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Transnucleosidation: An Improved Method for Transglycosylation from Pyrimidines to Purines

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Transglycosylation from acylated pyrimidine nucleoside to purines was originally developed by Miyaki, *et al.* To apply this method to the naturally occurring pyrimidine nucleosides having a labile sugar moiety, we studied the improvement of this reaction. As model compounds, tri-O-acetyl-3-benzoyluridine (**1**) and tetraacetylcytidine (**2**) were employed. Reaction conditions and yields were greatly improved by utilizing (1) trimethylsilyl derivatives of exo-N-acylpurines as a glycosyl acceptor, (2) trimethylsilyl trifluoromethanesulfonate as a catalyst in acetonitrile–dichloroethane. Because of the mild reaction conditions and high yield, this procedure may be regarded as a versatile method for transglycosylation, which was shown by the successful preparation of purine analogs of the polyoxin and octosyl acid nucleosides having labile amino- or anhydrosugar uronic acid.

Keywords——transnucleosidation; transglycosylation, from pyrimidines to purines; trimethylsilyl trifluoromethanesulfonate; polyoxin, adenine analog of; octosyl acid, adenine analog of; octosyl acid, guanine analog of; octosyl acid, theophilline analog of

In the course of our study concerning chemical modification of the nucleoside antibiotic polyoxins[2] and the shunt metabolites, octosyl acids,[3] we needed to explore an efficient method to convert their pyrimidine bases into purines. In 1970, an unique ribosyl migration reaction from pyrimidines to purines was reported by Miyaki, Saito, and Shimizu.[4] However, since their procedure was too drastic to apply to the labile sugar skeletons[5] of the polyoxins and octosyl acids, extensive improvement of the reaction conditions and yield was absolutely required. We have been able to solve this problem applying the recent advanced method for the nucleoside synthesis, which utilizes silylated heterocycles (silyl Hilbert Johnson reaction) in the presence of Friedel Crafts catalysts.[6,7] This paper describes details of the improvement of this transglycosylation reaction using cytidine and uridine derivatives as model compounds. Synthesis of some purine analogs of octosyl acid was also described.

For the activation of the glycosyl bond of the starting pyrimidine nucleoside, N-acylation of pyrimidines as utilized by Miyaki, *et al.*[4] was most favorable. Attempted activation by the 5,6-double bond saturation was not effective. Thus, we utilized 1-β-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-3-benzoyluracil (**1**) and 1-β-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-N[4]-acetylcytosine (**2**) as glycosyl donors (Chart 1). As a glycosyl acceptor, silylated heterocycles were most attractive. Reaction was performed in dichloroethane–acetonitrile in the presence of Friedel Crafts catalysts.

1) Location: *2–1 Hirosawa, Wako-shi, Saitama 351, Japan*; *a*) Present address: *Research Division, Kaken Chemical Co., Ltd., 2–28–8 Honkomagome, Bunkyo-ku, Tokyo 113, Japan.*
2) K. Isono, K. Asahi, and S. Suzuki, *J. Am. Chem. Soc.*, **91**, 7490 (1969).
3) K. Isono, P.F. Crain, and J.A. McCloskey, *J. Am. Chem. Soc.*, **97**, 943 (1975).
4) M. Miyaki, A. Saito, and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **18**, 2459 (1970).
5) α-Hydrogen (H-5′) of the α-amino acid residue of the polyoxin nucleoside, when protected such as acylamino ester, becomes extremely susceptible to β-elimination of 4′-oxygen and subsequent elimination of the aglycon under alkaline condition.[2] The furanose ring of octosyl acid is highly strained and susceptible to the ring cleavage by solvolysis.[1]
6) U. Niedballa and H. Vorbrüggen, *Angew. Chem.*, **82**, 449 (1970); *idem.*, *J. Org. Chem.*, **39**, 3654 (1974).
7) H. Vorbrüggen and K. Krolikiewicz, *Angew. Chem.*, **87**, 417 (1975).

