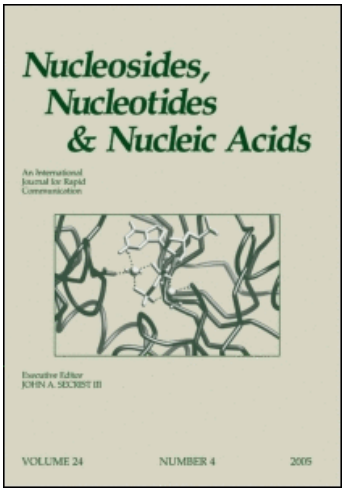

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RIBOSYLATION OF THE BASE RESIDUE OF INOSINE DERIVATIVES BY PHASE-TRANSFER CATALYSIS

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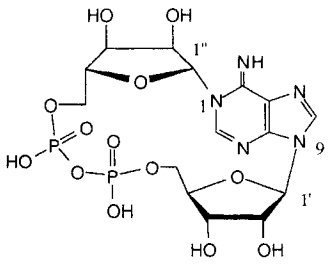
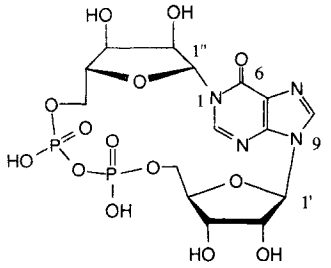
Abstract: Reaction of 2',3',5'-*O*-silylated inosine derivative **1** with 2,3-*O*-isopropylidene-5-*O*-tritylribosyl chloride (**3**) in a two-phase (CH_2Cl_2-aq. NaOH) system in the presence of Bu_4NBr gave three products, *i.e.*, 6-*O*-α-, 6-*O*-β-, and N^1-β-isomers of glycosides **4**, **5a**, and **5b**. A similar PTC reaction of **1** with 2,3,5-tri-*O*-benzylribosyl bromide (**9**) gave four regio- and stereo-isomers involving the N^1-β-glycoside **10**. Reaction of **1** with 2,3,5-tri-*O*-benzoylribosyl bromide (**11**) afforded three products involving the desired N^1-β-glycoside **12b**, which could be deprotected to give N^1-ribosylinosine (**15b**) as a useful intermediate for the synthesis of cIDPR.

INTRODUCTION

Cyclic adenosine diphosphoribose (cyclic ADP-ribose or cADPR), a recently discovered metabolite of nicotinamide adenine dinucleotide (NAD),[1] is a potent calcium-releasing agent postulated to be a new second messenger. The structure of cADPR was determined by FAB mass,[2] UV,[3] NMR,[4] and X-ray[5] analyses. These data suggest that



Cyclic ADP-Ribose



Cyclic IDP-Ribose

* This paper is dedicated to Prof. Yoshihisa Mizuno on the occasion of his 75th birthday.

cADPR has two *N*-glycosyl bonds. One is the *N*-glycosyl bond of the adenosine unit and the other exists between the N^1-position of adenosine and the C1" position of the ribose unit. In a biological process, cADPR is formed as a result of intramolecular cyclization of NAD by a cyclase with simultaneous elimination of the nicotinamide residue.

Recently, much attention has been paid to cADPR as one of the most interesting nucleotide derivatives since extensive studies of its calcium-releasing activity have been reported.[6] Particularly, analogs of cADPR would be useful as antagonists or inhibitors for elucidation of the mechanism of its calcium-releasing process. However, only a few papers have been reported about the synthesis of 1,9-diribofuranosylpurine derivatives of this type.[7,8]

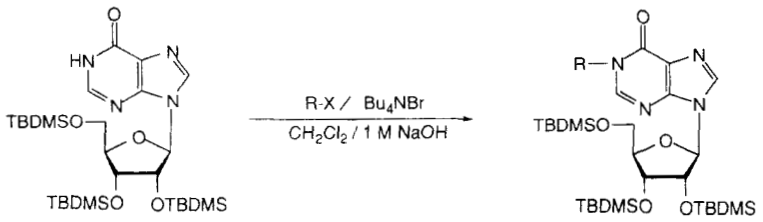
In this paper, we wish to report the synthesis of N^1-ribosylinosine as an important intermediate of cyclic inosine diphosphoribose (cIDPR) as an analog of cADPR.

RESULTS AND DISCUSSION

To find a straightforward method for the synthesis of 1,9-diribofuranosylpurine derivatives *via* direct N^1-ribosylation of inosine derivatives, several methods used widely for glycoside synthesis in carbohydrate chemistry have been examined.[9] First, we attempted to use the Fischer-Helferich, the Koenigs-Knorr methods and their cognates, and the anomeric alkylation method in order to obtain N^1-ribofuranosylinosine derivatives. These methods, however, have failed. Because these reactions were carried out in acidic conditions, the hypoxantine ring of inosine was blocked with Lewis acids because of its basicity to lose its activity as a ribosyl donor site. In nucleic acid chemistry, several methods for *N*-glycosyl bond formation are known: The Fusion, Hilbert-Johnson, Vorbrüggen, and Hg salt methods.[10] These methods, however, did not give N^1-ribofuranosylinosine.

A lot of applications of phase transfer catalysis (PTC) to the *N*-alkylation of amides have been reported.[11] In the field of nucleic acids, several examples are known about the phase-transfer catalysis concerning glycosyl bond formation[12] or *N*-alkylation of nucleosides.[13] Therefore, our interest was focused on the PTC reaction which would provide N^1-ribofuranosylinosine derivatives. The amide proton of inosine has a pKa value of 8.8[13] that is acidic enough to be dissociated by basic media such as dil. NaOH[12] or K_2CO_3/crown ether[14] under PTC conditions.

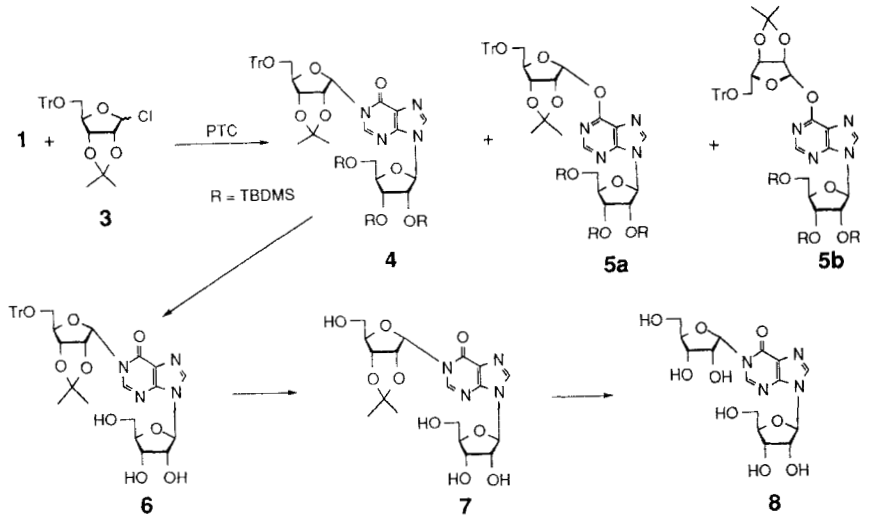
First, to ascertain this possibility, 2',3',5'-*O*-tris(*tert*-butyldimethylsilyl)inosine (**1**)[15] was allowed to react with methyl iodide and benzyl bromide in a two-phase system of CH_2Cl_2-1 M NaOH in the presence of Bu_4NBr. The amide anion of **1** can be delocalized to several positions including the N^1-, N^3-, N^7- and 6-*O* positions, but these reactions gave the corresponding N^1-alkylated products **2a** and **2b** as the main product in 80% and



1

2a: R = CH_3
2b: R = Bn

Scheme 1



Scheme 2

75% yields, respectively. In the former, a trace amount (1.3%) of 6-*O*-methylated species was formed.

