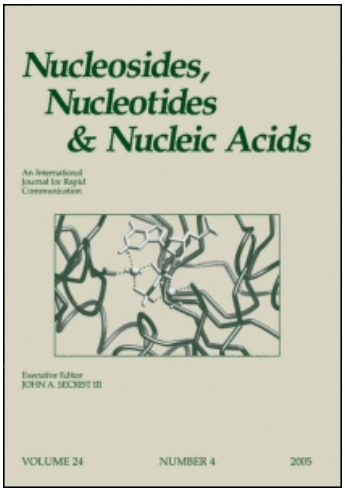


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Partial Protection of Carbohydrate Derivatives. Part 23.[1] Simple, Efficient Procedure for the Preparation of 3'- and 2'-0-(Tetrahydropyran-2-YL)Ribonucleoside Derivatives Involving Highly Regioselective 2',5'-DI-O-Acylation or that Followed by Acyl Migration on Silica Gel and Subsequent O-(Tetrahydropyran-2-YL)Ation

Kazuo Kamaike[a]; Fumihiko Uemura[a]; Shun-Ichi Yamakage[a]; Shigeyoshi Nishino[a]; Yoshiharu Ishido[a]
[a] Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Tokyo, Japan

To cite this Article Kamaike, Kazuo , Uemura, Fumihiko , Yamakage, Shun-Ichi , Nishino, Shigeyoshi and Ishido, Yoshiharu(1987) 'Partial Protection of Carbohydrate Derivatives. Part 23.[1] Simple, Efficient Procedure for the Preparation of 3'- and 2'-0-(Tetrahydropyran-2-YL)Ribonucleoside Derivatives Involving Highly Regioselective 2',5'-DI-O-Acylation or that Followed by Acyl Migration on Silica Gel and Subsequent O-(Tetrahydropyran-2-YL)Ation', Nucleosides, Nucleotides and Nucleic Acids, 6: 4, 699 — 736
To link to this Article: DOI: 10.1080/15257778708073420
URL: http://dx.doi.org/10.1080/15257778708073420

NUCLEOSIDES & NUCLEOTIDES, 6(4), 699-736 (1987)

PARTIAL PROTECTION OF CARBOHYDRATE DERIVATIVES. PART 23.[1] SIMPLE, EFFICIENT PROCEDURE FOR THE PREPARATION OF 3'- AND 2'-O-(TETRAHYDROPYRAN-2-YL)RIBONUCLEOSIDE DERIVATIVES INVOLVING HIGHLY REGIOSELECTIVE 2',5'-DI-O-ACYLATION OR THAT FOLLOWED BY ACYL MIGRATION ON SILICA GEL AND SUBSEQUENT O-(TETRAHYDROPYRAN-2-YL)ATION

Kazuo Kamaike, Fumihiko Uemura, Shun-ichi Yamakage, Shigeyoshi Nishino, and Yoshiharu Ishido*

Department of Chemistry, Faculty of Science,
Tokyo Institute of Technology,
O-okayama, Meguro-ku, Tokyo 152, Japan

Abstract: Acylation of ribonucleosides with an acyl chloride (1.2 – 1.5 and 2.2 – 3.0 mol. equiv. toward the D-ribofuranosyl moiety) in pyridine was induced with high regioselectivity to give the corresponding 2'-acylates and 2',5'-diacylates, respectively, which were effectively converted into the corresponding 3'-acylates and 3',5'-diacylates, respectively, by passage down a column of silica gel, followed by crystallization from a solvent. All of the 2',5'- and 3',5'-diacylates thus obtained were converted to the corresponding 3'- and 2'-O-(tetrahydropyran-2-yl) derivatives by the usual manner, i.e., (tetrahydropyran-2-yl)ation and subsequent O-deacylation.

INTRODUCTION

The tetrahydropyran-2-yl (THP) group is one of the most widely used protecting groups for the 2'-hydroxyl function of a ribonucleoside in RNA-type oligonucleotide synthesis.[2] Preparation of the 2'-O-(THP)-ribonucleoside derivatives has been performed mainly by two methods, i.e., 1) 2',3'-O-Isopropylidenation of a ribonucleoside, which is followed by a sequence of reactions of 5'-O-acetylation, 2',3'-O-deisopropylidenation, 2',3'-orthoacetate formation, partial hydrolysis of the orthoester, isolation of the 3',5'-diacetate, and (tetrahydropyran-2-yl)ation;[3] 2) Introduction of the 1,1,3,3-tetraisopropyl-1,3-disiloxan-1,3-diyl protecting group at the 3' and 5' positions of a ribonucleoside,

followed by 2'-O-(tetrahydropyran-2-yl)ation and then unmasking of the disiloxan protecting group.[4] The former is tedious to perform involving many steps of reactions, but the latter is a relatively simple but very costly method for the temporary, simultaneous blocking of 3' and 5' hydroxyl groups of a ribonucleoside. In this regard, an approach through the 3',5'-diacylates would seem to be more advantageous than the latter provided that we could develop an excellent procedure for the preparation of 3',5'-di-O-acylribonucleosides.

The unusual acidity of the 2'-hydroxyl group of ribonucleosides has been demonstrated by selective, but low-yield 2'-O-benzylation of uridine and cytidine with benzyl bromide – sodium hydride,[5] partial methylation of adenosine with diazomethane, giving a 3:1 mixture of 2'- and 3'-O-methyladenosine,[6] which was chromatographically separated on a column of strongly basic ion-exchange resin,[7] and X-ray crystal structure analysis of a series of purine ribonucleosides,[8] which showed that C(2') – O(2') is the shortest among the alcoholic functions at the 2', 3', and 5' positions, in addition to the pKa values (ca. 12) of some ribonucleosides; the acidity was explained as arising from their 2'-hydroxyl groups.[9] We have therefore set out to establish procedures for regioselective 2'-O-deacylation of fully acylated purine and pyrimidine ribonucleosides through hydrazine hydrate in 1:4 acetic acid – pyridine,[10] hydroxyaminium acetate in pyridine,[11] and potassium t-butoxide in an aprotic solvent.[12] Alternatively, the unusual acidity was further proved by preferential formation of 2',5'-diribonucleotides in the Mg^{+2} mediated coupling of a ribonucleoside 5'-phosphorimidazolide with the methyl ester of a 5'-ribonucleotide,[13] and by highly regioselective but moderate-yield 2'-O-acyltion (24 – 60%, isolated by preparative HPLC) of 5'-O-dimethoxytritylribonucleosides;[14] oligonucleotide synthesis by use of such resulting mixture of 2'- and 3'-acylates as its intermediates disadvantageously involves chromatographic separation of 2',5'- and 3',5'-phosphodiesters.

In view of this aspect, we explored di-O-acylation of ribonucleosides by drop-by-drop addition of an acyl chloride in pyridine, and found that the second acylation occurred at O-5' next to O-2' (preponderant over O-3' in the first stage), that treatment on silica gel of the resulting diacylates converted them into a mixture predominantly containing the 3',5'-diacylates, and that these products could be con-

Table 1. Regeioselective O-Monoacylation of Ribonucleosides with an Acyl Chloride [a]

Entry	1		RCl in Pyridine		Solvent	Reaction	Reaction	Yield (%) of			
								Column chromatog.		Crystallization	
	B	(mmol)	(mmol)	(mL)	(mL)	temp.	time[a] (h)	(2 + 4)	(3 + 5)	4	5
1	U	4	BzCl (4.8)	5	Py[b] (14)	ice-NaCl	2.0	79	20	64	15
2	U	2	BzCl (2.4)	3	Py (7)	room temp.	2.0	68	29	48	22
3	U	4	An[c]Cl(6.0)	6	Py (14)	ice-NaCl	2.0	76	21	57	15
4	A	4	BzCl (4.8)	5	Py (40) - DMF (20)	ice-NaCl	1.5	54	18	41	15
5	A	2	BzCl (2.4)	2.5	Py (20) - DMF (10)	room temp.	1.0	46	27	41	18
6	A	2	AnCl (3.0)	3	Py (20) - DMF (10)	ice-NaCl	1.5	66	29	60	25
7	A	2	AnCl (3.0)	3	Py (20) - DMF (10)	room temp.	2.0	54	38	45	24
8	A^{Bz}	4	BzCl (4.8)	5	Py (30)	ice-NaCl	1.5	67	26	47	-[d]
9	A^{Bz}	4	AnCl (4.8)	5	Py (30)	ice-NaCl	2.5	66	14	49	10
10	C^{An}	2	BzCl (3.0)	3	Py (15)	ice-NaCl	1.5	73	18	63	11
11	C^{An}	2	AnCl (3.0)	3	Py (15)	ice-NaCl	1.5	70	10	-[d]	9

[a] All of the reaction times include 30 min for drop-by-drop addition of each acyl chloride. [b] Py stands for pyridine. [c] An stands for anisoyl. [d] Not crystallized.

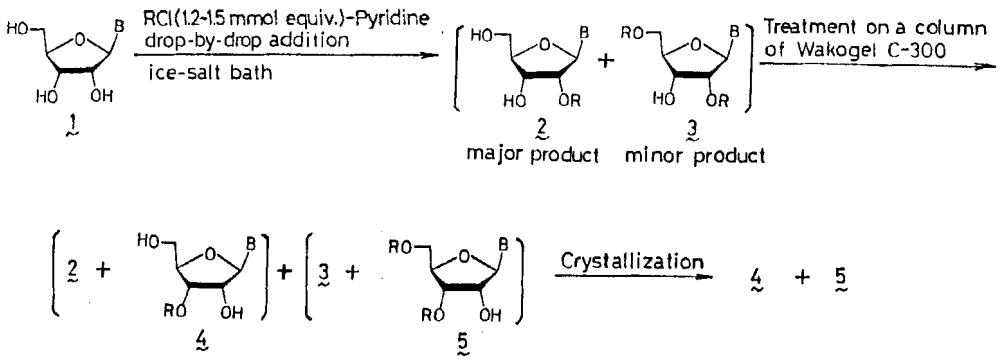
verted ito 3'- and 2'-O-(tetrahydropyran-2-yl)ribonucleosides, respectively, in a usual manner. We now report the results obtained in full herein.