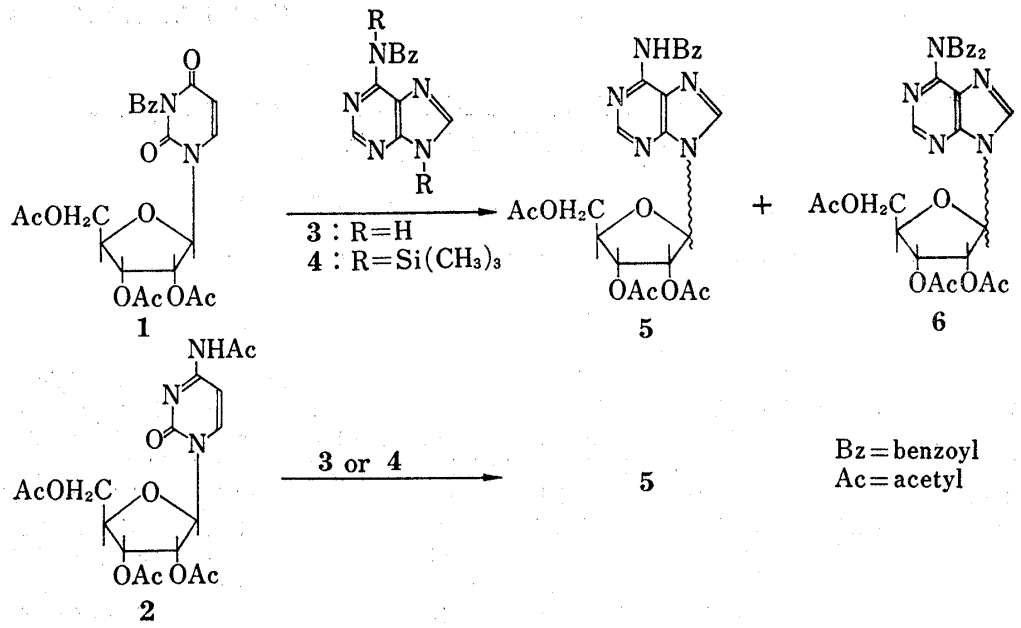

Chart 1

TABLE I. Reaction Conditions of Transribosylation and Yields of Adenine Nucleoside

Exp. No.	Donor (mmol)	Acceptor (mmol)	Catalyst (mmol)	Solvent	Benzoyl chloride (mmol)	Refluxing time (hr)	Yield (%) 5 α	5 β	6 α	6 β
1	**1** (0.2)	**3** (0.3)	$SnCl_4$ (0.4)	CH_3CN–$(CH_2)_2Cl_2$	1.2	24	23[a]		0	
2	**1** (0.3)	**4** (0.4)	$SnCl_4$ (0.6)	$(CH_2)_2Cl_2$	1.8	24	Trace		0	
3	**1** (0.3)	**4** (0.4)	$SnCl_4$ (0.6)	CH_3CN–$(CH_2)_2Cl_2$	1.8	2	40[a]		0	
4	**1** (0.5)	**4** (0.75)	$TMSOSO_2CF_3$ (0.5)	CH_3CN–$(CH_2)_2Cl_2$	0.8	2	0	9	0	49
5	**1** (0.5)	**4** (0.75)	$TMSOSO_2CF_3$ (0.5)	CH_3CN–$(CH_2)_2Cl_2$	0	10	0	26	0	30
6	**2** (0.5)	**3** (0.75)	$SnCl_4$ (0.85)	CH_3CN–$(CH_2)_2Cl_2$	0	24	0	22	0	0
7	**2** (0.5)	**4** (0.75)	$SnCl_4$ (0.85)	CH_3CN–$(CH_2)_2Cl_2$	0	24	0	45	0	0
8	**2** (0.5)	**4** (0.75)	$TMSOSO_2CF_3$ (0.5)	CH_3CN–$(CH_2)_2Cl_2$	0	15	0	81	0	0

a) Mixture of α- and β-anomers.

Reaction coditions and yields are summarized in Table I. Compound **1** was tested as a glycosyl donor in the first series of experiments (Exp. 1—5). When it was reacted with N^6-benzoyladenine in dichloroethane–acetonitrile in the presence of stannic chloride and benzoyl chloride, the reaction was found to proceed at the refluxing temperature (~80°) (Exp. 1, Table I). This is in contrast to that high temperature (130—140°) was required when the reaction was coducted in xylene–nitrobenzene.[4] The product was an anomeric mixture (approximately 1:1) as shown by thin-layer chromatography. By replacing N^6-benzoyladenine (3) with its bis-trimethylsilyl derivative[8] (**4**), the reaction temperature and yield were

8) T. Nishimura and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 352 (1964).

much improved (Exp. 3). The presence of acetonitrile is important because it cannot be replaced with dichloroethane alone (Exp. 2). The use of newly developed catalyst, trimethylsilyl trifluoromethanesulfonate ($Me_3SiOSO_2CF_3$)[7,9] instead of stannic chloride resulted in considerable increase in yield. Furthermore, the product was found to be exclusively β-anomer of N^6,N^6-dibenzoyladenine derivative (Exp. 4). Benzoyl chloride could be eliminated when this catalyst was used. In this case, the yield was almost unchanged, although longer reaction time was required and the product was a mixture of mono- and dibenzoyl derivatives (Exp. 5). Apparently, 3-benzoyl group of **1** was transacylated to N-6 of the product.

The similar results were obtained when tetraacetylcytidine (**2**) was used as a glycosyl donor (Exp. 6—8, Table I). The yield was almost two-fold by replacing N^6-benzoyladenine (**3**) with its bis-trimethylsilyl derivative (**4**) (Exp. 6 *vs.* Exp. 7), and further doubled by replacing stannic chloride with trimethylsilyl trifluoromethanesulfonate (Exp. 7 *vs.* 8). In all the cases, the product was exclusively β-anomer. As a glycosyl donor, **2** was more effective than **1** (Exp. 8 *vs.* Exp. 5).