Next, to construct the glycosyl bond between the N^1-position of inosine and the C1 position of ribose, 2,3-*O*-isopropylidene-5-*O*-tritylribosyl chloride (**3**)[16] was chosen as the glycosyl donor.

This reaction gave N^1-α-ribosylinosine derivative **4** and α- and β-stereoisomers of 6-*O*-ribosylinosine derivatives **5a** and **5b** in 56, 16, 12% yields, respectively. The use of various quaternary ammonium salts such as Bu_4NHSO_4, Et_3BnNBr, and Bu_4NCl or the use of weaker basic conditions such as 0.1 M NaOH and 1 M K_2CO_3 did not affect the

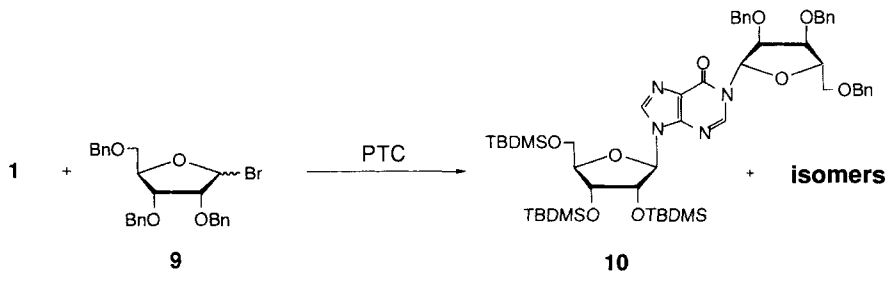
ratio of these products. In all cases, the desired N^1-β-glycoside was not formed. The structure of these compounds were characterized by ^{1}H- and ^{13}C-NMR. It is known that the ^{13}C resonance signal of the methyl group of 6-*O*-methylinosine appears at higher magnetic field by ca. 10 ppm than that of the methyl group of N^1-methylinosine.[17] On the basis of this fact, the product having a resonance peak of C1" at 88.62 ppm was assigned as N^1-α-ribosylinosine derivative **4**, while a set of products having resonance signals of C1" at 98.90 and 104.20 ppm were determined to be 6-*O*-α- and 6-*O*-β-ribosylinosine derivatives **5a** and **5b**, respectively.

The NOE experiments showed that **4** exhibits a clear NOE between 2-H of inosine and 1"-H of ribose. On the other hand, compounds **5a** and **5b** had no NOEs between these protons. In compound **4**, clear NOEs between 1"-H and 2-H and between 1'-H and 8-H were observed. On the other hand, compound **5a** or **5b** showed a NOE between 1'-H and 8-H but no NOE between 1"-H and 2-H. The stereochemistry of **4**, **5a**, and **5b** was determined by their $J_{1"H\text{-}2"H}$ values. In general, 2',3'-*O*-isopropylideneriboside derivatives having a β-substituent at C1 have singlet peaks of 1-H because the dihedral angle of H(1)-C(1)-C(2)-H(2) is nearly 90 °, while those having an α-substituent exhibit a distinct H-H coupling between 1-H and 2-H.[6] Actually, compounds **4** and **5a** showed clear $J_{1",2"}$ values of 4.0 Hz and 4.6 Hz, respectively. On the other hand, compound **5b** showed a singlet resonance of 1"-H. All attempts of thermal conversion of **5a** or **5b** to **4** was unsuccessful.

Treatment of **4** with Bu_4NF in THF gave a desilylated product **6** in 92 % yield. Hydrolysis of **6** with 80% acetic acid resulted in formation of a detritylated product **7** in 63% yield. During this acid treatment, considerable decomposition of **7** was observed. To remove the isopropylidene group from **7**, further reaction with 80% acetic acid at 60 °C gave a completely deprotected material **8** in 32% yield (judged from NMR) with cleavage of the glycosyl bond at the N^1site.

We investigated the effect of ribose protecting groups on the stereo- and regio-selectivity of products. Reaction of **1** with 2,3,5-tri-*O*-benzylribosyl bromide (**9**)[18] was carried out under similar conditions. As a consequence, the desired N^1-β-glycoside **10** was obtained in 12% yield. Other three (N^1-α-, 6-*O*-α- and 6-*O*-β-) isomers were also formed in this reaction. (Scheme 3) The TBDMS group was removed by TBAF treatment but the debenzylation of the resulting product failed. The hydrogenolysis on Pd/C resulted in undesired cleavage of the N^1-C1" bond.

Next, a similar PTC reaction of **1** with 2,3,5-tri-*O*-benzoylribosyl bromide (**11**)[19] was done but the bromide **11** was immediately hydrolyzed to give no glycoside products. Matsuda and his coworkers have recently reported an alkylation of inosine derivatives by the use of K_2CO_3 and 18-C-6 ether.[14] To avoid competitive hydrolysis of **11**, this



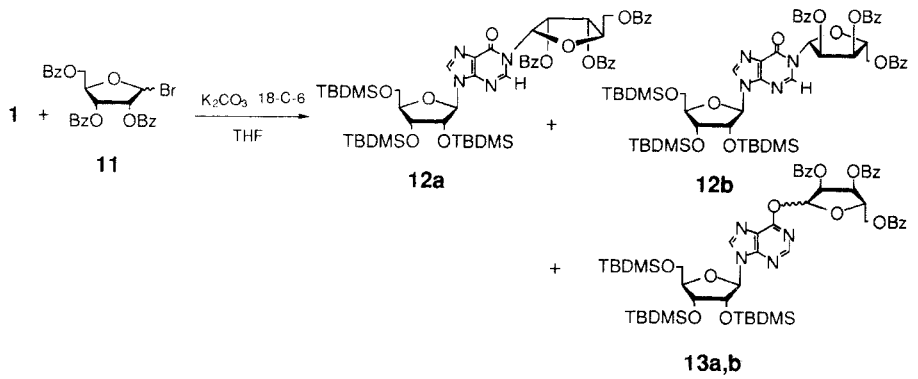
Scheme 3

anhydrous PTC reaction was employed. Under such conditions, reaction of **1** with **11** gave a mixture of four isomeric glycosides **12a,b** and **13a,b** and hydrolysis of riboside **11** did not occur in these conditions. The crude mixture was purified by silica gel column chromatography to give the desired N^1-β-glycoside **12b** and its stereoisomer **12a** in 11% and 8% yields, respectively. (Scheme 4)

The structure of **12a** and **12b** was determined by NOE experiments. In the case of **12b**, a distinct NOE was observed between 2-H (inosine) and 1"-H (ribose) which showed that this glycoside has the N^1-glycosyl bond. A strong NOE between 2-H (inosine) and 2"-H (ribose) was also observed which indicated that this glycosyl bond has a β-configuration as shown in Figure 1. On the other hand, the NOESY spectrum of **12a** showed a strong NOE between 2H (inosine) and 4"-H (ribose) (data not shown).