RESULTS AND DISCUSSION

Regioselective Acylation of Ribonucleosides

O-Monoacylation: The acylation of uridine (1a), adenosine (1b), N^6-benzoyladenosine (1c), and N^4-anisoylcytidine (1f) was first performed by the use of benzoyl chloride and anisoyl chloride as the acylating agent; the results obtained and the conditions used are summarized in Table 1 (cf. Scheme 1). All of the reactions were performed by the used of an acyl chloride (1.2 – 1.5 mol. equiv. relative to the ribonucleoside) through the dilution – drop-by-drop addition procedure. Each of the resulting mixtures was monitored by ^{1}H-n.m.r. spectroscopy, exemplified by the case of 1a. Fig. 1(A) shows the anomeric proton region of its spectrum, showing the predominant formation of 2'-O-benzoyluridine (2a) over its 3'-benzoate (4a) by the H-1' doublet at δ 6.18. The signal pattern of this region changed into that shown in Fig. 1(B) upon passage down a column of silica gel,[15] showing effective isomerization of 2a into 4a by the appearance of another H-1' doublet at δ 5.99. Compound 4a, isolated by crystallization, gave a doublet at δ 5.99, shown in Fig. 1(c). Entries 1 and 2 (Table 1) show the results obtain-

Scheme 1



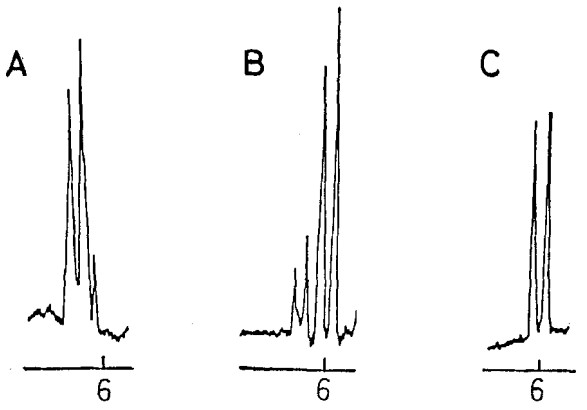


Fig. 1

ed by the reactions at ca. -15°C and at room temperature, respectively. Chromatographic separations of the resulting mixtures gave 2a and 4a (79% and 68% yields, respectively) and 2',5'-di-O-benzoyluridine (3a) and 3',5'-di-O-benzoyluridine (5a)(20% and 29% yields, respectively), respectively. Crystallization of both of the mixtures from ethanol gave 4a (64% and 48% yields, respectively) and 5a (15% and 22% yields), respectively. Similar trends as above were observed in all of the reactions whose results are shown in Entries 3 – 11 in Table 1.

O-Diacylation: The above study on O-monoacylation of some ribonucleosides proved that the minor products formed were the corresponding 2',5'-diacylates, which demonstrated that the second acylation took place at O-5', and that we should thus be able to isolate a mixture of ribonucleoside diacylates predominantly containing the 2',5'-diacylates and/or that their isomerization on silica gel should provide the corresponding 3',5'-diacylates as crystalline products. Therefore, O-diacylation of 1a, 1b, 1c, cytidine (1d), 1f, guanosine (1h), and N^2-isobutyrylguanosine (1i) was conducted by the use of benzoyl, anisoyl, and pivaloyl chloride (2.2 – 3.0 mol. equiv. relative to the D-ribofuranosyl moiety); the results obtained and the conditions used are summarized in Table 2 (cf. Scheme 2). Chromatographic separation of each of the resulting mixtures on a column of Wakogel C-300 gave a mixture of 3 plus 5 predominant over that of 2 plus 4 and the corresponding 2',3',5'-triacylates (6) in the acceptable isolated yields shown in the last

Table 2. Regioselective O-Diacylation of Ribonucleosides with an Acyl Chloride

Entry	1		RCl in Pyridine		Solvent	Reaction
	B	(mmol)	(mmol)	(mL)	(mL)	temp.
1	U	15	BzCl (33.0)	15	Py[b] 60	ice-NaCl
2	U	50	BzCl (110)	55	Py 200	ice-NaCl
3	U	5	BzCl (12.0)	12	Py 35	room temp.
4	U	4	An[c]Cl (10.0)	10	Py 5	ice-NaCl
5	U	2	Piv[d]Cl (5.0)	-	Py 5	ice-NaCl
6	A	2	BzCl (4.8)	5	Py (20) - DMF (10)	ice-NaCl
7	A	2	BzCl (4.8)	5	Py (20) - DMF (10)	room temp.
8	A	2	AnCl (6.0)	6	Py (20) - DMF (10)	ice-NaCl
9	A	5	AnCl (12.0)	12	Py (50) - DMF (25)	room temp.
10	A	2	PivCl (8.0)	-	Py (20) - DMF (10)	ice-NaCl
11	A^{Bz}	1	BzCl (2.4)	2.5	Py 7.5	ice-NaCl
12	A^{Bz}	50	AnCl (150)	75	Py 200	ice-NaCl
13	C	1	BzCl (3.6)	4	Py (8) - DMF (4)	ice-NaCl
14	C	2	AnCl (7.2)	8	Py (16) - DMF (8)	ice-NaCl
15	C	1	PivCl (6.0)	-	Py (8) - DMF (4)	ice-NaCl
16	C^{An}	50	BzCl (120)	60	Py 200	ice-NaCl
17	C^{An}	2	AnCl (6.0)	6	Py 15	ice-NaCl
18	G	1	PivCl (3.3)	-	Py 10	room temp.
19	G	1	PivCl (5.0)	-	Py 5	room temp.
20	G^{iBu}	50	BzCl (120)	60	Py 200	ice-NaCl
21	G^{iBu}	2	BzCl (4.8)	5	Py 14	room temp.
22	G^{iBu}	1	AnCl (3.0)	3	Py 7	ice-NaCl
23	G^{iBu}	1	AnCl (2.8)	3	Py 7	room temp.

[a] Time required for drop-by-drop addition of an acyl chloride.

[b] Py stands for pyridine.

[c] An stands for anisoyl group.

[d] Piv stands for pivaloyl group.

[e] The acyl chloride was added at one time.

Total reaction time[a] (D-b-d add.[a])		Yield (%) of Column chromatog. (2 + 4)	(3 + 5)	6	Crystallization 4	5	6
1.5	(1.0)	10	75	14	9	65	13
2.5	(2.0)	13	71	15	12	68	11
2.0	(0.75)	5	73	22	5	62	22
2.0	(0.5)	2	77	21	trace	71	18
1.5	(-[e])	-	97	-	-	-[f]	-
1.0	(0.5)	-	77	21	-	60	-
1.0	(0.5)	14	71	10	7	55	-
2.5	(0.5)	19	72	8	17	65	-
2.0	(0.75)	17	72	9	13	58	-
1.5	(-[e])	-	77	10	-	-[f]	-
1.5	(0.5)	-	75	18	-	-[f]	-
4.0	(2.0)	21	71	5	16	67	-
1.0	(0.5)	16[g]	58[g]	23[g]	-[f]	36[g]	20[g]
2.0	(0.5)	9[h]	55[h]	33[h]	-[f]	36[h]	29[h]
4.5	(-[e])	-	87[i]	-	-	-[f]	-
2.5	(2.0)	6	60	27	5	56	24
2.0	(0.5)	28	56	16	-[f]	38	14
3.0	(-[e])	-	75(19[j])	6	-	57(9[j])	-[f]
2.0	(-[e])	-	18(64[j])	7(10[j])	-	11(56[j])	-[f]
2.5	(2.0)	-	76	21	-	73	-[f]
1.0	(0.5)	-	67	15	-	44	-[f]
1.0	(0.5)	-	84	12	-	70	-[f]
1.0	(0.5)	-	75	20	-	65	-[f]

[f] Not crystallized.

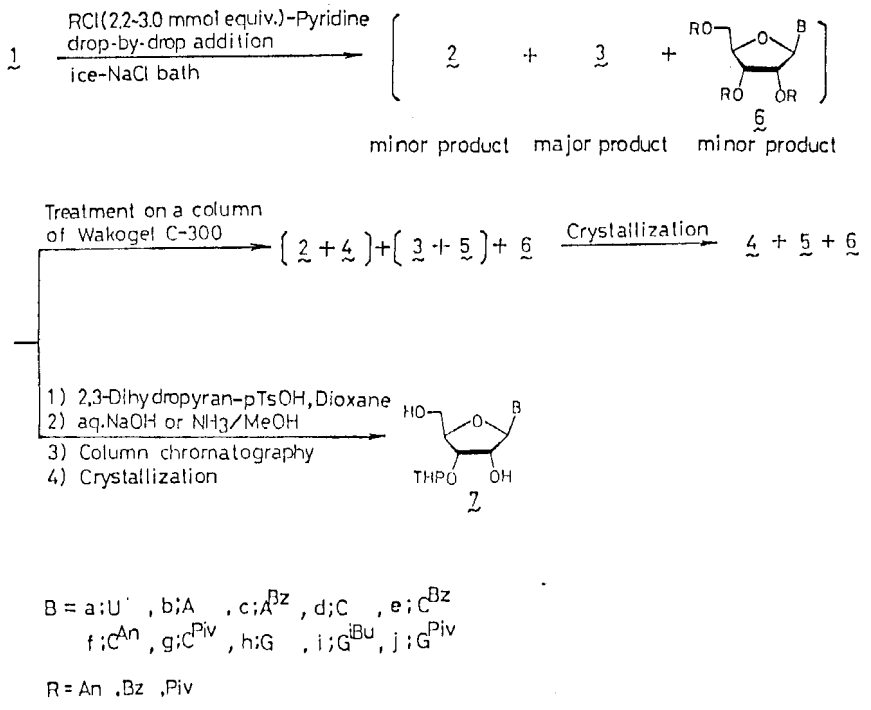
[g] Benzoyl group was also introduced at N-4 position.

[h] Anisoyl group was also introduced at N-4 position.

[i] Pivaloyl group was also introduced at N-4 position.

[j] Pivaloyl group was also introduced at N-2 position.

Scheme 2



column of the table. Crystallization of both of the mixtures (2 plus 4 and 3 plus 5, respectively) from an alcohol gave 4 and 5, respectively, in the yields also shown in the last column of Entries 1 – 4, 6 – 9, 12 – 14, and 16 – 23. These acylation reactions were, similar to the above O-monoacylation, monitored by ^{1}H-n.m.r. spectroscopy as shown in Fig. 2, being exemplified also by that of 1a. O-Dibenzoylation of 1a (Entry 1) gave the mixture affording an anomeric proton doublet at δ 6.09, which shows that this product is composed almost entirely of 2',5'-di-O-benzoyluridine (3a) [See Fig. 2(A)]. This signal pattern was conspicuously changed into that in Fig. 2(B) upon treatment with Wakogel C-300, which implies that the appearance of an anomeric proton doublet at δ 5.93; this doublet signal was superimposable with that of 3',5'-di-O-benzoyluridine (5a) [See Fig. 2(C)] obtained by crystallization of the product from the Wakogel C-300 treatment. Especially, it is noteworthy that with the present procedure is also possible to per-

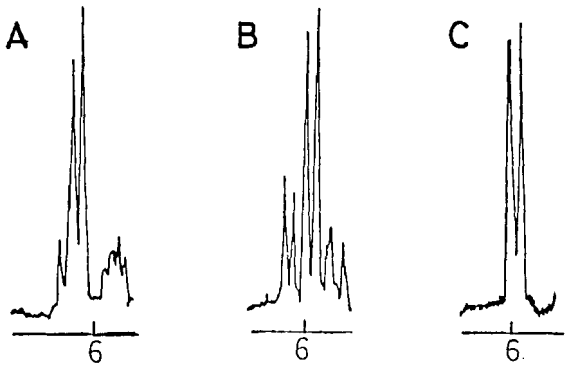


Fig. 2

form 50 mmol-scale preparation of 5a (R = Bz)(Entry 2), 5c (R = An) (Entry 12), 5f (R = Bz)(Entry 16), and 5i (R = Bz)(Entry 20) in 68%, 67%, 56%, and 73% yields, respectively, as crystalline products. Moreover, Entries 5 and 15 provided us very useful results, giving mixtures almost composed from 3a (R = Piv) and 3g (R = Piv) quantitatively (Their thin layer chromatograms gave only one spot corresponding to the products on developing with 9:1 chloroform – methanol); 3a and 3g were thus used for their 3'-O-(tetrahydropyran-2-yl)ation effectively as will be described below.