Nearly quantitative yield was obtained when trimethylsilyltheophylline (**7**) was used as a glycosyl acceptor under the best conditions (Exp. 9). N^2-Acetyl-tris(trimethylsilyl)guanine (**9**) was also found to be an acceptor. Under the best conditions, the product was mostly a 9-β-isomer (**10**), yield being 66%. A minor product (2%) is considered to be a 7-isomer from the ultraviolet (UV) spectra.

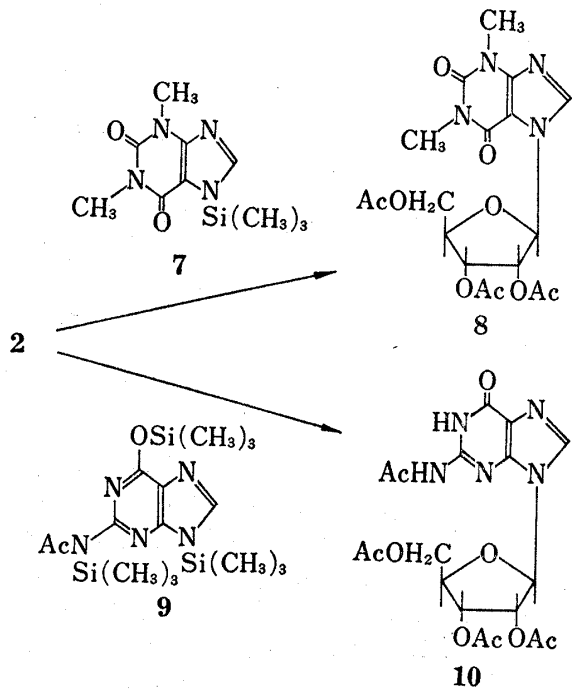

Chart 2

In summary, transglycosylation from pyrimidines to purines was best achieved by using (1) tetraacetylcytidine (**2**) as a glycosyl donor, (2) acetonitrile–dichloroethane as a solvent, (3) trimethylsilyl trifluoromethanesulfonate as a catalyst, and (4) trimethylsilyl derivatives of exo-N-acylpurines as a glycosyl acceptor.

This reaction may be regarded as a versatile method for "transnucleosidation".[10] We have successfully applied this method for the preparation of adenine analogs of naturally occurring pyrimidine nucleosides such as octosyl acids and polyoxins, which were communicated earlier.[11,12] Adenine analog of octosyl acid was found to be a competitive inhibitor of cyclic AMP phosphodiesterases from various animal tissues.[13] In addition, we have been able to synthesize theophylline and guanine analogs of octosyl acid. Octosyl acid A[3] (**11**) was converted to N^4-acetyl-5-carbomethoxyuronamide of the corresponding cytosine derivative (**12**) in 5 steps.[11] Transglycosylation from **12** to trimethylsilyl derivative of theophylline (**7**) was performed at the refluxing temperature in acetonitrile–dichloroethane for

9) Trimethylsilyl perchlorate can be used as effectively. However, it was abandoned because of its explosive nature.
10) A term, "transnucleosidation" was proposed by J. Beranek and H. Hrebabecky [*Nucleic Acid Research*, 3, 1387 (1976)]. However, their procedure is consisted from two steps; cleavage of purine nucleoside by acetyl bromide and formation of nucleoside bond with silylated pyrimidine base.
11) T. Azuma, K. Isono, P.F. Crain, and J.A. McCloskey, *Tetrahedron Lett.*, **1976**, 1687.
12) T. Azuma, K. Isono, P.F. Crain, and J.A. McCloskey, *Chem. Commun.*, **1977**, 159.
13) Personal communication from Dr. J.P. Miller of ICN Nucleic Acid Research Institute.