The desired isomer **12b** were treated with NaOMe in MeOH at room temperature for 25 min to remove the benzoyl groups. Treatment of the resulting product **14b** with TBAF afforded the desired ribosylated inosine **15b**. During this deprotection process, no isomerization and decomposition was observed. The ^{1}H-^{1}H COSY NMR spectrum of **15b** showed clearly a set of two different ribose protons such as 1'- and 1"-protons which appeared as doublets at 6.04 ($J_{1',2'}$ = 5.7 Hz) and 6.48 ($J_{1",2"}$ = 3.6 Hz) ppm, respectively, as shown in Figure 2.

The UV spectrum of **15b** showed λmax at 250 nm and a shoulder around 270 nm as shown in Figure 3. This UV curve of **15b** resembles essentially that of N^1-methylinosine, which strongly suggests the N^1-ribosylinosine. The α-isomer **15a** showed a similar UV property but has a different ^{1}H-NMR spectrum which exhibited two anomeric protons as doublets at 6.09 (1'-H, $J_{1',2'}$ = 5.6 Hz) and 6.23 (1"-H, $J_{1",2"}$ = 3.0 Hz) ppm.



Scheme 4

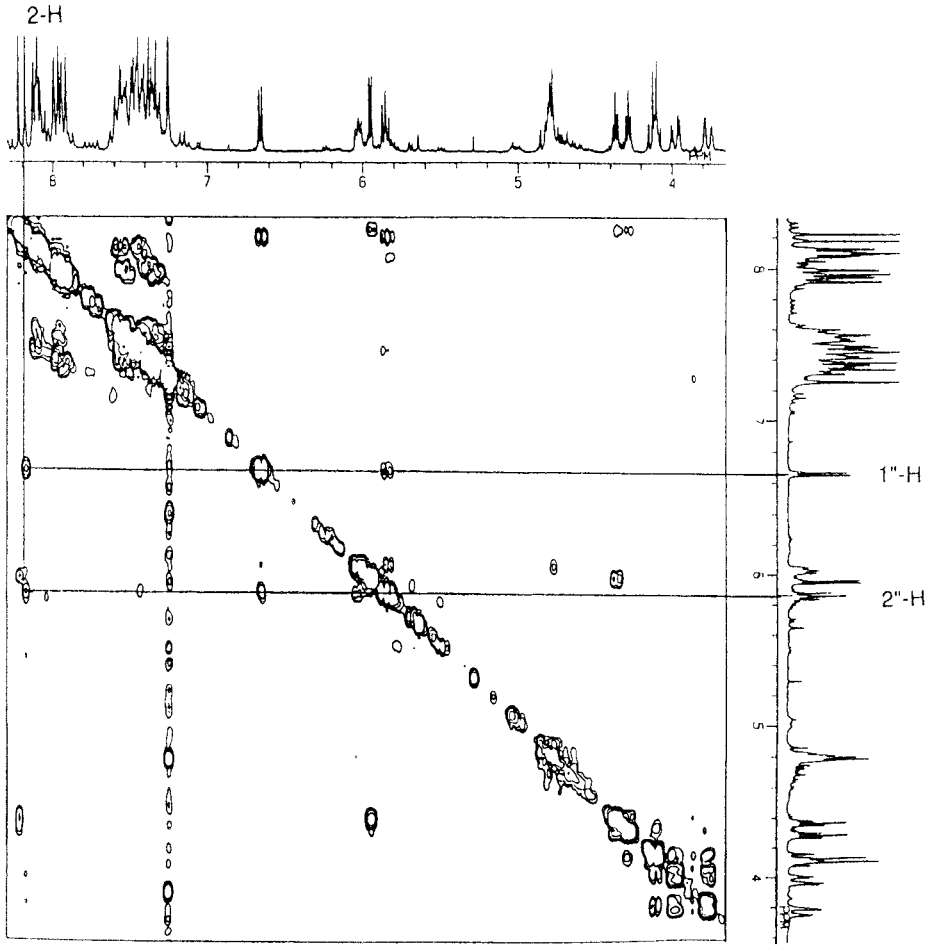
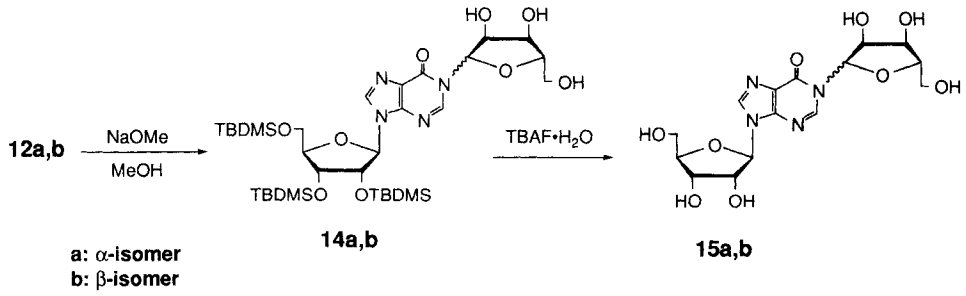


Figure 1. 270 MHz NOESY spectrum of protected N^1-β-ribosylinosine derivative (**12b**)