(Tetrahydropyran-2-yl)ation of Ribonucleoside Diacylates

(Tetrahydropyran-2-yl)ation has been performed with 2,3-dihydropyran – TsOH on a ribonucleoside 3',5'-diacetate, which was prepared from a 5'-O-acetyl-2',3'-O-(2-methoxyethylidene)ribonucleoside by partial hydrolysis and subsequent fractional crystallization[16] or from a 2',3',5'-triacetate by regioselective hydrazinolysis,[17] and, recently, with a 3',5'-O-(1,1,3,3-tetraisopropyl-1,3-dioxan-1,3-diyl)ribonucleoside.[4] As for the 3'-position, on the other hand, (4-methoxytetrahydropyran-4-yl)ation had been performed on a 2',5'-di-O-acetylribonucleoside, which was obtained by the orthoester approach[18] or on a 2',5'-bis(t-butyldimethylsilyl)ribonucleoside;[19] the 3'-derivatives have considerable importance due to the recent discovery of ppp$^{5'}$A$^{2'}$p$^{5'}$A$^{2'}$p$^{5'}$A.[20] Moreover, a recent study on the stability of the tetrahydropyran-2-yl group under a variety of acidic conditions for 5'-O-dedimethoxytritylation proved its utility in the solid-phase synthesis of oligoribonucleotides.[21]

Table 3. Three-step Synthesis of 3'-O-(Tetrahydropyran-2-yl) ribonucleosides (7) Involving 2',5'-O-Diacylation, 3'-O-(Tetrahydropyran-2-yl)ation, and O-Deacylation

Entry	1 B	(mmol)	Regioselective diacylation RCl	Pyridine (mL)	Solvent (mL)	Total reaction time (h) (D-b-d add.[c])
1	U	4	An[d]Cl(10)	10	Py[e](14)	1.5 (0.5)
2	U	4	BzCl (8)	8	Py (14)	1.0 (0.5)
3	U	50	Piv[f]Cl(125)	-	Py(250)	1.5 (-[g])
4	A	4	AnCl (12)	12	Py(40)-DMF(20)	1.5 (0.5)
5	A	4	BzCl (10)	10	Py(40)-DMF(20)	1.5 (0.5)
6	A	2	PivCl (8)	-	Py(20)-DMF(10)	1.0 (-[g])
7	A^{Bz}	50	BzCl(120)	60	Py(200)	4.0 (2.0)
8	C	50	PivCl(300)	-	Py(250)[h]	2.0 (-[g])
9	G^{iBu}	50	BzCl(105)	525	Py(200)	2.5 (2.0)

[a] 1, 4-Dioxane (2.5 mL toward 1 mmol of 1) was used as solvent.

[b] 2M aq. NaOH (1.25 mL) and 2:1 EtOH - pyridine (2 mL) were used toward 1 mmol of each of a nucleoside at room temperature for A; the same reagent and solvent system at 0°C for B; methanolic ammonic (saturated at 0°C; 2.5 mL toward 1 mmol of a nucleoside) was added for C.

[c] Time required for drop-by-drop addition in total reaction time.

[d] An stands for anisoyl group.

[e] Py stands for pyridine.

(Tetrahydropyran-2-yl)ation[a]			O-Deacylation		Yield (%) of crystalline 7
2,3-Dihydropyran (mmol)	TsOH (mmol)	Reaction time (h)	Conditions[b]	Reaction time (h)	less + more polar (total)
30	1.0	0.5	A	0.5	23 + 27 (50)
37	1.1	0.5	C	12.0	21 + 26 (47)
375	50	0.5	A	0.5	11 + 59 (70)
30	4.0	0.5	A	0.5	27 + 24 (51)
30	4.0	0.5	A	0.5	28 + 22 (50)
15	2.0	0.5	A	2.0	24 + 19 (43)
375	50	0.5	B	0.25	27 + 29 (56)
375	50	1.0	A	3.0	mix.[i] (80)
375	50	0.5	B	0.25	28 + 27 (55)

[f] Piv stands for pivaloyl group.

[g] The acyl chloride was added at one time.

[h] This reaction was started with a suspension of cytidine.

[i] A small amount of the 2'-isomers was present, the 3'-O-(tetrahydropyran-2-yl) cytidine diastereomers were isolated after conversion into the corresponding N^4-anisoyl derivatives, respectively.

The results above described thus prompted us to perform 2'- and 3'-O-(tetrahydropyran-2-yl)ation of the diacylated nucleosides in order to demonstrate utility of the foregoing preparative procedure for 2',5'- and 3',5'-di-O-acylribonucleosides.

3'-O-(Tetrahydropyran-2-yl)ation of the 2',5'-Diacylates (3); The 2',5'-di-O-acylation of ribonucleosides has been proved to proceed with high regioselectivity as above, although we were unable to isolate the diacylates as crystalline products. The resulting mixtures were thus forwarded to (tetrahydropyran-2-yl)ation with 2,3-dihydropyran – TsOH, followed by O-deacylation, giving the corresponding 3'-O-(tetrahydropyran-2-yl)ribonucleosides; the results obtained and the conditions used are summarized in Table 3. As may be seen from Entries 1 – 3, the pivaloyl group is the best among the temporary protecting groups for 1a, and 50 mmol-scale preparation gave the diastereoisomers of 3'-O-(tetrahydropyran-2-yl)uridine (7a) in 11% and 59% yields as crystalline products. Entry 7 shows that the combination of 1c with the benzoyl group for temporary protection of the two hydroxyl groups is the best (cf. Entries 4 – 7), and its 50 mmol-scale preparation afforded the diastereoisomers of N^6-benzoyl-3'-O-(tetrahydropyran-2-yl)adenosine (7c) in 27% and 29% yields as crystalline prodcuts. Entry 8 demonstrates that 50 mmol-scale preparation by the use of the pivaloyl group for the temporary protection, proceeding with such high regioselectivity, afforded an inseparable mixture of the diastereoisomers of 3'-O-(tetrahydropyran-2-yl)cytidine (7d) in 80% yield, which contained a small amount of the 2'-isomer as a contaminant; this mixture was successfully separated after conversion into their N^4-anisoyl derivatives (7f) in 39% and 29% yields as crystalline products. The combination of 1i with the benzoyl group for the temporary protection (Entry 9) was found to give the diastereoisomers of N^2-isobutyryl-3'-O-(tetrahydropyran-2-yl)guanosine (7i) in 28% and 27% yields as crystalline products also in a 50 mmol-scale preparation. All the structures of these products were confirmed by ^{1}H-n.m.r. spectroscopy after deriving them into the corresponding 2',5'-diacetates.

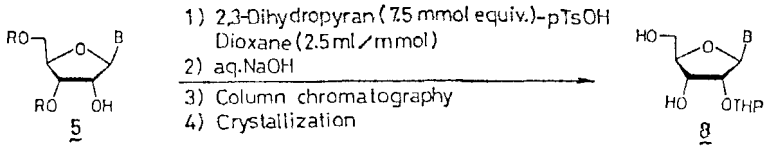
2'-O-(Tetrahydropyran-2-yl)ation of the 3',5'-Diacetates (5): Compounds 5 were also converted into the corresponding 2'-O-(tetrahydropyran-2-yl)ribonucleosides (8) in the same way as above; the results obtained and the conditions used are summarized in Table 4 (cf. Scheme

Table 4. Two-step Synthesis of 2'-O-(Tetrahydropyran-2-yl)ribonucleosides (8) from 5 Invonving (Tetrahydropyran-2-yl)ation and O-Deacylation

Entry	5 B	R	(Tetrahydropyran-2-yl)ation[a] TsOH (mol. equiv.)	Reaction time (h)	O-Deacylation[b] Temp. (°C)	Reaction time (h)	Yield (%) of crystalline 8 less + more polar		(Total)
1	U	Bz	0.25	1.0	room temp.	0.25	30	55	(85)
2	A	Bz	1.0	1.0	room temp.	0.25	50	38	(88)
3	A^{Bz}	An	1.0	0.5	0	1.0	33	51	(84)
4	C^{An}	Bz	1.0	0.5	0	0.25	45	39	(84)
5	G^{iBu}	Bz	1.0	1.0	0	0.25	17	58	(75)

[a] All of (tetrahydropyran-2-yl)ation reactions were performed by the use of 2,3-dihydropyran (7.5 mol. equiv. toward 5) and 1,4-dioxane (2.5 mL toward 1 mmol of 5). [b] 2M aq. NaOH (1.25 mL) and 2:1 EtOH - Pyridine (2 mL) were used toward 1 mmol of 5.

Scheme 3



3). Entries 1 – 5 all demonstrate the utility of such an approach to the preparation of 2'-O-(tetrahydropyran-2-yl)uridine (8a) [30% and 55% yields from 5a (R = Bz)], -adenosine (8b) [50% and 38% yields from 5b (R = Bz)], -N^6-benzoyladenosine (8c) [33% and 51% yields from 5c (R = An)], -N^4-anisoylcytidine (8f) [45% and 39% yields from 5f (R = Bz)], and -N^2-isobutyrylguanosine (8i) [17% and 58% yields from 5i (R = Bz)] as crystalline products. All the structures of these products were confirmed by ^{1}H-n.m.r. spectroscopy after deriving them into the corresponding 3',5'-diacetates.

The present procedure is thus concluded to provide us with very useful synthetic intermediates leading to an oligoribonucleotide involving intramolecular 2',5'- and 3',5'-phosphodiester linkages, more simply and/or efficiently than the known methods.[4,16,17,18,19]

EXPERIMENTAL

Melting points were determined by a Yanagimoto micro-melting-point apparatus, and are uncorrected. T.l.c. was conducted on Merck silica gel F_{254} by developing with 9:1 chloroform – methanol (Solvent A) or 6:4 benzene – acetone (Solvent B). Column chromatography was performed on silica gel (Wakogel C-300, purchased from Wako Pure Chemicals, Co. Ltd) by the use of chloroform – methanol or benzene – acetone system as the eluant. Elemental analyses were achieved with a Perkin-Elmer 240-002 apparatus. ^{1}H-N.m.r. spectra were recorded with a Varian T-60 instrument for solutions in a solvent chosen from chloroform-d, dimethyl sulfoxide-d_6, or a mixture with methanol-d_4 whose addition improved a spectrum by sharpening each of the signals, with tetramethylsilane as the internal standard. U.v. spectra were recorded with a Varian Techtron Uv-Vis Spectrophotometer Model 635 for solutions in ethanol in the cases of the ribonucleoside acylates, and for those in 95% aqueous ethanol in the cases of (tetrahydropyran-2-yl)ribonucleoside derivatives.