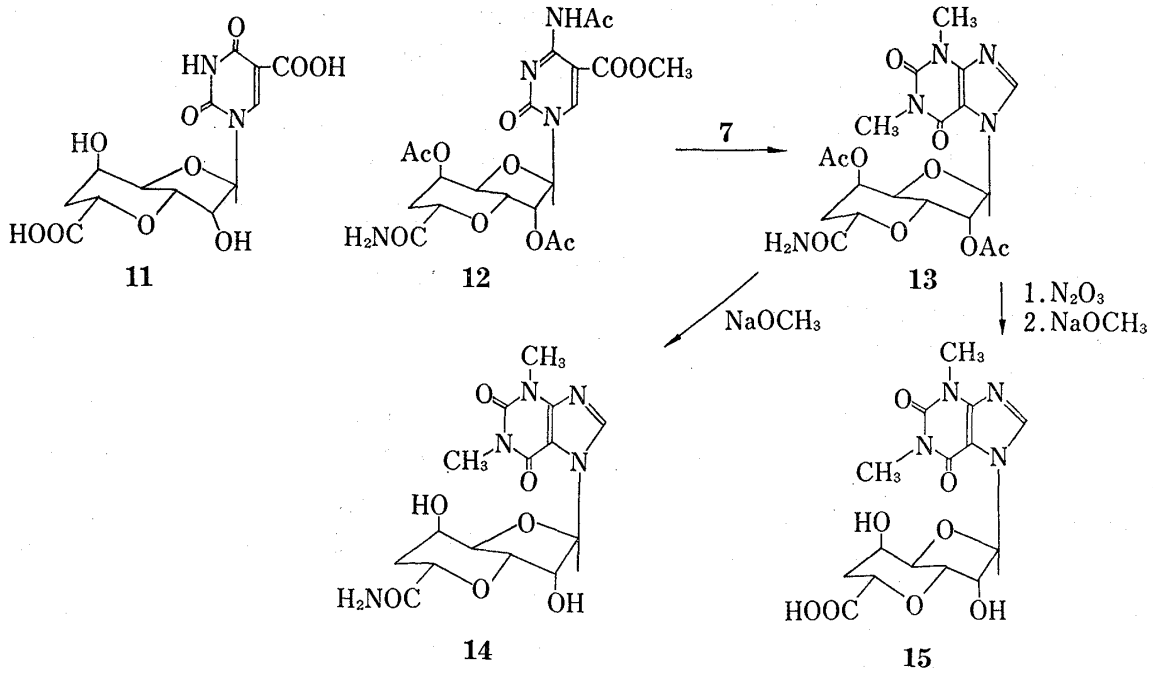

Chart 3

20 hr in the presence of $Me_3SiOSO_2CF_3$ (Chart 3). Yield of crystalline 7-glycoside (**13**) was 55%. β-Configuration of nucleoside bond was concluded from NMR ($J_{1',2'}=\sim 0$) which is characteristic to octosyl acids A and B.[3] Treatment of **13** with 0.2 N $NaOCH_3$ in MeOH afforded crystalline deacylated uronamide **14**. Crystalline free acid (**15**) was obtained by treatment of **13** with nitrous anhydride in acetic acid[14] followed by deacylation. Similar reaction of **12** with tris-trimethylsilyl-N^2-acetylguanine (**9**) afforded 9-β-nucleoside (**16**) (10%) and 7-isomer (**17**) (6%). Deacylation with $NaOCH_3$ in MeOH, followed by alkaline hydro-

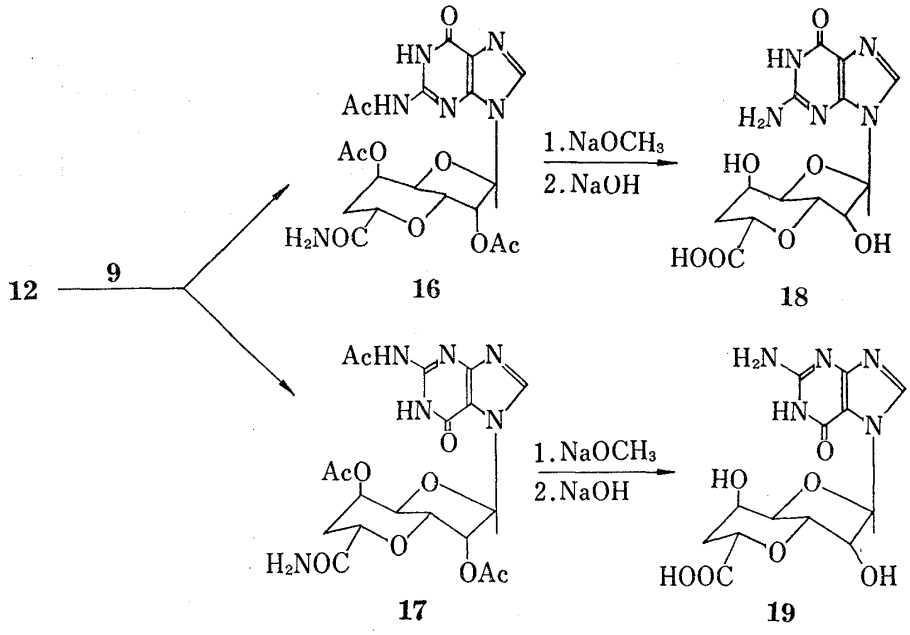

Chart 4

14) C.D. Hurd and J.C. Sowden, *J. Am. Chem. Soc.*, **60**, 235 (1938).

lysis afforded free guanine nucleosides, **18** and **19** respectively (Chart 4). Mass spectrometric analysis of these octosyl acid analogs will be published elsewhere.[15]

As further extension of this reaction, we are currently involved in transglycosylation from pyrimidines to pyrimidines and purines to pyrimidines.

Experimental

All melting points were taken on a micro hot stage apparatus and are not corrected. UV spectra were run on a Hitachi Model 124 spectrometer. ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded on a Varian HA-100 or a JNM-PFT-100 spectrometer. Chemical shifts were recorded in δ value from internal or external tetramethylsilane. Coupling constants were expressed in Hz. Abbreviation used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were measured by a Perkin Elmer 141 polarimeter and circular dichroism (CD) spectra were taken on a JASCO J-20 spectropolarimeter. For thin-layer chromatography, Silica Gel G (E. Merck AG) and Avicel SF microcrystalline cellulose were used. Mallinecrodt's Silicic Acid AR was used for column chromatography.