Scheme 5

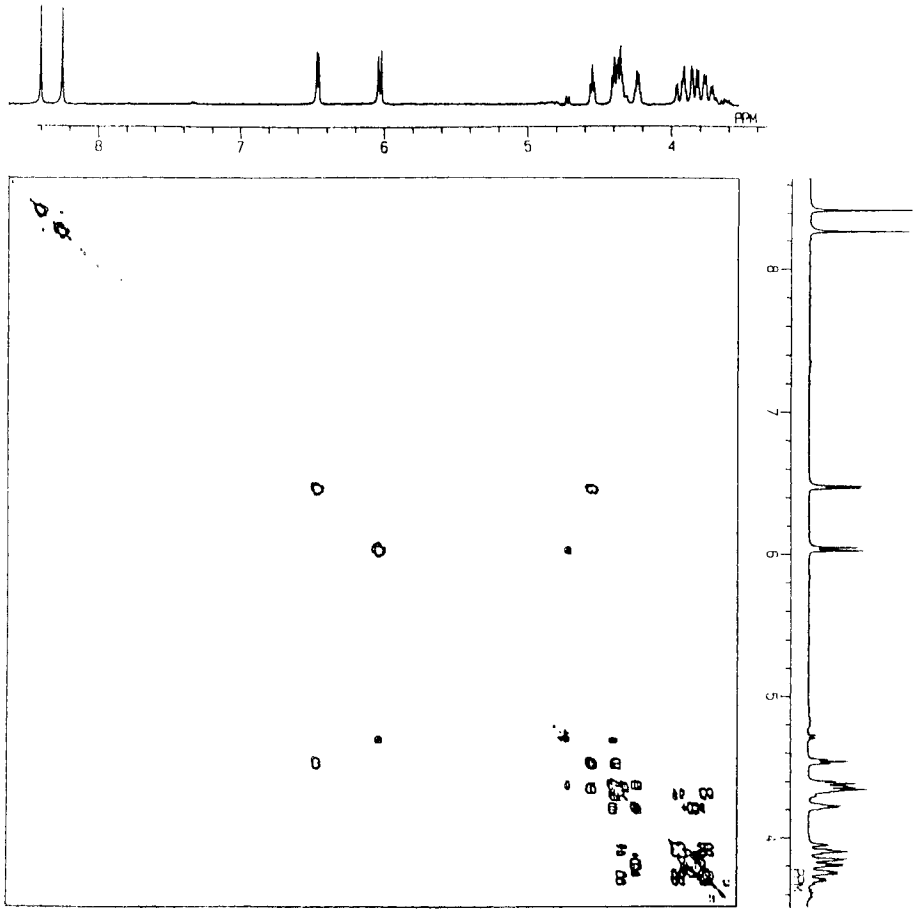


Figure 2. 270 MHz COSY spectrum of N^1-β-ribosylinosine (**15b**)

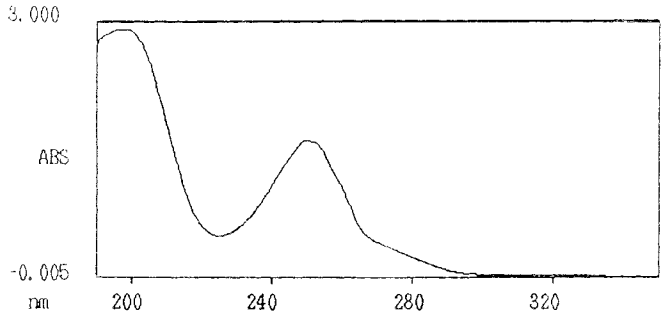


Figure 3. UV spectrum of N^1-β-ribosylinosine (**15b**) in H_2O

Although the yield of **15b** was very low, the present strategy could give a first clue to synthesize an inosine analogue of ADPR. However, further extensive improvement should be done in the future.

We are now studying further application of this important intermediate to the synthesis of cIDPR.

EXPERIMENTAL

General Remarks. ^{1}H-NMR spectra were recorded at 270 MHz on a JEOL GX270 spectrometer with Me_4Si (for water-insoluble materials) or DSS (for water-soluble materials) as the internal standard. ^{13}C-NMR spectra were measured at 67.8 MHz on a JEOL-GX 270 spectrometer with TMS as the internal standard. UV spectra were obtained on a Hitachi U-2000 spectrophotometer. Paper chromatography was performed by use of a descending technique with Whatman 3MM papers and Toyo Roshi 51 papers using the following solvent system: 2-propanol-conc. aqueous ammonia-water, 7 : 1 : 2, v/v/v. Column chromatography was performed with silica gel C-200 purchased from Wako Co., Ltd., and a minipump for a goldfish bowl was conveniently used to attain sufficient pressure for rapid chromatographic separation. TLC was performed on precoated TLC plates of silica gel 60 F-254 (Merck). All solvents were distilled and dried over molecular sieves 3A. Inosine was purchased from Yamasa Shouyu and ribose and the other chemical reagents were purchased from Tokyo Kasei. Elemental analyses were performed by the Microanalytical Laboratory, Tokyo Institute of Technology, at Nagatsuta.

***N*^{1}-Methyl-2,3,5-*O*-tris(*t*-butyldimethylsilyl)inosine (2a).** A 1 M solution of NaOH (8 ml) was added to a solution of **1** (500 mg, 0.82 mmol) and methyl iodide (464 mg, 3.28 mmol) in CH_2Cl_2 (8 ml) containing Bu_4NBr (1.05 mg, 3.28 mmol) and

the resulting mixture was vigorously stirred for 12 h at room temperature. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on a column of silica gel with hexane-AcOEt (5 : 1, v/v) to give **2a** (424 mg, 80%): ^{1}H-NMR ($CDCl_3$) δ -0.29 (3 H, s, MeSi), -0.27 (3 H, s, MeSi), 0.09 (3 H, s, MeSi), 0.09 (3 H, s, MeSi), 0.12 (3 H, s, MeSi), 0.12 (3H, s, MeSi), 0.75 (9 H, s, *t*BuSi), 0.92 (9H, s, *t*BuSi), 0.93 (9 H, s, *t*BuSi), 3.63 (3 H, s, Me), 3.75 (1 H, dd, 5"-Ha, $J_{4',5'a}$ = 2.6 Hz and J_{gem} = 11.5 Hz), 3.96 (1 H, dd, 5'-Hb, $J_{4',5'b}$ = 3.6 Hz and J_{gem} = 11.5 Hz), 4.11 (1 H, m, 4'-H), 4.28 (1 H, t , 3'-H $J_{3',4'}$ = 3.6 Hz), 4.47 (1 H, t, 2'-H, $J_{2',3'}$ = 4.5 Hz), 5.96 (1 H, d, 1'-H, $J_{1',2'}$ = 4.8 Hz), 7.96 (1 H, s, 8-H), 8.12 (1 H, s, 2-H); ^{13}C-NMR ($CDCl_3$) δ -5.22, -5.19, -4.71, -4.46 (MeSi), 17.81, 18.06, 18.41 ($(CH_3)_3\underline{C}Si$), 25.53, 25.86, 26.12 ($(\underline{C}H_3)_3CSi$), 34.14 (Me), 62.43 (C5'), 71.83 (C3'), 76.53 (C2'), 85.48 (C4'), 88.00 (C1'), 124.65 (C5), 138.69 (C8), 146.94 (C4), 147.57 (C2), 157.07 (C6).