Syntheses of 3'-O-Acylribonucleosides

3'-O-Benzoyluridine (4a, R = Bz; cf. Entries 1 and 2 in Table 1): To a solution of 1a (0.9768 g, 4 mmol) in dried pyridine (14 mL), chilled in an ice-NaCl bath, was added a solution of benzoyl chloride (0.56 mL, 4.8 mmol) in dried pyridine (5 mL) dropwise during 30 min with stirring. The mixture was monitored by t.l.c. with Solvent A; each t.l.c. plate was first developed with diethyl ether as the eluant prior to developing with Solvent A in order to remove pyridine. The mixture was quenched with water (4 mL) when the spot of monobenzoyluridine (R_F 0.18) became the largest, and extracted with chloroform (20 mL and 10 mL x 2). The organic layer was, after washing with water (20 mL x 2), dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue containing a minor component (di-O-benzoyluridine; R_F 0.35)[The anomeric proton region of ^{1}H-n.m.r. spectrum is shown in Fig. 1(A)] was then subjected to chromatography on a column (10 cm, length x 4 cm, diameter) of silica gel with 98:2 chloroform – methanol, giving di-O-benzoyluridine (0.3619 g, 20% yield), and with 95:5 chloroform – methanol as the eluant, giving mono-O-benzoyluridine (1.0979 g, 79% yield)[The anomeric proton region of the ^{1}H-n.m.r. spectrum is shown in Fig. 1(B).

The monobenzoate mixture thus obtained was recrystallized 2 – 3 times to give 3'-O-benzoyluridine (4a, R = Bz; 0.8924 g, 64% yield, m. p. 213 – 214°C (from ethanol)[lit.[22] 212 – 214°C (from ethanol) and lit.[23] 213 – 214°C (from aqueous ethanol)]. ^{1}H-n.m.r. spectrum was superimposable with those reported,[22,23] and its anomeric proton region is shown in Fig. 1(C).

The dibenzoate mixture obtained above was recrystallized 2 – 3 times to give 3',5'-di-O-benzoyluridine (5a, R = Bz; 0.2715 g, 15% yield), m.p. 198 – 199°C (from methanol)[lit.[10] 199.5 – 200.5°C (from methanol) and lit.[11] 199 – 200°C (from methanol)]. ^{1}H-N.m.r. spectrum was superimposable with those reported.[10,11]

Syntheses of the following acylates were performed essentially in the same way as above unless otherwise noticed, under the conditions described in Table 1.

Monoanisoylation of 1a (cf. Entry 3): The reaction of 1a (0.9768 g) with anisoyl chloride (1.023 g) afforded 4a (R = An; 0.8589 g, 57% yield) and 3',5'-di-O-anisoyluridine (5a, R = An; 0.3148 g, 15% yield).

Compound 4a (R = An) had m.p. 181 – 182°C (from methanol), R_F 0.18 (Solvent A), u.v.: λ_{max} 260 nm (ε 23500) and λ_{min} 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.73 – 3.93 (5H, m, H-5', 5", and OCH_3), 4.17 – 4.25 (1H, m, H-4'), 4.47 (1H, dd, $J_{1',2'}$ 6 Hz, $J_{2',3'}$ 5.5 Hz, H-2'), 5.37 (1H, dd, $J_{3',4'}$ 3 Hz, H-3'), 5.65 (1H, d, $J_{5,6}$ 8 Hz, H-5), 6.01 (1H, d, H-1'), 6.90 (2H, d, J 9 Hz, Ph proton x 2), 7.90 (1H, d, H-6), and 7.97 (2H, d, Ph proton x 2).

Anal. Calcd for $C_{17}H_{18}N_2O_8$: C, 53.97; H, 4.80; N, 7.40. Found: C, 53.90; H, 4.79; N, 7.24.

Compound 5a (R = An) had m.p. 133 – 134°C (from 9:1 methanol – chloroform), R_F 0.35 (Solvent A), u.v.: λ_{max} 258 nm (ε 40000) and λ_{min} 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.81 (6H, s, OCH_3 X 2), 4.43 – 4.90 (4H, m, H-2', 4', 5', and 5"), 5.32 – 5.43 (1H, m, H-3'), 5.55 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.91 (1H, d, $J_{1',2'}$ 4.5 Hz, H-1'), 6.91 (4H, d, J 9 Hz, Ph proton x 4), 7.56 (1H, d, H-6), 7.87 (2H, d, Ph proton x 2), and 7.95 (2H, d, Ph proton x 2).

Anal. Calcd for $C_{25}H_{24}N_2O_{10}$: C, 58.58; H, 4.72, N, 5.47. Found: C, 58.37; H, 4.74; N, 5.40.

Monobenzoylation of 1b (cf. Entry 4 in Table 1): The reaction of 1b (1.0688 g) with benzoyl chloride (0.56 mL) gave 3'-O-benzoyladenosine (4b, R = Bz; 0.6145 g, 41% yield) and 3',5'-di-O-benzoyladenosine (5b, R = Bz; 0.2865 g, 15% yield).

Compound 4b (R = Bz) had m.p. 206 – 207°C (from ethanol)[lit.[23] 205 – 206°C (from aqueous ethanol)], R_F 0.22 (Solvent A); ^{1}H-n.m.r. spectrum was superimposable with that reported.[23]

Compound 5b (R = Bz) had m.p. 194 – 195°C (from 19:1 methanol – chloroform)[lit.[10,11] 193 – 194°C (from methanol)], R_F 0.32 (Solvent A); ^{1}H-n.m.r. spectrum was superimposable with those reported.[10,11]

Monoanisoylation of 1b (cf. Entry 6 in Table 1): The reaction of 1b (0.5345 g) with anisoyl chloride (0.5118 g) gave 4b (R = An; 0.4813 g, 60% yield) and 3',5'-di-O-anisoyladenosine (5b, R = An; 0.2660 g, 25% yield).

Compound 4b (R = An) had m.p. 212 – 213°C (from methanol), R_F 0.22 (Solvent A), u.v.: λ_{max} 259 nm (ε 31500) and λ_{min} 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.73 – 3.92 (5H, m, H-5', 5", and OCH_3), 4.28 – 4.40 (1H, m, H-4'), 5.02 (1H, dd, $J_{1',2'}$ 7 Hz, $J_{2',3'}$ 5.5 Hz, H-2'), 5.57 (1H, dd, $J_{3',4'}$ 1.5 Hz, H-3'), 6.06 (1H, d, H-1'), 6.97

(2H, d, J 9 Hz, Ph proton x 2), 8.02 (2H, d, J 9 Hz, Ph proton x 2), 8.13 (1H, s, H-8), and 8.27 (1H, s, H-2).

Anal. Calcd for $C_{18}H_{19}N_5O_6$: C, 53.68; H, 4.77; N, 17.45. Found: C, 53.57; H, 4.77; N, 17.45.

Compound 5b (R = An) had m.p. 133 – 134°C (from 19:1 methanol – chloroform), R_F 0.32 (Solvent A), u.v.: λ_{max} 258 nm (ε 45500) and λ_{min} 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.83 (6H, s, OCH_3 x 2), 4.47 – 4.70 (3H, m, H-4', 5', and 5''), 5.27 (1H, dd, $J_{1',2'}$ 6 Hz, $J_{2',3'}$ 4.5 Hz, H-2'), 5.76 (1H, dd, $J_{3',4'}$ 2 Hz, H-3'), 6.07 (1H, d, H-1'), 6.95 (2H, d, J 9 Hz, Ph proton x 2), 7.00 (2H, d, J 9 Hz, Ph proton x 2), 7.89 (2H, d, J 9 Hz, Ph proton x 2), 8.00 (2H, d, J 9 Hz, Ph proton x 2), 8.07 (1H, s, H-8), and 8.28 (1H, s, H-2).

Anal. Calcd for $C_{26}H_{25}N_5O_8 \cdot \frac{1}{2}H_2O$: C, 57.35; H, 4.81; N, 12.86. Found: C, 57.28; H, 4.76; N, 13.03.

Monobenzoylation of 1c (cf. Entry 8 in Table 1): The reaction of 1c (1.4854 g) with benzoyl chloride (0.56 mL) gave N^6-benzoyl-3'-O-benzoyladenosine (4c, R = Bz; 0.8939 g, 46% yield), m.p. 200 – 200.5°C (from ethanol) [lit.[24] 195 – 198°C (from ethanol), lit.[25] 188°C (from methanol), R_F 0.35 (Solvent A), ^{1}H-n.m.r. spectrum was superimposable with that reported.[25]

Monoanisoylation of 1c (cf. Entry 9 in Table 1): The reaction of 1c (1.4854 g) with anisoyl chloride (0.8188 g) gave N^6-benzoyl-3'-O-anisoyladenosine (4c, R = An; 0.9923 g, 49% yield) and -3',5,-di-O-anisoyladenosine (5c, R = An; 0.2598 g, 10% yield).

Compound 4c (R = An) had m.p. 158 – 160°C (from ethanol), R_F 0.35 (Solvent A), u.v.: λ_{max} 272 nm (ε 31800), 260 nm (ε 31600), λ_{min} 266 nm (ε 31300), and 233 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.07 – 3.87 (5H, m, H-5', 5'', and OCH_3), 4.30 4.40 (1H, m, H-4'), 5.10 (1H, dd, $J_{1',2'}$ 6.5 Hz, $J_{2',3'}$ 5.5 Hz, H-2'), 5.60 (1H, dd, $J_{3',4'}$ 2 Hz, H-3'), 6.20 (1H, d, H-1'), 6.93 (2H, d, J 9 Hz, Ph proton x 2), 7.35 – 7.57 and 7.87 – 8.10 (7H, m x 2, Ph proton x 7), and 8.62 (2H, s, H-2 and 8).

Anal. Calcd for $C_{25}H_{23}N_5O_7 \cdot \frac{1}{4}H_2O$: C, 58.88; H, 4.64; N, 13.73. Found: C, 58.72; H, 4.86; N, 13.57.

Compound 5c (R = An) had m.p. 134 – 135°C (from 19:1 methanol – chloroform), R_F 0.47 (Solvent A), u.v.: λ_{max} 260 nm (ε 47300) and λ_{min} 224 nm, ^{1}H-n.m.r. (DMSO-d_6 – $CDCl_3$ – TMS): δ 3.78 (3H, s, OCH_3), 3.82

(3H, s, OCH_3), 4.57 – 4.73 (3H, m, H-4', 5', and 5''), 5.27 (1H, t, H-2'), 5.73 (1H, m, H-3'), 6.20 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), 6.85 (2H, d, J 9 Hz, Ph proton x 2), 6.88 (2H, d, J 9 Hz, Ph proton x 2), 7.35 – 8.15 (9H, m x 2, Ph proton x 9), 8.46 (1H, s, H-8), and 8.53 (1H, s, H-2).

Anal. Calcd for $C_{33}H_{29}N_5O_9$: C, 60.27; H, 4.79; N, 10.65. Found: C, 60.40; H, 4.59; N, 10.79.

Monobenzoylation of 1f (cf. Entry 10 in Table 1): The reaction of 1f (0.7548 g) with benzoyl chloride (0.35 mL) gave N^4-anisoyl-3'-O-benzoylcytidine (4f, R = Bz; 0.6048 g, 63% yield) and -3',5'-di-O-benzoylcytidine (5f, R = Bz; 0.1288 g, 11% yield).

Compound 4f (R = Bz) had m.p. 149 – 150°C (from methanol), R_F 0.35 (Solvent A), u.v.: λ_{max} 285 nm (ε 24900), 230 nm, and λ_{min} 245 nm (ε 12400), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.67 – 3.90 (5H, m, H-5', 5'', and OCH_3), 4.27 – 4.37 (1H, m, H-4'), 4.52 (1H, t, H-3'), 5.33 (1H, t, H-2'), 6.02 (1H, d, $J_{1',2'}$ 4.5 Hz, H-1'), 6.93 (2H, d, J 9 Hz, Ph proton x 2), 7.20 – 7.60 and 7.84 – 8.10 (10H, m x 2, H-5 and Ph proton x 9), and 8.38 (1H, d, $J_{5,6}$ 7 HZ, H-6).