Transribosylation of 1 to 4 (Exp. 3)——A mixture of **1** (142 mg), **4** (131 mg), benzoyl chloride (0.2 ml), and $SnCl_4$ (0.07 ml) in dichloroethane ($(CH_2)_2Cl_2$) (2.8 ml) and acetonitrile (CH_3CN) (2 ml) was refluxed for 2 hr. After the reaction mixture was cooled, $CHCl_3$ (10 ml) was added and filtered. The filtrate was washed with saturated $NaHCO_3$ solution, then with water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to dryness. The residue was chromatographed on a silica gel column (10 g). The products (anomeric mixture) were eluted with $CHCl_3$–MeOH (100: 1), affording a colorless syrup of N^6-monobenzoyl derivative **5** (59 mg). UV λ_{max}^{EtOH} nm: 233, 278.

It was dissolved in 0.2 N $NaOCH_3$ in MeOH (2 ml) and refluxed for 1 hr. After the reaction solution was neutralized by bubbling CO_2, it was concentrated *in vacuo* to dryness. The residual syrup was subjected to chromatography on Dowex 1 (OH^-)[16] (12 ml). The column was eluted with MeOH–H_2O (20: 80). From the fractions eluted faster, 13.8 mg of α-adenosine was obtained. It was recrystallized from aqueous ethanol, mp 206—209°. *Anal.* Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.85; H, 4.94; N, 26.40. $[\alpha]_D^{20}$ +24.9° (c=0.981, H_2O). UV nm (ε): $\lambda_{max}^{H_2O}$ 259 (14900); $\lambda_{max}^{0.1N\ HCl}$ 257 (14500); $\lambda_{max}^{0.1N\ NaOH}$ 260 (15100).

From the fractions eluted later, 17.2 mg of β-adenosine was obtained. It was recrystallized from water, colorless needles, mp 233—235°. *Anal.* Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.66; H, 4.95; N, 26.20. $[\alpha]_D^{20}$ −60.4° (c=1.022, H_2O). UV nm (ε): $\lambda_{max}^{H_2O}$ 260 (14700); $\lambda_{max}^{0.1N\ HCl}$ 257 (14400); $\lambda_{max}^{0.1N\ NaOH}$ 260 (14800).

Transribosylation of 1 to 4 (Exp. 4)——A solution of **1** (237 mg) in 2 ml of CH_3CN, a solution of **4** (288 mg) in 1.7 ml of $(CH_2)_2Cl_2$, a solution of $Me_3SiOSO_2CF_3$ (111 mg) in 0.5 ml of $(CH_2)_2Cl_2$, and benzoyl chloride (0.09 ml) were mixed. The resulting solution was refluxed for 2 hr. After it was cooled, $CHCl_3$ (20 ml) was added. After work-up as described in the preceding paragraph, the products were purified by silica gel chromatography ($CHCl_3$–MeOH, 100: 1). N^6,N^6-Dibenzoyladenine derivative (**6**) was obtained as a syrup (147 mg), UV λ_{max}^{EtOH} nm (ε): 251 (20900), 273 (16300). MS *m/e*: 601 (M^+). NMR ($CDCl_3$) δ: 2.07 (s, 6H, 2×C<u>H</u>$_3$COO), 2.13 (s, 3H, C<u>H</u>$_3$COO), 4.39 (m, 3H, H-4′,5′), 5.64 (t, 1H, H-3′), 5.91 (t, 1H, H-2′), 6.21 (d, 1H, H-1′, $J_{1',2'}$=5.4), 7.3—7.9 (m, 10H, benzoyl H), 8.18 (s, 1H, H-8), 8.62 (s, 1H, H-2).

From the fractions eluted later, crystalline N^6-monobenzoyladenine derivative (**5**) was obtained (22 mg); mp 86—88°. *Anal.* Calcd. for $C_{23}H_{23}N_5O_8 \cdot 0.5H_2O$: C, 54.57; H, 4.77; N, 13.83. Found: C, 54.26; H, 4.87; N, 13.72. UV λ_{max}^{EtOH} nm (ε): 233 (15700), 280 (19500). NMR ($CDCl_3$) δ: 2.08; 2.12, 2.16 (s, each 3H, C<u>H</u>$_3$COO), 4.45 (m, 3H, H-4′,5′), 6.28 (d, 1H, H-1′, $J_{1',2'}$=5.2), 7.4—8.1 (m, 5H, benzoyl H), 8.22 (s, 1H, H-8), 8.75 (s, 1H, H-2), 9.43 (broad s, 1H, N<u>H</u>Bz). **5** and **6** were separately dissolved in 5 ml of 0.2 N $NaOCH_3$ in MeOH. After refluxing for 1 hr, the solution was neutralized with CO_2 and concentrated *in vacuo* to dryness. The residue was chromatographed on a Dowex-1 (OH^-, 10 ml) column. From the fractions eluted by 20% aqueous MeOH, crystalline β-adenosine was obtained from both **5** and **6**, mp 233—235°. UV nm: $\lambda_{max}^{H_2O}$ 260, $\lambda_{max}^{0.1N\ HCl}$ 257, $\lambda_{max}^{0.1N\ NaOH}$ 260.