***N*^{1}-Benzyl-2,3,5-*O*-tris(*t*-butyldimethylsilyl)inosine (2b).** In a manner similar to that described in the above experiment, this compound was prepared. **2b**: ^{1}H-NMR ($CDCl_3$) δ -0.20 (3 H, s, MeSi), -0.13 (3 H, s, MeSi), 0.09 (3 H, s, MeSi), 0.08 (3 H, s, MeSi), 0.12 (3 H, s, MeSi), 0.13 (3 H, s, MeSi), 0.83 (9 H, s, *t*BuSi), 0.92 (9 H, s, *t*BuSi), 0.94 (9 H, s, *t*BuSi), 3.96 (1 H, dd, 5"-Ha, $J_{4',5'a}$ = 2.6 Hz and J_{gem} = 11.2 Hz), 3.96 (1 H, dd, 5'-Hb, $J_{4',5'b}$ = 3.6 Hz and J_{gem} = 11.2 Hz), 4.11 (1 H, m, 4'-H), 4.27 (1 H, t, 3'-H, $J_{3',4'}$ = 3.8 Hz), 4.45 (1 H, t, 2'-H, $J_{2',3'}$ = 4.3 Hz), 5.28 (2 H, s, CH_2), 5.96 (1 H, d, 1'-H, $J_{1',2'}$ = 4.8), 7.28-7.32 (5 H, m, Ph), 7.99 (1 H, s, 8-H), 8.16 (1 H, s, 2-H); ^{13}C-NMR ($CDCl_3$) δ -5.40, -5.11, -4.74, -4.65, -4.43 (MeSi), 17.81, 18.02, 18.51 ($(CH_3)_3\underline{C}Si$), 25.60, 25.78, 26.05 ($(\underline{C}H_3)_3CSi$), 48.95 (CH_2), 62.40 (C5'), 71.77 (C3'), 77.19 (C2'), 85.48 (C4'), 87.79 (C1'), 124.85 (C5), 127.90, 128.19, 128.94, 136.13 (Ph), 138.70 (C8), 146.84 (C4), 147.25 (C2), 156.62 (C6).

Ribosylation of inosine derivatives with 3 to give 4, 5a, and 5b. A 1 M solution of NaOH (15 ml) was added to a solution of **1** (976 mg, 1.59 mmol) and **3** (2.16 g, 4.8 mmol) in CH_2Cl_2 (15 ml) containing Bu_4NBr (2.57 g, 7.20 mmol) and the resulting mixture was vigorously stirred for 12 h at room temperature. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography with hexane : AcOEt (9 : 1 → 3 : 1, v/v) gave three glycoside isomers: **6-*O*-(5-*O*-Trityl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2',3',5'-*O*-tris(*t*-butyldimethylsilyl)inosine (5b).** This compound was first eluted from the column (199 mg, 12%): ^{1}H-NMR ($CDCl_3$) δ -0.36 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.16 (3 H, s, $SiCH_3$), 0.17 (3 H, s, $SiCH_3$), 0.76 (9 H, s, *t*Bu), 0.94 (9 H, s, *t*Bu), 0.98 (9 H, s, *t*Bu), 1.36 (3 H, s, isop CH_3), 1.55 (3 H, s, isop CH_3), 3.28 (2 H, m, 5"-Ha,b), 3.80 (1 H, dd, 5'-Ha, $J_{4',5'a}$ = 2.3 Hz, J_{gem} = 11.2 Hz), 4.05 (1

H, dd, 5'-Hb, $J_{4',5'b}$ = 4.3 Hz, J_{gem} = 11.2 Hz), 4.14 (1 H, br s, 4"-H), 4.32 (1 H, m, 4'-H), 4.48 (1 H, t, 3'-H, $J_{3',4'}$ = 4.0 Hz), 4.78 (1 H, d, 3"-H, $J_{3",4"}$ = 3.8 Hz), 4.76 (1 H, t, 2'-H, $J_{2',3'}$ = 4.6 Hz), 4.98 (1 H, d, 2"-H, $J_{2",3"}$ = 5.9 Hz), 6.06 (1 H, d, 1'-H $J_{1',2'}$ = 5.0 Hz), 6.76 (1 H, s, 1"-H), 7.15-7.38 (15 H, m, Tr), 8.27 (1 H, s, 8-H), 8.57 (1 H, s, 2-H); ^{13}C-NMR ($CDCl_3$) δ -5.32, -5.27, -4.79, -4.72, -4.45 (MeSi), 17.79, 18.06, 18.54 ($(CH_3)_3\underline{C}Si$), 25.62, 25.82, 26.09 ($(\underline{C}H_3)_3CSi$), 25.28, 26.61 (isop CH_3), 62.53, 64.11 (C5' and C5"), 72.02, 75.77 (C3' and C3"), 82.08, 85.23 (C2' and C2"), 85.57, 86.84 (C4' and C4"), 88.50 (C1'), 104.20 (C1"), 112.86 (isop C), 121.97 (C5), 126.90, 127.09, 127.70, 127.90, 128.60, 141.54 (Ph), 143.66 (C8), 151.78 (C2), 158.77 (C6). Anal. Calcd for $C_{55}H_{85}N_5O_9Si_3$: C, 63.23; H, 8.20; N, 6.70. Found: C, 63.35; H, 7.91; N, 6.88.

6-*O*-(5-*O*-Trityl-2,3-*O*-isopropylidene-α-D-ribofuranosyl)-2',3',5'-*O*-tris(*t*-butyldimethylsilyl)inosine (5a). This compound was eluted after **5b** from the column (265 mg, 16%): ^{1}H-NMR ($CDCl_3$) δ -0.35 (3H, s, $SiCH_3$), -0.06 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.78 (9H, s, tBu), 0.94 (9H, s, tBu), 0.95 (9H, s, tBu), 1.30 (3H, s, isop CH_3), 1.49 (3H, s, isop CH_3), 3.16 (1H, dd, 5"-Ha, $J_{4",5"a}$ = 3.0 Hz and J_{gem} = 10.2 Hz), 3.52 (1H, dd, 5"-Hb, $J_{4",5"b}$ = 3.3 Hz and J_{gem} = 10.2 Hz), 3.78 (1H, dd, 5'-Ha, $J_{4',5'a}$ = 3.0 Hz and J_{gem} =11.2 Hz), 4.03 (1H, dd, 5'-Hb, $J_{4',5'b}$ = 4.3 Hz, J_{gem} = 11.2 Hz), 4.13 (1H, m, 4'-H), 4.30 (1H, t, 3'-H, $J_{3',4'}$ = 4.0 Hz), 4.70-4.77 (3H, m, 2'-H, 3"-H and 4"-H), 5.14 (1H, t, 2"-H, $J_{2",3"}$ = 4.3 Hz), 6.08 (1H, d, 1'-H, $J_{1',2'}$ = 5.9 Hz), 7.08 (1H, d, 1"-H, $J_{1",2"}$ = 4.6 Hz), 7.19-7.49 (15H, m, Tr), 8.24 (1H, s, 8-H), 8.55 (1H, s, 2-H); ^{13}C-NMR ($CDCl_3$) δ -5.33, -5.17, -4.68, -4.45, -3.95 (MeSi), 17.82, 18.07, 18.49 ($(CH_3)_3\underline{C}Si$), 25.44, 25.66, 25.84 ($(\underline{C}H_3)_3CSi$), 26.05, 27.06 (isop CH_3), 62.751, 64.00 (C5' and C5"), 72.32, 75.65 (C3' and C3"), 81.24 , 82.80 (C2' and C2"), 85.91, 86.86 (C4' and C4"), 88.23 (C1'), 98.90 (C1"), 115.31 (isop C), 127.11, 127.47, 127.65, 127.92, 128.08, 128.66 (Ph), 126.91 (C5), 143.68 (C8), 151.80 (C2), 159.35 (C6). Anal. Calcd for $C_{55}H_{85}N_5O_9Si_3$: C, 63.23; H, 8.20; N, 6.70. Found: C, 63.08; H, 8.45; N, 7.04.