Anal. Calcd for $C_{24}H_{23}N_3O_8$: C, 59.87; H, 4.81; N, 8.87. Found: C, C, 59.74; H, 4.91; N, 8.75.

Compound 5f (R = Bz) had m.p. 203 – 204°C (from ethanol), R_F 0.52 (Solvent A), u.v.: λ_{max} 285 nm (ε 25000), 233 nm, and λ_{min} 248 nm (ε 12400), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.82 (3H, s, OCH_3), 4.48 – 4.73 (4H, m, H-2', 4', 5', and 5''), 5.30 – 5.50 (1H, m, H-3'), 5.94 (1H, d, $J_{1',2'}$ 4 Hz, H-1'), 6.99 (2H, d, J 9 Hz, Ph proton x 2), 7.20 – 7.60 and 7.82 – 8.17 (14H, m x 2, H-5, 6, and Ph proton x 12).

Anal. Calcd for $C_{31}H_{27}N_3O_9$: C, 63.59; H, 4.65; N, 7.18. Found: C, 63.39; H, 4.79; N, 7.16.

Syntheses of 3',5'-Di-O-acylribonucleosides

3' 5'-Di-O-benzoyluridine (5a, R = Bz; cf. Entry 1 and 2 in Table 2): To a solution of 1a (3.6631 g) in dried pyridine (60 mL), chilled in an ice-NaCl bath, was added a solution of benzoyl chloride (3.8 mL) in dried pyridine (15 mL) dropwise during 1 h with stirring. The mixture was monitored by t.l.c. with Solvent A; each t.l.c. plate was first developed with diethyl ether prior to developing with Solvent A. The mixture was quenched with water (15 mL) when the spot of dibenzoates became the largest, and evaporated to a gum. The gum was then taken up into

chloroform (150 mL), and washed with 5% aqueous sodium bicarbonate solution (75 mL x 2) and water (75 mL) successively. The organic layer was, after drying over anhydrous magnesium sulfate and filtered, evaporated to dryness. The residue gave an ^{1}H-n.m.r. spectrum with signals in the anomeric proton region as shown in Fig. 2(A), and thin layer chromatogram showing one major spot of dibenzoates (R_F 0.35) and two major spots of monobenzoates (R_F 0.18) and tribenzoate (R_F 0.58). It was subjected to chromatography on a column (20 cm, length x 4.5 cm, diameter) of Wakogel C-300 to give 2',3',5'-tri-O-benzoyluridine (6a, R = Bz; 1.2060 g, 14% yield) on elution with 99:1 chloroform – methanol, dibenzoates [5.0767 g, 75% yield; See Fig. 2(B)] with 98:2 chloroform – methanol, and monobenzoates (0.5052 g, 10% yield) with 95:5 chloroform – methanol. Recrystallization of the monobenzoate mixture (2 – 3 times) gave 4a (R = Bz; 0.4554 g, 9% yield), m.p. 213 – 214°C (from methanol). Recrystallization of the dibenzoate mixture (2 – 3 times) gave 5a (R = Bz; 4.4156 g, 65% yield), m.p. 198 – 199°C (from methanol) [See Fig. 2(C)]. Recrystallization of 6a (R = Bz) gave 1.1019 g, 13% of a pure sample, m.p. 144 – 145°C (from methanol) [lit.[26] 142 – 143°C (from benzene), R_F 0.58 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 4.63 – 4.80 (3H, m, H-4', 5', and 5''), 5.60 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.80 – 5.95 (2H, m, H-2' and 3'), 6.23 (1H, d, $J_{1',2'}$ 4 Hz, H-1'), 7.07 – 7.57 and 7.73 – 8.10 (16H, m x 2, H-6 and Ph proton x 15).

Fifty mmol-scale reaction by the use of 1a (12.2100 g) and benzoyl chloride (12.8 mL) gave 4a (R = Bz; 2.1954 g, 12% yield), 5a (R = Bz; 15.3144 g, 68% yield), and 6a (R = Bz; 3.0434 g, 11% yield).

Dianisoylation of 1a (cf. Entry 4 in Table 2): The reaction of 1a (0.9768 g) with anisoyl chloride (1.7059 g) gave 5a (R = An; 1.4605 g, 71% yield) and 2',3',5'-tri-O-anisoyluridine (6a, R = An; 0.4745 g, 18% yield).

Compound 5a (R = An) had m.p. 133 – 134°C (from 9:1 methanol – chloroform).

Compound 6a (R = An) had m.p. 195 – 196°C (from methanol), R_F 0.58 (Solvent A), u.v.: λ_{max} 258 nm (ε 53700) and λ_{min} 225 nm, ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 3.80 – 3.87 (9H, m, OCH_3 x 3), 4.57 – 4.77 (3H, m, H-4',5', and 5''), 5.50 – 5.83 (3H, m, H-2', 3', and 5), 6.26 (1H, d, $J_{1',2'}$ 4.5 Hz, H-1'), 6.76, 6.79, and 6.87 (6H, d x 3, J 9 Hz, Ph proton x 6), 7.40 (1H, $J_{5,6}$ 8 Hz, H-6), 7.81; 7.84, and 7.96 (6H, d x 3, J 9 Hz, Ph proton x 6).

Anal. Calcd for $C_{33}H_{30}N_2O_{12}$: C, 61.30; H, 4.68; N, 4.33. Found: C, 61.17; H, 4.74; N, 4.61.

Dibenzoylation of 1b (cf. Entry 6 in Table 2): The reaction of 1b (0.5345 g) with benzoyl chloride (0.56 mL) gave 5b (R = Bz; 0.5640 g, 60% yield) and 2',3',5'-tri-O-benzoyladenosine (6a, R = Bz; 0.2425 g, 21% yield).

Compound 5b (R = Bz) had m.p. 194 – 195°C (from 19:1 methanol – chloroform).

Compound 6b (R = Bz) was a glass, R_F 0.46 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – CD_3OD – TMS): δ 4.67 – 4.81 (3H, m, H-4', 5', and 5''), 6.17 – 6.43 (3H, m, H-1', 2', and 3'), 7.10 – 7.42 and 7.67 – 8.00 (16H, m x 2, H-8 and Ph proton x 15), and 8.10 (1H, s, H-2), being superimposable with that reported.[27]

Dianisoylation of 1b (cf. Entry 8 in Table 2): The reaction of 1b (0.5345 g) with anisoyl chloride (1.0236 g) gave 4b (R = An; 0.1550 g, 19% yield), 5b (R = An; 0.6960 g, 65% yield), and 6b (R = An; 0.1047 g, 8% yield).

Compound 4b (R = Bz) had m.p. 212 – 213°C (from methanol), and 5b (R = An) m.p. 133 – 134°C (from 19:1 methanol – chloroform).

Compound 6b (R = An) was a glass, R_F 0.46 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – CD_3OD – TMS): δ 3.75 – 3.83 (9H, s x 3, OCH_3 x 3), 4.68 – 4.85 (3H, m, H-4', 5', and 5''), 6.07 – 6.48 (3H, m, H-1', 2', and 3'), 6.73, 6.76, and 6.78 (6H, d x 3, J 8.5 Hz, Ph proton x 6), 7.78, 7.84, and 7.90 (6H, d x 3, J 8.5 Hz, Ph proton x 6), 8.03 (1H, s, H-8), and 8.13 (1H, s, H-2).

Anal. Calcd for $C_{34}H_{31}N_5O_{10}\cdot 1.75H_2O$: C, 58.24; H, 4.71; N, 9.99. Found: C, 58.02; H, 4.83; N, 9.79.

Dianisoylation of 1c (cf. Entry 12 in Table 2): The reaction of 1c (18.5676 g) with anisoyl chloride (25.5900 g) gave 4c (R = An; 4.0866 g, 16% yield), 5c (R = An; 21.3760 g, 67% yield), and N^6-benzoyl-2',3',5'-tri-O-anisoyladenosine (6c, R = An; 1.7675 g, 5% yield).

Compound 4c (R = An) had m.p. 158 – 160°C (from ethanol), and 5c (R = An) had m.p. 134 – 135°C (from 19:1 methanol – chloroform).

Compound 6c (R = An) was a glass, R_F 0.67 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 3.75 – 3.83 (9H, s x 3, OCH_3 x 3), 4.40 – 4.83 (3H, m, H-4', 5', and 5''), 6.03 – 6.50 (3H, m, H-1', 2', and 3'), 6.74,–6.81, and 6.83 (6H, m x 2, J 8.5 Hz, Ph proton x 6), 7.20 – 7.48 and 7.67 –

8.10 (11H, m x 2, Ph proton x 11), 8.23 (1H, s, H-8), and 8.57 (1H, s, H-2).

Anal. Calcd for $C_{41}H_{35}N_5O_{11}\cdot 2H_2O$: C, 60.81; H, 4.60; N, 8.65. Found: C, 60.71; H, 4.67; N, 8.70.

Dibenzoylation of 1d (cf. Entry 13 in Table 2): The reaction of 1d (0.2432 g) with benzoyl chloride (0.43 mL) gave a mixture of N^4-benzoyl-2'- (2e, R = Bz) and -3'-O-benzoylcytidine (4e, R = Bz) (0.0730 g, 16% yield), N^4-benzoyl-3',5'-di-O-benzoylcytidine (5e, R = Bz; 0.2002 g, 36% yield), and N^4-benzoyl-2',3',5'-tri-O-benzoylcytidine (6e, R = Bz; 0.134 g, 20% yield).

Compound 5e (R = Bz) had m.p. 204 – 205°C (from 19:1 methanol – chloroform) [lit.[22] 198 – 202°C (from ethanol) and lit.[28] 193 – 194°C (from ethanol)], R_F 0.52 (Solvent A), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 4.60 – 4.78 (4H, m, H-2', 4', 5', and 5''), 5.27 – 5.50 (1H, m, H-3'), 5.96 (1H, d, $J_{1',2'}$ 3.5 Hz, H-1'), 7.23 – 7.62 and 7.83 – 8.18 (17H, m x 2, H-5, 6, and Ph proton x 15).

Compound 6e had m.p. 210 – 211°C (from ethanol) [lit.[28] 208 – 209°C (from ethanol) and lit.[29] 202 – 203.5°C (from ethyl acetate)], R_F 0.66 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 4.72 – 4.80 (3H, m, H-4', 5', and 5''), 5.80 – 5.97 (2H, m, H-2' and 3'), 6.21 (1H, d, $J_{1',2'}$ 2.5 Hz, H-1'), 7.20 – 7.53 and 7.73 – 8.10 (22H, m x 2, H-5, 6, and Ph proton x 20).

Trianisoylation of 1d (cf. Entry 14 in Table 2): a) The reaction of 1d (0.4864 g) with anisoyl chloride (1.2282 g) gave a mixture of N^4-anisoyl-2'- (2f, R = An) plus -3'-O-anisoylcytidine (4f, R = An) (0.0914 g, 9% yield), N^4-anisoyl-3',5'-di-O-anisoylcytidine (5f, R = An; 0.4739 g, 37% yield), and N^4-anisoyl-2',3',5'-tri-O-anisoylcytidine (6f, R = An; 0.4520 g, 29% yield).