Transribosylation of 1 to 4 (Exp. 5)——A solution of **1** (237 mg) in CH_3CN (2 ml), a solution of **4** (288 mg) in $(CH_2)_2Cl_2$ (1.7 ml), a solution of $Me_3SiOSO_2CF_3$ (111 mg) in $(CH_2)_2Cl_2$ (0.5 ml) were mixed. The solution was refluxed for 10 hr. After work-up as described in the preceding paragraph, **5** (66 mg) and **6** (89 mg) were obtained. After deacylation, isolation and identification with β-adenosine was performed as described in the preceding paragraph.

Transribosylation of 2 to 4 (Exp. 7)——A solution of **2** (206 mg), **4** (288 mg), and $SnCl_4$ (0.1 ml) in a mixture of $(CH_2)_2Cl_2$ (1.75 ml) and CH_3CN (2 ml) was refluxed for 24 hr. After work-up, the product was purified by silicic acid chromatography (24 g) ($CHCl_3$–MeOH, 100: 1). A pure syrup of **5** (103 mg) was

15) P.F. Crain, J.A. McCloskey, and K. Isono, in preparation.
16) C.A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).

obtained. UV λ_{max}^{EtOH} nm (ε): 232 (15600), 279 (19500). After deacylation with 0.2 N $NaOCH_3$ in MeOH, β-adenosine was obtained and identified as described.

Transribosylation of 2 to 4 (Exp. 8)——A solution of **2** (206 mg) in CH_3CN (2 ml), a solution of **4** (288 mg) in $(CH_2)_2Cl_2$ (1.7 ml), and $Me_3SiOSO_2CF_3$ (111 mg) in $(CH_2)_2Cl_2$ (0.5 ml) were mixed. The solution was refluxed for 15 hr. After work-up, 202 mg of **5** was obtained. β-Adenosine was identified after deacylation.

Trimethylsilyltheophylline (7)——To a suspension of theophylline (5.4 g) in dry benzene (60 ml) was added 3.91 g of trimethylsilyl chloride. The solution of triethylamine (3.64 g) in benzene (30 ml) was then added dropwise with stirring for 30 min. After stirring was continued overnight at room temperature, the solution was refluxed for 2 hr. The solution was filtered and the filtrate was concentrated to a small volume. Colorless crystals of **7** (6.25 g) were obtained, mp 161—164°. MS *m/e*: 252 (M^+). Satisfactory elemental analysis was not attained because of its ease for decomposition with moisture.

Transribosylation of 2 to 7 (Exp. 9)——A solution of **2** (206 mg) in CH_3CN (4 ml), **7** (190 mg), and a solution of $Me_3SiOSO_2CF_3$ (111 mg) in $(CH_2)_2Cl_2$ (0.5 ml) were mixed. The solution was refluxed for 10 hr. After work-up and silica gel chromatography ($CHCl_3$–MeOH, 100: 1), amorphous powder (212 mg) of theophylline 7-nucleoside (**8**) was obtained. UV λ_{max}^{EtOH} nm (ε): 230 sh, 275 (8400). NMR ($CDCl_3$) δ: 2.10 (s, 6H, $2\times C\underline{H}_3COO$), 2.14 (s, 3H, $C\underline{H}_3COO$), 3.37, 3.57 (s, each 3H, N–$C\underline{H}_3$), 4.40 (m, 3H, H-4′,5′), 5.42 (diffuse t, 1H, H-3′), 5.66 (t, 1H, H-2′), 6.32 (d, 1H, H-1′, $J_{1',2'}=3.9$), 7.92 (s, 1H, H-8). The powder (106 mg) was treated with 0.2 N $NaOCH_3$ in MeOH, followed by Dowex-1 (OH^-) chromatography (5 ml, MeOH–H_2O, 30: 70), affording crystalline 7-β-ribofuranosyltheophylline (69 mg). It was recrystallized from water, mp 184—185°. *Anal.* Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.36; H, 5.18; N, 18.18. UV nm (ε): $\lambda_{max}^{H_2O}$ 275 (8500), $\lambda_{max}^{0.1N\ HCl}$ 275 (8700), $\lambda_{max}^{0.1N\ NaOH}$ 275 (8200). $[\alpha]_D^{20}$ +26.8° (c=1.37, H_2O).

N^2-Acetyl-tris(trimethylsilyl)guanine (9)——N^2-Acetylguanine[17] (1.93 g) was suspended in 40 ml of dry benzene followed by the addition of 4.35 g of trimethylsilyl chloride. A benzene solution (30 ml) of triethylamine (4.05 g) was added dropwise with stirring for 30 min. After stirring for additional 2 hr, the solution was refluxed for 2.5 hr. The reaction mixture was filtered and the filtrate was fractionally distilled. Colorless syrup (1.42 g) of **9** was obtained, bp145°/1 mmHg. MS *m/e*: 368 ($M^+-C_2H_2O$). Elemental analysis was not satisfactory because of decomposition with moisture.

