**, *32*, 7832-7838.
2. Wagner, R. W. *Nature*, **1994**, 372, 333-335.
3. Cummins, L. L.; Owens, S. R.; Risen, L. M.; Lesnik, E. A.; Freir, S. M.; McGee, C. J.; Guinosso, J.; Cook, P. D. *Nucleic Acids Res.* **1995**, *23*, 2019-2029.
4. Beigelman, L.; McSwiggen, J. A.; Draper, K. G.; Gonzalez, C.; Jensen, K.; Karpeisky, A. M.; Modak, A. S.; Matulic-Adamic, J.; DiRenzo, A. B.; Haeberli, P.; Sweedler, D.; Tracz, D.; Grimm, S.; Wincott, F. E.; Thackray, V. G.; Usman, N. *J. Biol. Chem.* **1995**, *270*, 25702-25708.
5. Beigelman, L.; Karpeisky, A.; Matulic-Adamic, J.; Haeberli, P.; Sweedler, D.; Usman, N. *Nucleic Acids Res.* **1995**, *23*, 4434-4442.
6. Robins, M. J.; Naik, S. R.; Lee, A. S. K. *J. Org. Chem.* **1974**, *39*, 1891-1899.

7. Markiewics, W. T. *J. Chem. Research (S)* **1979**, 24-25.; *J. Chem. Research (M)* **1979**, 0181-0197.
8. Kamimura, T.; Masegi, T.; Hata, T. *Chem. Lett.* **1982**, 965-968.
9. Inoue, H.; Hayase, Y.; Imura, A.; Iwai, S.; Miura, K.; Ohtsuka, E. *Nucleic Acids Res.* **1987**, *15*, 6131-6148.
10. Sproat, B. S.; Beijer, B.; Iribarren, A. *Nucleic Acids Res.* **1990**, *18*, 41-49.
11. Ross, B. S.; Springer, R. H.; Tortorici, Z.; Dimock, S. XII International Round Table Nucleosides, Nucleotides and their Biological Applications, La Jolla, California, 1996, Abstract p 240.
12. Chanteloup, L.; Thuong, N. T. *Tetrahedron Lett.* **1994**, *35*, 877-880.
13. Edmonds, C. G.; Crain, P. F.; Hashizume, T.; Gupta, R.; Stetter, K. O.; McCloskey, J. A. *J. Chem. Soc., Chem. Commun.* **1987**, 909-910.
14. (a) Chapman, A. W. *J. Chem. Soc.* **1925**, *127*, 1992-1998. (b) Idem. *ibid.* **1927**, 1743-1751. (c) Idem. *ibid.* **1929**, 569-572.
15. Schulenberg, J. W.; Archer, S. *Org. React. vol. 14. Sterling-Winthrop Research Institute, Rensselaer, New Yorrk* **1965**, 1-51
16. Cramer, F.; Hennrich, N. *Chem. Ber.* **1961**, *94*, 976-989.
17. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234-1255.
18. Emerson, T. R.; Swan, R. J.; Ulbricht, T. L. V. *Biochemistry*, **1967**, *6*, 843-850.
19. Nishimura, T.; Shimizu, B.; Iwai, I. *Biochim. Biophys. Acta.* **1968**, *157*, 221-232.
20. Ikehara, M.; Kaneko, M.; Nakahara, Y.; Yamada, S.; Uesugi, S. *Chem. Pharm. Bull.* **1971**, *19*, 1381-1388.
21. Sekine, M. *J. Org. Chem.* **1989**, *54*, 2321-2326.
22. Robins, M. J.; Wilson, J. S.; Sawyer, L.; James, M. N. G. *Can. J. Chem.* **1983**, *61*, 1911-1920.
23. Nishimura, T.; Shimizu, B.; Iwai, I. *Chem. Pharm. Bull.* **1964**, *12*, 1471-1478.
24. Agback, P.; Glemarec, C.; Sund, C.; Chattopadhyaya, J. *Tetrahedron*, **1992**, 48, 6537-6554.
25. Schmidt, R. R.; Michel, J.; Roos, M. *Liebigs Ann. Chem.* **1984**, 1343-1357.
26. Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, 1826-1847.
27. Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212-235.
28. Sugimoto, M.; Numata, M.; Koike, K.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *156*, c1-c5.
29. Numata, M.; Sugimoto, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *203*, 205-217.
30. Schirmer, R. E.; Davis, J. P.; Noggle, J. H.; Hart, P. A. *J. Am. Chem. Soc.* **1972**, *94*, 2561-2572.

31. Gajda, T.; Koziara, A.; Zawadzki, S.; Zwierzak, A. *Synthesis*, **1979**, 549-552.
32. Sekine, M. *Natural Product Lett.* **1993**, *1*, 251-255.
33. (a) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654-3660. (b) Idem. *ibid.* **1974**, *39*, 3660-3663. (c) Idem. *ibid.* **1974**, *39*, 3664-3667. (d) Idem. *ibid.* **1974**, *39*, 3668-3671. (e) Idem. *ibid.* **1974**, *39*, 3672-3674.
34. Mukaiyama, T.; Suda, S. *Chem. Lett.* **1990**, 1143-1146.
35. Mukaiyama, T.; Matsubara, K.; Suda, S. *Chem. Lett.* **1991**, 981-984.

Received 1/19/98
Accepted 3/23/98