Compound 5f had m.p. 207 – 209°C (from 19:1 methanol – chloroform), R_F 0.5 (Solvent A), u.v.: λ_{max} 300 nm (shoulder), 260 nm (ε 45200), and λ_{min} 230 nm, ^{1}H-n.m.r. DMSO-d_6 – CD_3OD – TMS): δ 3.82 (9H, s, OCH_3), 4.40 – 4.73 (4H, m, H-2', 4', 5', and 5''), 5.20 – 5.45 (1H, m, H-3'), 5.93 (1H, d, $J_{1',2'}$ 3.5 Hz, H-1'), 6.82 – 7.08 (6H, m, Ph proton x 6), 7.27 (1H, d, $J_{5,6}$ 7 Hz, H-5), 7.77 – 8.13 (7H, m, H-6 and Ph proton x 6).

Anal. Calcd for $C_{33}H_{31}N_3O_{11}$: C, 61.39; H, 4.84; N, 6.51. Found: C, 61.26; H, 4.79; N, 6.43.

Compound 6f had m.p. 169 – 170°C (from ethanol) [lit.[30] 162 – 163°C (from 2-butanone)], R_F 0.62 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 3.83 – 3.93 (12H, m, OCH_3 x 4), 4.77 – 4.86 (3H, m, H-4', 5', and 5''), 5.90 – 5.97 (2H, m, H-2' and 3'), 6.40 – 6.46 (1H, br. d, H-1'), 6.85 – 7.13 (8H, m, Ph proton x 8), 7.60 (1H, d, $J_{5,6}$ 8 Hz, H-5), 7.87 – 8.53 (9H, m, H-6 and Ph proton x 8).

b) The reaction of 1f (0.7548 g) with anisoyl chloride (1.0236 g) gave a mixture of 2f (R = An) plus 4f (R = An) (0.2879 g, 28% yield), 5f (R = An; 0.4870 g, 38% yield), and 6f (R = An; 0.2187 g, 14% yield).

Compound 5f (R = An) had m.p. 207 – 209°C (from 19:1 methanol – chloroform), and 6f (R = An) m.p. 169 – 170°C (from ethanol).

Dibenzoylation of 1f (cf. Entry 16 in Table 2): The reaction of 1f (18.8677 g) with benzoyl chloride (14.0 mL) gave 4f (R = Bz; 1.1223 g, 5% yield), 5f (R = Bz; 16.5189 g, 56% yield), and N^4-anisoyl-2',3',5'-tri-O-benzoylcytidine (6f, R = Bz; 8.3143 g, 24% yield).

Compound 6f (R = Bz) had m.p. 227 – 228°C (from 19:1 methanol – chloroform), R_F 0.64 (Solvent A), u.v.: λ_{max} 282 nm (ε 29800), 233 nm, and λ_{min} 250 nm (ε 16700), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 3.82 (3H, s, OCH_3), 4.67 – 4.83 (3H, m, H-4', 5', and 5''), 5.90 – 6.20 (3H, m, H-1', 2', and 3'), 6.95 (2H, d, J 8.5 Hz, Ph proton x 2), 7.17 – 8.23 (19H, m, H-5, 6, and Ph proton x 17).

Anal. Calcd for $C_{38}H_{31}N_3O_{10}$: C, 66.18; H, 4.53; N, 6.09. Found: C, 65.88; H, 4.58; N, 6.12.

Dipivaloylation of 1h (cf. Entry 18 in Table 2): The reaction of 1h (0.2832 g) with pivaloyl chloride (0.41 mL) gave 3',5'-di-O-pivaloylguanosine (5h, R = Piv; 0.2572 g, 57% yield), N^2-pivaloyl-3',5'-di-O-pivaloylguanosine (5j, R = Piv; 0.0557 g, 9% yield), and 2',3',5'-tri-O-pivaloylguanosine (6h, R = Piv; 0.0343 g, 6% yield)

Compound 5h (R = Piv) had m.p. 173 – 174°C (from ethanol), R_F 0.18 (Solvent A), u.v.: λ_{max} 275 nm (shoulder), 257 nm (ε 13600), and λ_{min} 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.15 and 1.22 (18H, s x 2, t-Bu x 2), 4.07 – 4.39 (3H, m, H-4', 5', and 5''), 4.85 (1H, t, $J_{2',3'}$ 6Hz, H-2'), 5.17 (1H, dd, $J_{3',4'}$ 1.5 Hz, H-3'), 5.68 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), and 7.82 (1H, s, H-8).

Anal. Calcd for $C_{20}H_{29}N_5O_7 \cdot H_2O$: C, 51.17; H, 6.66; N, 14.92. Found: C, 51.38; H, 6.33; N, 14.78.

Compound 5j (R = Piv) had m.p. 184 – 185°C (from methanol), R_F 0.33 (Solvent A), u.v.: λ_{max} 278 nm (ε 12400), 258 nm (ε 15300), λ_{min} 272 nm (ε 12000), and 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.13, 1.23, and 1.28 (27H, s x 3, t-Bu x 3), 4.22 – 4.32 (3H, m, H-4', 5', and 5''), 4.87 (1H, t, H-2'), 5.25 (1H, dd, $J_{2',3'}$ 6 Hz, $J_{3',4'}$ 2 Hz, H-3'), 5.83 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), and 8.08 (1H, s, H-8).

Anal. Calcd for $C_{25}H_{37}N_5O_8$: C, 56.06; H, 7.01; N, 13.08. Found: C, 55.78; H, 6.83; N, 13.37.

Compound 6h (R = Piv) had R_F 0.28 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – CD_3OD – TMS): δ 1.20 – 1.40 (27H, m, t-Bu x 3), 4.30 – 4.43 (3H, m, H-4', 5', and 5''), 5.57 – 5.93 (3H, m, H-1', 2', and 3'), and 7.60 (1H, s, H-8).

Tripivaloylation of 1h (cf. Entry 19 in Table 2): The reaction of 1h (0.2832 g) with pivaloyl chloride (0.61 mL) gave 5h (R = Piv; 0.0503 g, 11% yield), 5j (R = Piv; 0.2991 g, 56% yield), 6h (R = Piv; 0.0398 g, 7% yield), and N^2-pivaloyl-2',3',5'-tri-O-pivaloylguanosine (6j, R = Piv; 0.0619g, 10% yield).

Compound 6j (R = Piv) was a glass, R_F 0.48 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – CD_3OD – TMS): δ 1.12, 1.22, 1.27, and 1.37 (36H, s x 4, t-Bu x 4), 4.33 – 4.40 (3H, m, H-4', 5', and 5''), 5.77 – 6.05 (3H, m, H-1', 2', and 3'), and 7.79 (1H, s, H-8).

Anal. Calcd for $C_{30}H_{45}N_5O_9 \cdot 1.5H_2O$: C, 55.72; H, 7.25; N, 10.83. Found: C, 55.81; H, 7.18; N, 10.76.

Dibenzoylation of 1i (cf. Entry 20 in Table 2): The reaction of 1i (17.6667 g) with benzoyl chloride (14 mL) gave N^2-isobutyryl-3',5'-di-O-benzoylguanosine (5i, R = Bz; 20.6258 g, 73% yield) and N^2-isobutyryl-2',3',5'-tri-O-benzoylguanosine (6i, R = Bz; 6.9694 g, 21% yield).

Compound 5i (R = Bz) had m.p. 188 – 189°C (from 19:1 methanol – chloroform), R_F 0.31 (Solvent A), u.v.: λ_{max} 276 nm (ε 15700), 259 nm (ε18400), 235 nm, λ_{min} 270 nm (ε 15400), and 246 nm (ε 17000), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.10 and 1.21 [6H, s x 2, $C(CH_3)_2$], 2.60 – 2.93 (1H, m, $CHMe_2$), 4.62 – 4.70 (3H, m, H-4', 5', and 5''), 5.02 (1H, t, H-2'), 5.56 – 5.73 (1H, m, H-3'), 6.01 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 7.27 – 7.60 and 7.83 – 8.13 (11H, m x 2, H-8 and Ph proton x 10).

Anal. Calcd for $C_{28}H_{27}N_5O_8$: C, 59.89; H, 4.85; N, 12.47. Found: C, 59.74; H, 4.90; N, 12.75.

Compound 6i (R = Bz) was a glass, R_F 0.44 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.17 and 1.27 (6H, s x 2, CH_3 x 2), 2.52 – 3.00 (1H, m, $COCHMe_2$), 4.67 – 4.78 (3H, m, H-4', 5', and 5''), 6.15 – 6.32 (3H, m, H-1', 2', and 3'), 7.07 – 7.47 and 7.63 – 8.05 (16H, m x 2, H-8 and Ph proton x 15).

Anal. Calcd for $C_{35}H_{31}N_5O_9 \cdot H_2O$: C, 61.49; H, 4.87; N, 10.24. Found: C, 61.19; H, 4.70; N, 10.00.

Dianisoylation of 1i (cf. Entry 22 in Table 2): The reaction of 1i (0.3533 g) with anisoyl chloride (0.5118 g) gave N^2-isobutyryl-3',5'-di-O-anisoylguanosine (5i, R = An; 0.4361 g, 70% yield) and -2',3',5'-tri-O-anisoylguanosine (6i, R = An; 0.0925 g, 12% yield).

Compound 5i had m.p. 147 – 148°C (from 19:1 methanol – chloroform), R_F 0.31 (Solvent A), u.v.: λ_{max} 258 nm (ε 44800) and λ_{min} 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.12 and 1.23 [6H, s x 2, $C(CH_3)_2$], 2.70 – 3.00 (1H, m, $CHMe_2$), 3.81 and 3.85 (6H, s x 2, OCH_3 x 2), 4.57 – 4.65 (3H, m, H-4', 5', and 5''), 4.96 (1H, t, H-2'), 5.53 – 5.70 (1H, m, H-3'), 6.01 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 6.90 (2H, d, J 9 Hz, Ph proton x 2), 6.96 (2H, d, J 9 Hz, Ph proton x 2), 7.87 (2H, d, J 9 Hz, Ph proton x 2), 7.95 (2H, d, J 9 HZ, Ph proton x 2), and 7.98 (1H, s, H-8).

Anal. Calcd for $C_{30}H_{31}N_5O_{10} \cdot H_2O$: C, 56.34; H, 5.20; N, 10.95. Found: C, 56.45; H, 4.91; N, 10.90.

Compound 6i (R = An) was a glass, R_F 0.42 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.18 and 1.28 (6H, s x 2, CH_3 x 2), 2.50 – 2.87 (1H, m, $COCHMe_2$), 3.67 – 3.87 (9H, m, OCH_3 x 3), 4.63 – 4.73 (3H, m, H-4', 5', and 5''), 6.08 – 6.28 (3H, m, H-1', 2', and 3'), 6.63 – 6.97 (6H, m, Ph proton x 6), and 7.63 – 8.00 (7H, m, Ph proton x 6, and H-8).

Anal. Calcd for $C_{38}H_{37}N_5O_{12} \cdot H_2O$: C, 58.98; H, 5.08; N, 9.05. Found: C, 58.69; H, 4.96; N, 9.02.