***N*^{1}-(5-*O*-Trityl-2,3-*O*-isopropylidene-α-D-ribofuranosyl)-2',3',5'-*O*-tris(*t*-butyldimethylsilyl)inosine (4).** This compound was eluted after **5a** from the column (930 mg, 56%): ^{1}H-NMR ($CDCl_3$) δ -0.12 (3 H, s, $SiCH_3$), -0.01 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.15 (3 H, s, $SiCH_3$), 0.16 (3 H, s, $SiCH_3$), 0.84 (9 H, s, *t*Bu), 0.95 (9 H, s, *t*Bu), 0.97 (9 H, s, *t*Bu), 1.25 (3 H, s, isop CH_3), 1.38 (3 H, s, isop CH_3), 3.23 (1 H, dd, 5"-H, $J_{4",5"a}$ = 3.6 Hz and J_{gem} = 10.6 Hz), 3.50 (1 H, dd, 5"-H, $J_{4',5"}$ = 3.9 Hz and J_{gem} = 10.6 Hz), 3.80 (1 H, dd, 5'-H,

$J_{4',5'}$ = 2.6 Hz and J_{gem} = 11.6 Hz), 4.00 (1 H, dd, 5"-H, $J_{4',5"}$ = 3.6 Hz and J_{gem} =11.6 Hz), 4.17-4.09 (1 H, m, 4'-H), 4.33 (1 H, t, 3'-H, $J_{3',4'}$ = 3.9 Hz), 4.50 (1 H, br s, 4"-H), 4.57 (1 H, t, 2'-H, $J_{2',3'}$ = 4.6 Hz), 4.66 (1 H, d, 3'-H, $J_{3',4'}$ = 3.2 Hz), 5.08 (1 H, dd, 2"-H, $J_{2",3"}$ = 5.9 Hz), 6.01 (1 H, d, 1'-H, $J_{1',2'}$ = 5.0 Hz), 6.87 (1 H, d, 1"-H, $J_{1",2"}$ = 4.0 Hz), 7.48-7.21 (15 H, m, Tr), 8.15 (1 H, s, 8-H), 8.26 (1 H, s, 2-H); ^{13}C-NMR ($CDCl_3$) δ -3.95, -4.23, -4.27, -4.54, -4.92 (MeSi), 18.99, 18.52, 18.33 ($(CH_3)_3\underline{C}Si$), 24.60 (isop CH_3), 26.54, 26.29 ($(\underline{C}H_3)_3CSi$), 82.71, 82.89 (C2' and C2"), 85.84, 86.75 (C4' and C4"), 88.23 (C1'), 88.62 (C1"), 113.46 (isop C), 129.04, 128.54, 128.41, 128.26, 127.93, 127.76 (Ph), 127.45 (C5), 139.03 (C8), 145.57 (C4), 147.99 (C2), 156.47 (C6). Anal. Calcd for $C_{55}H_{85}N_5O_9Si_3$: C, 63.23; H, 8.20; N, 6.70. Found: C, 63.68; H, 7.87; N, 6.29.

***N*^{1}-(5-*O*-Trityl-2,3-*O*-isopropylidene-α-D-ribofuranosyl)inosine (6).** TBAF•H_2O (306 mg, 1.16 mmol) was added to a solution of **4** (300 mg, 0.29 mmol) and the mixture was stirred for 30 min at room temperature. The solvent was removed under reduced pressure. The residue was dissolved pyridine (1 ml) and this solution was subjected to a column of Dowex 50W X 8 (pyridine form, 10 ml). Elution was performed with pyridine-water (2:5, v/v, 100 ml) and then with pyridine-water (1:1, v/v, 50 ml). The eluate was concentrated *in vacuo* and the residue was purified by chromatography on a column of silica gel with MeOH : CH_2Cl_2 (1 : 99 → 3 : 97, v/v) to give **6** (182 mg, 92%): ^{1}H-NMR ($CDCl_3$) δ 1.19, 1.25 (3 H, s, isop CH_3), 3.16 (1 H, dd, 5"-Ha, $J_{4",5"a}$ = 2.6 Hz and J_{gem} = 10.5 Hz), 3.56 (1 H, dd, 5"-Hb, $J_{4",5"}$ = 3.0 Hz and J_{gem} = 10.5 Hz), 3.76-3.96 (2 H, m, 5'-Ha,b), 4.29 (1 H, m, 4'-H), 4.45 (1 H, br s, 4"-H), 4.51 (1 H, m, 3'-H), 4.77 (1 H, m, 2'-H), 5.09 (1 H, t, 2"-H, $J_{1",2"}$ = 6.2 Hz), 5.98 (1 H, d, 1'-H, $J_{1',2'}$ = 6.0 Hz), 6.86 (1 H, d, 1"-H, $J_{1",2"}$ = 4.3 Hz), 7.24-7.44 (15 H, m, Tr), 8.09 (1 H, s, H-8), 8.31 (1 H, s, H-2); ^{13}C-NMR ($CDCl_3$) δ 23.17, 23.64 (isop CH_3), 61.60, 63.97 (C5' and C5"), 70.63, 74.33 (C3' and C3"), 81.41, 81.69 (C2' and C2"), 85.93, 86.06 (C4' and C4"), 87.03, 89.69 (C1' and C1"), 112.26 (isop C), 123.40 (C5), 126.45, 127.21, 128.24, 142.25, 144.55 (Ph), 139.48 (C8), 145.12 (C4), 146.06 (C2), 155.23 (C6). Anal. Calcd for $C_{37}H_{38}N_4O_9$: C, 65.03; H, 5.61; N, 8.20. Found: C, 65.09; H, 5.69; N, 8.59.

***N*^{1}-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)inosine (7).** Compound **6** (67 mg, 0.097 mmol) was dissolved in 80% acetic acid (1 ml), and the mixture was stirred for 12 h at room temperature. The solvent was removed *in vacuo*. The residue was purified by paper chromatography (*i*-PrOH : conc. NH_3 : H_2O, 7:1:2, v/v/v). Elution with water gave **7** (27 mg, 63%): ^{1}H-NMR (D_2O) δ 1.26, 1.14 (3 H, s, isop CH_3), 3.77-3.90 (4 H, m, 5'-Ha,b and 5"-Ha,b), 4.21 (1 H, m, 4'-H), 4.39 (1 H, m, 3'-H), 4.61-4.68 (2 H, m, 2'-H, 4"-H), 4.99 (1 H, d, 3"-H, $J_{3",4"}$ = 3.0 Hz), 5.00 (1 H, t , 2"-H, $J_{2",3"}$ =

5.9 Hz), 6.00 (1 H, d, 1'-H, $J_{1',2'}$ = 5.6 Hz), 6.46 (1 H, d, 1"-H, $J_{1",2"}$ = 4.8 Hz), 8.27 (1 H, s, H-8), 8.36 (1 H, s, H-2); ^{13}C-NMR (D_2O) δ 23.15, 23.72 (isop CH_3), 61.60, 61.78 (C5' and C5"), 70.45, 74.52 (C3' and C3"), 81.65, 81.88 (C2' and C2"), 86.04, 86.06 (C4' and C4"), 87.03, 89.69 (C1' and C1"), 112.26 (isop C), 123.40 (C5), 139.48 (C8), 145.12 (C4), 146.06 (C2), 155.23 (C6). Anal. Calcd for $C_{18}H_{23}N_4O_9$: C, 49.20; H, 5.28; N, 12.75. Found: C, 49.33; H, 5.28; N, 13.21.