Transribosylation of 2 to 9 (Exp. 10)——A solution of **2** (411 mg) in CH_3CN (8 ml), a solution of **9** (615 mg) in $(CH_2)_2Cl_2$ (0.8 ml), and $Me_3SiOSO_2CF_3$ (222 mg) in $(CH_2)_2Cl_2$ (1.0 ml) were mixed. The solution was refluxed for 20 hr. After work-up, the product was purified by silicic acid thin-layer chromatography ($CHCl_3$–MeOH, 10: 1). The lower *Rf* zone was eluted with acetone–acetic acid (95: 5). On evaporation of the solvent, 297 mg of colorless foam of 9-isomer (**10**) was obtained. UV λ_{max}^{EtOH} nm: 255, 261, 281. NMR ($CDCl_3$) δ: 2.07, 2.12, 2.16 (s, each 3H, $C\underline{H}_3COO$), 2.31 (s, 3H, $C\underline{H}_3CON$), 4.42 (m, 3H, H-4′,5′), 5.65 (broad m, 1H, H-3′), 5.92 (m, 2H, H-1′,2′), 7.74 (broad s, 1H, H-8), 9.87, 12.07 (broad s, 1H, N$\underline{H}$). The foam (291 mg) was dissolved in 0.2 N $NaOCH_3$ in MeOH (10 ml) and refluxed for 1 hr. The reaction solution was neutralized with acetic acid and water (20 ml) was added. The solution was passed through a column of Dowex 50 W (H^+), which was eluted with 1 N NH_4OH. Upon concentration, 9-β-D-ribofuranosylguanine (130 mg) was obtained as colorless crystals, mp>239° (dec.). *Anal.* Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.11; H, 4.56; N, 24.82. UV nm (ε): $\lambda_{max}^{H_2O}$ 253 (12900), 268 sh, $\lambda_{max}^{0.05N\ HCl}$ 257 (12300), 273 sh, $\lambda_{max}^{0.05N\ NaOH}$ 258 (11200), 266 (11200). $[\alpha]_D^{25}$ −71.9° (c=1.078, 0.1 N NaOH).

From the higher *Rf* zone, 9 mg of colorless syrup of 7-isomer was obtained. UV λ_{max}^{EtOH} nm: 255, 263, 285 sh. NMR ($CDCl_3$) δ: 2.10, 2.13, 2.17 (s, each 3H, $C\underline{H}_3COO$), 2.34 (s, 3H, $C\underline{H}_3CON$), 4.42 (m, 3H, H-4′,5′), 5.46 (diffuse t, 1H, H-3′), 5.74 (t, 1H, H-2′), 6.32 (d, 1H, H-1′, $J_{1',2'}=4.4$), 8.07 (s, 1H, H-8), 10.78, 12.28 (broad s, each 1H, N$\underline{H}$). By treatment with $NaOCH_3$ in MeOH, crystalline 7-ribofuranosylguanine was obtained, mp>245° (dec.). UV nm (ε): $\lambda_{max}^{H_2O}$ 237 sh, 287 (6700), $\lambda_{max}^{0.05N\ HCl}$ 250 (9100), 267 sh, $\lambda_{max}^{0.05N\ NaOH}$ 283 (6200).

Transglycosylation of 12 to 7. Synthesis of Theophylline-Octosyl Acid (14, 15)——A solution of 1-β-(3,7-anhydro-6-deoxy-2,5-di-O-acetyl-D-glycero-D-allooctofuranosyluronamide)-N^4-acetyl-5-methoxycarbonyl cytosine[11] (**12**, 248 mg) in CH_3CN (5 ml), a solution of $Me_3SiOSO_2CF_3$ (111 mg) in $(CH_2)_2Cl_2$ (5 ml), and trimethylsilyltheophylline (202 mg) were mixed. The suspension was refluxed for 20 hr. After work-up, crystalline 7-β-theophylline nucleoside (**13**, 137 mg) was obtained, mp 280—282°. UV λ_{max}^{EtOH} nm: 230 sh, 275. NMR (DMSO-d_6) δ: 2.06, 2.15 (s, each 3H, $C\underline{H}_3COO$), 1.80 (m, 1H, H-6′a), 2.49 (m, 1H, H-4′), 4.23 (q, 1H, H-7′), 4.45 (q, 1H, H-3′), 5.43 (m, 1H, H-5′), 5.46 (d, 1H, H-2′), 6.27 (s, 1H, H-1′), 6.92, 7.33 (broad s, each 1H, $CON\underline{H}_2$), 8.17 (s, 1H, H-8).

Compound **13** (30 mg) was dissolved in 0.2 N $NaOCH_3$ in MeOH (3 ml) and refluxed for 2.5 hr. The reaction solution was neutralized with AcOH. After standing overnight at 0°, crystalline free uronamide nucleoside (**14**, 12 mg) was obtained, mp 219—223°. *Anal.* Calcd. for $C_{15}H_{19}N_5O_7\cdot H_2O$: C, 45.11; H, 5.30; N, 17.54. Found: C, 45.40; H, 5.25; N, 17.87. UV nm (ε): $\lambda_{max}^{H_2O}$ 232 sh, 274.5 (7700): $\lambda_{max}^{0.1N\ HCl}$ 233 sh, 274 (8000); $\lambda_{max}^{0.1N\ NaOH}$ 274.5 (8100). NMR (DMSO-d_6) δ: 3.23, 3.42 (s, each 3H, N–$C\underline{H}_3$), 6.11 (s, 1H, H-1′), 7.21

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(broad s, 2H, $CONH_2$), 8.27 (s, 1H, H-8). $[\theta]_{271}=+6780°$ (H_2O).