3'-O-(Tetrahydropyran-2-yl)ation of the 2',5'-Diacylates Obtained by Regioselective Diacylation of Ribonucleosides and Subsequent O-Deacylation to 3'-O-(Tetrahydropyran-2-yl) Derivatives

3'-O-(Tetrahydropyran-2-yl)uridine (7a; cf. Entry 1 in Table 3): To a solution of 1a (0.9768 g) in dried pyridine (14 mL), chilled in an ice-NaCl bath, was added a solution of anisoyl chloride (1.7059 g) in pyridine (10 mL) during 30 min with stirring. Similar to the foregoing reactions, the progress of the reaction was monitored by t.l.c. in the same manner as already described. When the dianisoates [R_F 0.35 (Sol-

vent A)] became the largest spot in t.l.c, the mixture was quenched with water (4 mL) and, then extracted with dichloromethane (40 mL). The organic layer was washed with water (20 mL x 2) and dried over anhydrous magnesium sulfate. The organic solution was, after removing the descicant by filtration, evaporated to give a residue, which was, then, dissolved in toluene (10 mL) and co-evaporated twice in order to remove pyridine. The residue thus obtained was then dissolved in 1,4-dioxane (10 mL), and the resulting solution was treated with 2,3-dihydropyran (2.7 mL) and p-toluenesulfonic acid monohydrate (0.1902 g) as usual. After stirring for 30 min, the resulting mixture was neutralized with 5% aqueous sodium bicarbonate solution, and extracted with chloroform (40 mL); this solution was washed with water (20 mL x 2). The organic layer was evaporated and the residue was further dissolved in 2:1 ethanol – pyridine (7.5 mL), and to it was added 2M aqueous sodium hydroxide solution (5 mL). After stirring for 30 min at room temperature, the mixture was treated with Dowex 50W to neutralize. The resin was filtered off and washed with 2:1 ethanol – pyridine (ca. 40 mL). The filtrate and the washings were combined and evaporated to dryness. The residue was subjected to chromatography on a column (10 cm, length x 4 cm, diameter) of silica gel with chloroform – methanol system as the eluant to give diastereomers of 7a [R_F 0.21 and 0.17 (Solvent A)]. The less and more polar isomers were obtained as crystalline products in 23% (0.2966 g) and 27% (0.3521 g) yields, respectively.

Entries 2 and 3 in Table 3 show the results obtained by the use of anisoyl and pivaloyl chloride as acylating agents, respectively, in the same way as above described.

The less polar isomer of 7a had m.p. 193 – 194°C (from ethanol), R_F 0.21 (Solvent A) and 0.17 (Solvent B), u.v.: λ_{max} 262 nm (ε 10100) and λ_{min} 230 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.33 – 1.70 (6H, m, C-C$\underline{H}_2$ x 3), 3.43 – 4.13 (7H, m, H-2', 3', 4', 5', 5'', and C$\underline{H}_2$-O), 4.72 (1H, br. s, O-C$\underline{H}$-O), 5.58 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.72 (1H, d, $J_{1',2'}$ 4.5 Hz, H-1'), and 7.80 (1H, d, H-6).

Anal. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.09; H, 6.08; N, 8.53.

The more polar isomer of 7a had m.p. 192 – 193°C (from ethanol), R_F 0.17 (Solvent A), u.v.: λ_{max} 261 nm (ε 9400) and λ_{min} 230 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.33 – 1.70 (6H, m, C-C$\underline{H}_2$ x 3), 3.67 – 4.17

(7H, m, H-2', 3', 4', 5', 5'', and O-C<u>H</u>$_2$), 4.78 (1H, br. s, O-C<u>H</u>-O), 5.60 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.72 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), and 7.70 (1H, d, H-6).

<u>Anal</u>. Calcd for $C_{14}H_{20}N_2O_7$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.34; H, 6.01; N, 8.34.

3'-O-(<u>Tetrahydropyran-2-yl</u>)ation of <u>1b</u> (<u>cf</u>. Entries 4, 5, and 6 in Table 3): The reactions of <u>1b</u> (1.0688 g for Entries 4 and 5, and 0.5344 g for Entry 6) with anisoyl (2.0472 g), benzoyl (1.6 mL), and pivaloyl chloride (0.9 mL), which were respectively followed by a similar work-up as above described, gave the diastereomers of 3'-<u>O</u>-(tetrahydropyran-2-yl)adenosine (<u>7b</u>) in 51% [0.3780 g (less) + 0.3305 g (more polar)], 50% [0.3935 g (less) + 0.3092 g (more polar)], and 43% [0.1685 g (less) + 0.1313 g (more polar)] total yields.

The less polar isomer of <u>7b</u> had m.p. 175 – 176°C (from ethanol), R_F 0.26 (Solvent A), u.v.: λ_{max} 260 nm (ε 13100) and λ_{min} 227 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.30 – 1.87 (6H, m, C-C<u>H</u>$_2$ x 3), 3.27 – 4.43 (6H, m, H-3', 4', 5', 5'', and O-C<u>H</u>$_2$), 4.63 – 4.87 (2H, m, H-2' and O-C<u>H</u>-O), 5.95 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 8.12 (1H, s, H-8), and 8.29 (1H, s, H-2).

<u>Anal</u>. Calcd for $C_{15}H_{21}N_5O_5 \cdot \frac{1}{4}H_2O$: C, 50.63; H, 6.09; N, 19.68. Found: C, 50.56; H, 5.89; N, 19.46.

The more polar isomer of <u>7b</u> had m.p. 175 – 176°C (from 9:1 ethyl acetate – ethanol), R_F 0.22 (Solvent A), u.v.: λ_{max} 260 nm (ε 12900) and λ_{min} 226 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.33 – 1.83 (6H, m, C-C<u>H</u>$_2$ x 3), 3.13 – 4.40 (6H, m, H-3', 4', 5', 5'', and O-C<u>H</u>$_2$), 4.67 – 4.95 (2H, m, H-2' and O-C<u>H</u>-O), 5.90 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 8.10 (1H, s, H-8), and 8.23 (1H, s, H-2).

<u>Anal</u>. Calcd for $C_{15}H_{21}N_5O_5$: C, 51.28; H, 6.02; N, 19.93. Found: C, 50.98; H, 5.89; N, 19.66.

3'-O-(<u>Tetrahydropyran-2-yl</u>)ation of <u>1c</u> (<u>cf</u>. Entry 7 in Table 3): The reaction of <u>1c</u> (18.5676 g) with benzoyl chloride (14.0 mL), which was worked up similarly as above, gave the less and more polar diastereomers of <u>N</u>^{6}-benzoyl-3'-<u>O</u>-(tetrahydropyran-2-yl)adenosine (<u>7c</u>) in 27% (6.1568 g) and 29% (6.5558 g) yields, respectively.

The less polar isomer of <u>7c</u> had m.p. 109 – 110°C (from 5:1 ethyl acetate – benzene), R_F 0.44 (Solvent A), u.v.: λ_{max} 279 nm (ε 21200), 235 nm, and λ_{min} 245 nm (ε 10500), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.37 – 1.82 (6H, m, C-C<u>H</u>$_2$ x 3), 3.40 – 4.43 (6H, m, H-3', 4', 5', 5'', and O-C<u>H</u>$_2$), 4.65 – 4.85 (2H, m, H-2' and O-C<u>H</u>-O), 6.07 (1H, d, $J_{1',2'}$ 5.5

Hz, H-1'), 7.40 – 7.57 and 7.87 – 8.12 (5H, m x 2, Ph proton x 5), and 8.63 (2H, s, H-2 and 8).

Anal. Calcd for $C_{22}H_{25}N_5O_6$: C, 58.02; H, 5.53; N, 15.38. Found: C, 57.88; H, 5.55; N, 15.07.

The more polar isomer of 7c had m.p. 189 – 190°C (from ethanol), R_F 0.33 (Solvent A), u.v.: λ_{max} 279 nm (ε 21200), 235 nm, and λ_{min} 245 nm (ε 10500), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.33 – 1.87 (6H, m, C-CH_2 x 3), 3.50 – 4.43 (6H, m, H-3', 4', 5', 5'', and O-CH_2), 4.67 – 4.93 (2H, m, H-2' and O-CH-O), 6.03 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 7.37 – 7.53 and 7.87 – 8.07 (5H, m x 2, Ph proton x 5), and 8.55 (2H, s, H-2 and 8).

Anal. Calcd for $C_{22}H_{25}N_5O_6$: C, 58.02; H, 5.53; N, 15.38. Found: C, 57.96; H, 5.59; N, 15.46.

3'-O-(Tetrahydropyran-2-yl)ation of 1d (cf. Entry 8 in Table 3): The reaction of 1d (12.1609 g) with pivaloyl chloride (37.25 mL), which was worked up similarly as above, gave an inseparable mixture of the diastereomers of 3'-O-(tetrahydropyran-2-yl)cytidine (7d) in 80% (13.0935 g) yield. Moisture contained in 7d was removed by repeated coevaporation with dried pyridine three times. Compound 7d obtained was then subjected to N^4-anisoylation according to the procedure reported;[31] To a solution of the residue in dried pyridine (200 mL), was added chlorotrimethylsilane (25.6 mL, 200 mmol), and anisoyl chloride (10.2360 g, 60 mmol) after stirring for 1 h. After further stirring for 2 h at room temperature, the resulting mixture was treated with 29% aqueous ammoniacal solution (40 mL) and stirred for 15 min at room temperature. The reuslting solution was evaporated, and the residue was dissolved in chloroform (300 mL). The organic solution was successively washed with 5% aqueous sodium carbonate solution (200 mL x 2) and water (200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was subjected to chromatography on a column (20 cm, length x 4.5 cm, diameter) of silica gel with acetone (0 – 20%) – benzene ad the eluant to give the less and more polar diastereomers of N^4-anisoyl-3'-O-(tetrahydropyran-2-yl)cytidine (7f) in 39% (7.1990 g) and 29% (5.3191 g) yields starting from 7d.

The less polar isomer of 7f had m.p. 163 – 165°C (from ethyl acetate), R_F 0.31 (Solvent A) and 0.27 (Solvent B), u.v.: λ_{max} 288 nm (ε 24500) and λ_{min} 236 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.26 – 1.80 (6H, m, C-CH_2 x 3), 3.40 – 4.25 (7H, m, H-2', 3', 4', 5', 5'', and O-CH_2), 4.68

(1H, br. s, O-CH-O), 5.77 (1H, d, $J_{1',2'}$ 1.5 Hz, H-1'), 6.93 (2H, d, J 8.5 Hz, Ph proton x 2), 7.27 (1H, d, $J_{5,6}$ 7.5 Hz, H-5), 7.92 (2H, d, J 8.5 Hz, Ph protn x 2), and 8.41 (1H, d, H-6).

Anal. Calcd for $C_{22}H_{27}N_3O_8$: C, 57.26; H, 5.90; N, 9.11. Found: C, 57.05; H, 6.01; N, 9.18.