***N*^{1}-(α-D-Ribofuranosyl)inosine (8).** Compound **7** (20 mg, 0.046 mmol) was dissolved in 80% acetic acid (1 ml), and the mixture was stirred for 12 h at 60 °C . The solvent was removed in vacuo. The residue was purified by paper chromatography (*i*-PrOH : conc NH_3 : H_2O, 7:1:2, v/v/v). Elution with water gave **8** (6 mg, 32%): ^{1}H-NMR (D_2O) 3.62-3.90 (4 H, m, 5'-Ha, 5'-Hb, 5"-Ha, 5"-Hb), 4.21-4.68 (6 H, m, 2'-H, 2"-H, 3'-H, 3"-H, 4'-H, and 4"-H), 6.00 (1 H, d, 1'-H, $J_{1',2'}$ = 5.6 Hz), 6.45 (1 H, d, 1"-H, $J_{1",2"}$ = 4.8 Hz), 8.34 (1 H, s, H-8), 8.38 (1 H, s, H-2).

***N*^{1}-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-2',3',5'-*O*-tris(*t*-butyldimethylsilyl)inosine (10).** A 1M solution of NaOH (5 ml) was added to a solution of **1** (98 mg, 0.16 mmol) and **9** (309 mg, 0.64 mmol) in CH_2Cl_2 (5 ml) containing Bu_4NBr (51 mg, 0.16 mmol) and the resulting mixture was vigorously stirred for 12 h at room temperature. The usual workup followed by chromatography with Hexane : AcOEt (9:1-3:1) gave **10** (19 mg, 12%): ^{1}H-NMR ($CDCl_3$) δ -0.05 (3 H, s, $SiCH_3$), -0.01 (3 H, s, $SiCH_3$), 0.04 (3 H, s, $SiCH_3$), 0.05 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.81 (9 H, s, *t*Bu), 0.92 (9 H, s, *t*Bu), 0.94 (9 H, s, *t*Bu), 3.50-3.96 (5 H, m, 4"-H, 5'-Ha,b, 5"-Ha,b), 4.37-4.88 (10 H, m, CH_2, 2'-H, 3'-H, 4'-H, and 3"-H), 5.13 (1 H, t, 2"-H, $J_{2",3"}$ = 3.8 Hz), 5.85 (1 H, dd, 2'-H, $J_{1',2'}$ = 5.1 Hz), 5.79 (1 H, d, 1'-H, $J_{1',2'}$ = 5.1 Hz), 6.03 (1 H, m, 3"-H), 6.78 (1 H, s, 1"-H), 7.08-7.49 (15 H, m, Ph), 7.79 (1 H, s, 8-H), 8.26 (1 H, s, 2-H).

Ribosylation of inosine derivative 1 with 11 to give 12a, 12b, and 13a,b. Compound **11** (270 mg, 0.51 mmol) was added to a solution of **1** (80 mg, 0.13 mmol) in dry THF (2 ml) containing K_2CO_3 (71 mg, 0.51 mmol) and 18-C-6 (66 mg, 0.25 mmol). The resulting mixture was stirred for 12 h at room temperature. The usual workup followed by silica gel column chromatography with toluene : AcOEt (19 : 1 → 7 : 1) gave four glycoside isomers.**12a** (13 mg, 8%), **12b** (20 mg, 11%), and **13a,b** (120 mg, 70%).

***N*^{1}-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)-2',3',5'-*O*-tris(*t*-butyldimethylsilyl)inosine (12a).** ^{1}H-NMR ($CDCl_3$) δ -0.22 (3 H, s, $SiCH_3$), -0.04 (3 H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.13 (3 H, s, $SiCH_3$), 0.80 (9 H, s, *t*Bu), 0.92 (9 H, s, *t*Bu), 0.94 (9 H, s, *t*Bu), 3.79 (1 H, dd, 5'-Ha, $J_{4',5'}$ = 2.5 Hz and J_{gem} = 11.6 Hz), 3.99 (1 H, dd, 5'-Hb, $J_{4',5'b}$ = 3.6 Hz

and J_{gem} =11.6 Hz), 4.13 (1 H, m, 4'-H), 4.27 (1 H, t, 3'-H, $J_{3',4'}$ = 4.0 Hz), 4.41 (1 H, t, 2'-H, $J_{2',3'}$ = 4.3 Hz), 4.62 (1 H, dd, 5"-Ha), 4.81 (1 H, dd, 5"-Hb), 4.98 (1 H, m, 4"-H), 5.98 (1 H, d, 1'-H, $J_{1',2'}$ = 4.3 Hz), 6.03 (1 H, m, 3"-H), 6.24 (1 H, t, 2"-H), 7.06 (1 H, d, 1"-H, $J_{1",2"}$ = 4.3 Hz), 7.28-7.59 (9 H, m, Ph), 7.71-8.14 (6 H, m, Ph), 8.19 (1 H, s, 2-H), 8.43 (1 H, s, 8-H).

***N*^{1}-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2',3',5'-*O*-tris(t-butyldimethylsilyl)inosine (12b).** ^{1}H-NMR ($CDCl_3$) δ -0.16 (3 H, s, $SiCH_3$), -0.02 (3 H, s, $SiCH_3$), 0.07 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.79 (9 H, s, *t*Bu), 0.91 (9 H, s, *t*Bu), 0.93 (9 H, s, *t*Bu), 3.76 (1 H, dd, 5'-Ha, $J_{4',5'}$ = 2.5 Hz and J_{gem} = 11.6 Hz), 3.96 (1 H, dd, 5'-Hb, $J_{4',5'a}$ = 3.6 Hz and J_{gem} = 11.6 Hz), 4.12 (1 H, m, 4'-H), 4.28 (1 H, t, 3'-H, $J_{3',4'}$ = 4.0 Hz), 4.35 (1 H, t, 2'-H, $J_{2',3'}$ = 4.3 Hz), 4.78-4.81 (3 H, m, 4"-H and 5"-Ha,b), 5.85 (1 H, dd, 2"-H, $J_{2",3"}$ = 5.0 Hz), 5.95 (1 H, d, 1'-H, $J_{1',2'}$ = 4.3 Hz), 6.03 (1 H, m, 3"-H), 6.66 (1 H, d, 1"-H, $J_{1",2"}$ = 5.3 Hz), 7.31-7.60 (9 H, m, Ph), 7.91-8.13 (6 H, m, Ph), 8.18 (1 H, s, 2-H), 8.23 (1 H, s, 8-H).