Compound **13** (134 mg) was dissolved in AcOH (10 ml). The solution was cooled to 10° and N_2O_3 gas was bubbled for 2 hr.[14] After being allowed to stand additinal 2 hr at room temperature, ice-water (100 ml) was added to the reaction solution, which was neutralized with excess $NaHCO_3$. The solution was then acidified with concentrated HCl and extracted with $CHCl_3$. It was washed with 10% NaCl and dried over Na_2SO_4. After concentration, the residue (UV λ_{max}^{EtOH} 276 nm) was subjected to silica gel chromatography (acetone and AcOH–acetone, 1: 9). From the fractions eluted with AcOH–acetone, colorless crystals (40 mg) of the carboxylic acid were obtained, mp 199—205° (dec.). NMR (DMSO-d_6) δ: 2.04, 2.13 (s, each 3H, CH_3COO), 3.21 (s, 3H, N–CH_3), 6.23 (s, 1H, H-1′), 8.18 (s, 1H, H-8). Without further characterization, the crystals (40 mg) were dissolved in 0.2 N $NaOCH_3$ in MeOH (5 ml) and kept for 1 hr at room temperature. To this, water (10 ml) and AcOH (5 drops) were added and the solution was passed through a column of Dowex 50 W×8 (H^+). The effluent was concentrated *in vacuo* to dryness and the residue was recrystallized from EtOH, affording 27 mg of colorless needles of **15**, mp 161—169° (dec.). *Anal.* Calcd. for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.75; N, 14.66. Found: C, 47.17; H, 4.88; N, 14.47. UV nm (ε): $\lambda_{max}^{H_2O}$ 231 sh, 274 (7800); $\lambda_{max}^{0.05N\ HCl}$ 231 sh, 274 (7800); $\lambda_{max}^{0.05N\ NaOH}$ 274.5 (7700). $[\theta]_{271}=+7270°$ (H_2O). NMR (1 N ND_4OD) δ: 1.8—2.4 (m, 2H, H-6′), 3.41, 3.58 (s, each 3H, N–CH_3), 6.33 (s, 1H, H-1′), 8.32 (s, 1H, H-8).

Transglycosylation of 13 to 9. Synthesis of Guanine-Octosyl Acid (18, 19)——A solution of **12** (248 mg) in CH_3CN (5 ml), a solution of **9** (328 mg) in $(CH_2)_2Cl_2$ (0.9 ml), and a solution of $Me_3SiOSO_2CF_3$ (111 mg) in $(CH_2)_2Cl_2$ (0.5 ml) were mixed. The solution was refluxed for 20 hr. After work-up, the residue was purified by silicic acid thin-layer chromatography. From the lower band, 9-β-nucleoside (**16**, 23 mg) was obtained as a colorless syrup, UV nm: λ_{max}^{EtOH} 254 sh, 260, 278. From the higher band, crystalline 7-isomer (**17**, 15 mg) was obtained, UV nm: λ_{max}^{EtOH} 222.5, 265, 287 sh. Each compound was refluxed for 1 hr in 0.2 N $NaOCH_3$ in MeOH (2.5 ml), followed by refluxing for 45 min in 0.4 N NaOH (1.25 ml). The solution was cooled and passed through Dowex 50 W (H^+, 5 ml), which was eluted with 1 N NH_4OH. The eluate was further purified by cellulose thin-layer chromatography (BuOH–AcOH–H_2O, 4: 1: 2). From **16** (23 mg), 9-guanine-octosyl acid (**18**, 5 mg) was obtained as colorless powder, mp>275° (dec.). UV nm (ε): $\lambda_{max}^{H_2O}$ 252.5 (9800), 277 sh; $\lambda_{max}^{0.1N\ HCl}$ 257.5 (9600), 281 sh; $\lambda_{max}^{0.1N\ NaOH}$ 257 (8700), 268 (8700). NMR (1 N ND_4OD) δ: 6.37 (s, 1H, H-1′) 8.24 (s, 1H, H-8). MS (pentasilyl derivative): *m/e* 713 (M^+). $[\theta]_{247}=+78$ (H_2O). From **17** (12 mg), 7-guanine-octosyl acid (**19**, 3 mg) was obtained as colorless powder, mp>262° (dec.). UV nm: $\lambda_{max}^{H_2O}$ 283 (7500); $\lambda_{max}^{0.1N\ HCl}$ 230 sh, 254 (7800), 277.5 (8700); $\lambda_{max}^{0.1N\ NaOH}$ 243 sh, 284 (7800). MS (pentasilyl derivative): *m/e* 713 (M^+). Details of mass spectral analysis will be published elsewhere.[15] $[\theta]_{282}=+4050°$ (H_2O).

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