6-*O*-(2,3,5-Tri-*O*-benzoyl-α,β-D-ribofuranosyl)-2',3',5'-*O*-tris(*t*-butyldimethylsilyl)inosine (13a,b). This was obtained as a mixture of the α- and β-isomers which could not be separated. Since it was difficult to assign completely the ^{1}H-NMR spectrum of the mixture because of its complexity, the following characteristic ^{1}H-NMR signals are given: 3.76, 3.80 (2 H, m, 5'-Ha-α,β), 3.90, 4.05 (2 H, m, 5'-Hb-α,β), 4.14, 4.15 (1 H, m, 4'-Hα,β), 4.32 (2 H, m, 3'-Hα,β), 5.84, 6.14 (1 H, m, 2"-Hα,β), 6.06, 6.09 (1 H, m, 1'-Hα,β), 7.09, 7.44 (1 H, m, 1"-Hα,β), 8.38, 8.40 (1 H, s, 2-Hα,β), 8.46, 8.60 (1 H, s, 8-Hα,β).

***N*^{1}-(α,β-D-Ribofuranosyl)-2',3',5'-*O*-tris(*t*-butyldimethylsilyl)inosine (14a,b).** A 0.1 M solution of NaOMe in MeOH (1.0 ml) was added to a solution of **12b** (20 mg, 0.019 mmol) in MeOH (1.0 ml), and the solution was stirred at room temperature for 25 min. H_2O (5.0 ml) was added to the mixture and extraction was carried out with CH_2Cl_2-pyridine (5 : 1, v/v, 5.0 ml, x 2). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with CH_2Cl_2 : MeOH (99 : 1→ 95 : 5) to give **14b** (12 mg, 85%) as a colorless syrup: ^{1}H-NMR ($CDCl_3$) δ -0.16 (3 H, s, $SiCH_3$), -0.05 (3 H, s, $SiCH_3$), -0.01 (3 H, s, $SiCH_3$), 0.03 (3 H, s, $SiCH_3$), 0.04 (3 H, s, $SiCH_3$), 0.16 (3 H, s, $SiCH_3$), 0.18 (3 H, s, $SiCH_3$), 0.84 (9 H, s, *t*Bu), 0.89 (9 H, s, *t*Bu), 0.98 (9 H, s, *t*Bu), 3.76-4.17 (10 H, m, 2"-H, 3'-H, 3"-H, 4'-H, 4"-H, 5'-Ha,b, 5"-Ha,b), 4.29-4.36 (3 H, m, OH x 2, 2'-H), 4.90 (1 H, br s, OH), 5.89 (1 H, d, 1'-H, $J_{1',2'}$ = 4.3 Hz), 6.60 (1 H, d, 1"-H, $J_{1"2"}$ = 6.0 Hz), 8.10 (1 H, s, 8-H), 8.18 (1 H, s, 2-H); ^{13}C-NMR ($CDCl_3$) δ -4.31, -4.69, -4.85, -4.96, -5.37, -5.51 ($SiCH_3$), 17.81, 17.95, 18.55

((CH_3)$_3$CSi), 25.66, 25.73, 26.13 ((CH_3)$_3$CSi), 61.69, 62.24 (C5' and C5"), 70.44, 71.27 (C3' and C3"), 84.33, 84.40 (C4' and C4"), 85.99, 88.37 (C1' and C1"), 122.48 (C5), 138.13 (C8), 145.82 (C4), 146.27 (C2), 155.78 (C6).

Similarly, compound **14a** was obtained from **12a** (165 mg, 0.156 mmol). **14a** (63 mg, 60 %): ^{1}H-NMR ($CDCl_3$) δ -0.13 (3 H, s, $SiCH_3$), 0.00 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.14 (3 H, s, $SiCH_3$), 0.13 (3 H, s, $SiCH_3$), 0.81 (9 H, s, *t*Bu), 0.91 (9 H, s, *t*Bu), 0.95 (9 H, s, *t*Bu), 3.74-4.30 (10 H, br, OHx3, 3"-H, 4'-H, 4"-H, 5'-Ha,b, 5"-Ha,b), 4.42 (1 H, t, 2"-H, $J_{2",3"}$ = 4.3 Hz), 4.50 (1 H, t, 3'-H, J = 4.5 Hz), 4.77 (1 H, t, 2'-H, J = 5.3 Hz), 5.84 (1 H, d, 1'-H, J = 4.6 Hz), 5.95 (1 H, d, 1"-H, J = 4.6 Hz), 8.29 (1 H, s, 2H), 8.22 (1 H, s, 8-H); ^{13}C-NMR ($CDCl_3$) δ -5.44,-4.90, -4.78, -4.71, -4.35 ($SiCH_3$), 18.03, 18.53, 18.53 ((CH_3)$_3$CSi), 25.64, 25.81, 26.08 ((CH_3)$_3$CSi), 62.09, 62.27 (C5' and C5"), 70.71, 71.21 (C3' and C3"), 85.12, 86.43 (C4' and C4"), 88.48, 94.99 (C1' and C1"), 124.24 (C5), 139.17 (C8), 145.88 (C4), 147.42 (C2), 157.09 (C6).

***N*^{1}-(β-D-Ribofuranosyl)inosine (15b).** Tetrabutylammonium fluoride monohydrate (17 mg, 0.08 mmol) was added to a solution of compound **14b** (12 mg, 0.016 mmol) in THF (0.2 ml) and the solution was stirred at room temperature for 10 min. The solvent was removed *in vacuo*. The residue was dissolved in H_2O (1 ml). This solution was subjected to a column of Dowex 50W X 8 (pyridinium form, 3 ml). Elution was performed with water (50 ml). The eluate was removed *in vacuo* to give **15b** (6.0 mg, 96%) as a colorless syrup: ^{1}H-NMR (D_2O) δ 3.63-3.96 (4H, m, 5'-Ha,b, 5"-Ha,b,), 4.24-4.73 (6 H, m, 2'-H, 2"-H, 3'-H, 3"-H, 4'-H, and 4"-H), 6.04 (1 H, d, 1'-H, $J_{1',2'}$ = 5.7 Hz), 6.48 (1 H, d, 1"-H, $J_{1",2"}$ = 3.6 Hz), 8.28 (1 H, s, 8-H), 8.43 (1 H, s, 2-H); UV (H_2O) λmax 250 nm, λmin 225 nm, sh 270 nm.

***N*^{1}-(α-D-Ribofuranosyl)inosine (15a).** Similarly, compound **15a** was obtained from **14a** (47 mg, 0.067 mmol). **15a** (18 mg, 70%): ^{1}H-NMR (D_2O) δ 3.62-3.98 (4 H, m, 5'-Ha,b, 5"-Ha,b), 4.10-4.90 (6 H, 2'-H, 2"-H, 3'-H, 3"-H, 4'-H, and 4"-H), 6.09 (1 H, d, 1'-H, $J_{1',2'}$ = 5.6 Hz), 6.23 (1 H, d, 1"-H, $J_{1",2"}$ = 3.0 Hz), 8.34 (1 H, s, 2-H), 8.69 (1H, s, 8-H); UV (H_2O) λmax 248 nm, λmin 227 nm, sh 270 nm.

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