The more polar isomer of 7f had m.p. 197 – 198°C (from ethanol), R_F 0.30 (Solvent A), u.v.: λ_{max} 288 nm (ε 24200) and λ_{min} 236 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.23 – 1.70 (6H, m, C-CH_2 x 3), 3.53 – 4.27 (7H, m, H-2', 3', 4', 5', 5'', and C-CH_2), 4.74 (1H, br. s, O-CH-O), 5.80 (1H, d, $J_{1',2'}$ 3 Hz, H-1'), 6.92 (2H, d, J 8.5 Hz, Ph proton x 2), 7.25 (2H, d, $J_{5,6}$ 7.5 Hz, H-5), 7.92 (2H, d, J 8.5 Hz, Ph proton x 2), and 8.33 (1H, d, H-6).

Anal. Calcd for $C_{22}H_{27}N_3O_8 \cdot \frac{1}{4}H_2O$: C, 56.71; H, 5.95; N, 9.02. Found: C, 56.81; H, 6.01; N, 9.11.

3'-O-(Tetrahydropyran-2-yl)ation of 1i (cf. Entry 9 in Table 3): The reaction of 1i (17.6667 g) with benzoyl chloride (12.25 mL), which was worked up similarly as above, gave the less and more polar diastereomers of N^2-isobutyryl-3'-O-(tetrahydropyran-2-yl)guanosine (7i) in 28% (6.1462 g) and 27% (5.9318 g) yields, respectively. Purification of both of the isomers was performed by pouring their solution in dichloromethane (30 mL) into hexane (500 mL) under vigorous stirring.

The less polar isomer of 7i had m.p. 133 – 135°C, R_F 0.26 (Solvent A) and 0.12 (Solvent B), u.v.: λ_{max} 280 nm (ε 11700), 260 nm (ε 13600), 230 nm, λ_{min} 270 nm (ε 11200), and 238 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.17 and 1.28 [6H, s x 2, $C(CH_3)_2$], 1.37 – 1.83 (6H, m, C-CH_2 x 3), 2.50 – 2.97 (1H, m, $CHMe_2$), 3.53 – 4.73 (8H, m, H-2', 3', 4', 5', 5'', O-CH_2, and O-CH-O), 5.83 (1H, d, $J_{1',2'}$ 3 Hz, H-1'), and 8.02 (1H, s, H-8).

Anal. Calcd for $C_{19}H_{27}N_5O_7 \cdot \frac{1}{4}H_2O$: C, 51.64; H, 6.27; N, 15.85. Found: C, 51.47; H, 6.22; N, 15.53.

The more polar isomer of 7i had m.p. 136 – 138°C, R_F 0.22 (Solvent A) and 0.08 (Solvent B), u.v.: λ_{max} 280 nm (ε 10600), 260 nm (ε 11900), 230 nm, λ_{min} 270 nm (ε 10100), and 239 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.18 and 1.26 [6H, s x 2, $C(CH_3)_2$], 1.43 – 1.87 (6H, m, C-CH_2 x 3), 2.48 – 2.82 (1H, m, $CHMe_2$), 3.30 – 4.02 (4H, m, H-5', 5'', and O-CH_2), 4.22 – 4.88 (4H, m, H-2', 3', 4', and O-CH-O), 5.97 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), and 7.89 (1H, s, H-8).

Anal. Calcd for $C_{19}H_{27}N_5O_7$: C, 52.17; H, 6.22; N, 16.01. Found: C, 51.87; H, 6.10; N, 16.27.

2'-O-(Tetrahydropyran-2-yl)ation of the 3',5'-Diacylates Obtained by Regioselective Diacylation of Ribonucleosides, Followed by Acyl Migration on Silica Gel, and Subsequent O-Deacylation to 2'-O-(Tetrahydropyran-2-yl) Derivatives

2'-O-(Tetrahydropyran-2-yl)uridine (8a; cf. Entry 1 in Table 4): A solution of 5a (R = Bz; 13.5726 g) in dried 1,4-dioxane (75 mL) was treated with 2,3-dihydropyran (20.6 mL) and p-toluenesulfonic acid monohydrate (1.4625 g) at room temperature. After stirring for 30 min, the resulting mixture was neutralized with 5% aqueous sodium bicarbonate solution, extracted with chloroform (200 mL), and washed with water (100 mL x 2). The organic layer was evaporated and the residue was dissolved in 2:1 ethanol – pyridine (56.3 mL), to which was added 2M aqueous sodium hydroxide solution (37.5 mL). After stirring for 15 min at room temperature, the resulting mixture was neutralized with Dowex 50W. The resin was filtered off, and washed with 2:1 ethanol – pyridine (ca. 120 mL). The filtrate and washings were combined and evaporated to dryness. The residue was subjected to chromatography on a column (20 cm, length x 4.5 cm, diameter) of silica gel with chloroform – methanol system as the eluant to give the less and more polar diastereomers of 8a in 30% (2.9806 g) and 55% (5.4067 g) yields, respectively.

The less polar isomer of 8a had m.p. 159 – 160°C (from ethyl acetate) [lit.[16] 146 – 148°C (from ethyl acetate)], R_F 0.21 (Solvent A) and 0.16 (Solvent B), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.33 – 1.73 (6H, m, C-CH_2 x 3), 3.13 – 4.23 (7H, m, H-2',3',4', 5', 5'', and O-CH_2), 4.74 1H, br. s, O-CH-O), 5.58 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.84 (1H, d, $J_{1',2'}$ 3.5 Hz, H-1'), and 7.92 (1H, d, H-6), being superimposable with the data reported.[16]

The more polar isomer of 8a had m.p. 191 – 194°C (from ethanol) [lit.[16] 185 – 187°C (from ethanol)], R_F 0.15 (Solvent A), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.17 – 1.73 (6H, m, C-CH_2 x 3), 3.13 – 4.40 (7H, m, H-2', 3', 4', 5', 5'', and O-CH_2), 4.69 (1H, br. s, O-CH-O), 5.60 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.92 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), and 7.78 (1H, d, H-6), being superimposable with the data reported.[16]

2'-O-(Tetrahydropyran-2-yl)ation of 5b (R = Bz; cf. Entry 2 in Table 4): The reaction of 5b (R = Bz; 0.8805 g), followed by O-debenzoylation, gave the less and more polar diastereomers of 2'-O-(tetrahydropyran-2-yl)adenosine (8b) in 50% (0.3282 g) and 38% (0.2443 g) yields, respectively.

The less polar isomer of 8b had m.p. 170 – 171.5°C (from ethyl acetate) [lit.[16] 171 – 172.5°C (from ethyl acetate)], R_F 0.28 (Solvent A), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.17 – 1.73 (6H, m, C-C$\underline{H}_2$ x 3), 3.13 – 4.40 (7H, H-3', 4', 5', 5", O-C$\underline{H}_2$, and O-C$\underline{H}$-O), 4.81 (1H, t, H-2'), 6.11 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 8.15 (1H, s, H-8), and 8.34 (1H, s, H-2) [lit.[16] ^{1}H-n.m.r. (3:1 1,4-dioxane – D_2O): τ 1.69 (1H, s, H-2), 1.74 (1H, s, H-8), and 3.89 (1H, d, J 6.3 c/s, H-1')].

The more polar isomer of 8b had m.p. 199 – 200°C (from ethanol) [lit.[16] 199 – 201°C (from ethanol)], R_F 0.24 (Solvent A), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.15 – 1.67 (6H, m, C-C$\underline{H}_2$ x 3), 2.93 – 3.15 (2H, m, O-C$\underline{H}_2$), 3.50 – 3.70 (2H, m, H-5' and 5"), 3.93 – 4.10 (1H, m, H-4'), 4.20 – 4.43 (1H, m, H-3'), 4.68 (1H, br. s, O-C$\underline{H}$-O), 4.78 (1H, dd, $J_{1',2'}$ 7 Hz, $J_{2',3'}$ 5 Hz, H-2'), 6.03 (1H, d, H-1'), 8.10 (1H, s, H-8), and 8.27 (1H, s, H-2) [lit.[16] ^{1}H-n.m.r. (3:1 1,4-dioxane – D_2O): τ 1.74 (2H, s, H-2 and 8) and 3.86 (1H, d, J 6.6 c/s, H-1')].

2'-O-(Tetrahydropyran-2-yl)ation of 5c (R = An; cf. Entry 3 in Table 4): The reaction of 5c (R = An; 13.4320 g), followed by O-deanisoylation, gave the less and more polar isomers of N^6-benzoyl-2'-O-(tetrahydropyran-2-yl)adenosine (8c) in 33% (3.1406 g) and 51% (4.8693 g) yields, respectively. Purification of both isomers was performed by pouring their solution in chloroform (2 mL) into hexane (30 mL) under vigorous stirring.

The less polar isomer of 8c had m.p. 95 – 97°C, R_F 0.46 (Solvent A), u.v.: λ_{max} 278 nm (ε 19500), 237 nm, and λ_{min} 246 nm (ε 9900), ^{1}H-n.m.r. (DMSO-d_6 – $CDCl_3$ – TMS): δ 1.37 – 1.82 (6H, m, C-C$\underline{H}_2$ x 3), 3.40 – 3.57 (2H, m, O-C$\underline{H}_2$), 3.63 – 3.83 (2H, m, H-5' and 5"), 3.97 – 4.12 (1H, m, H-4'), 4.37 (1H, dd, $J_{3',4'}$ 3 Hz, H-3'), 4.62 (1H, br. s, O-C$\underline{H}$-O), 4.82 H-2'), 6.22 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), 7.37 – 7.63 and 7.87 – 8.13 (5H, m x 2, Ph proton x 5), and 8.68 (2H, s, H-2 and 8).

Anal. Calcd for $C_{22}H_{25}N_5O_6 \cdot \frac{1}{4}H_2O$: C, 57.45; H, 5.59; N, 15.22. Found: C, 57.53; H, 5.58; N, 14.96.

The more polar isomer of 8c had m.p. 100 – 102°C, R_F 0.34 (Solvent A), u.v.: λ_{max} 278 nm (ε 19600), 236 nm, and λ_{min} 246 nm (ε 9800), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.10 – 1.73 (6H, m, C-C$\underline{H}_2$ x 3), 3.02 – 3.27 (2H, m, O-C$\underline{H}_2$), 3.60 – 3.68 (2H, m, H-5' and 5''), 3.95 – 4.13 (1H, m, H-4'), 4.33 – 4.50 (1H, m, H-3'), 4.72 (1H, m, O-C$\underline{H}$-O), 4.85 (1H, dd, $J_{2',3'}$ 5 Hz, H-2'), 6.22 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 7.33 – 7.63 and 7.87 – 8.10 (5H, m x 2, Ph proton x 5), 8.64 (1H, s, H-8), and 8.67 (1H, s, H-2), being superimposable with that reported.[32]

Anal. Calcd for $C_{22}H_{25}N_5O_6 \cdot \frac{1}{4}H_2O$: C, 57.45; H, 5.59; N, 15.22. Found: C, 57.53; H, 5.59; N, 14.94.

2'-O-(Tetrahydropyran-2-yl)ation of 5f (R = Bz; cf. Entry 4 in Table 4): The reaction of 5f (R = Bz; 7.2220 g), followed by O-debenzoylation, gave the less and more polar diastereomers of N^4-anisoyl-2'-O-(tetrahydropyran-2-yl)cytidine (8f)[33] in 45% (2.707 g) and 39% (2.3420 g) yields, respectively.

The less polar isomer of 8f had m.p. 132 – 133°C (from 19:1 benzene – acetone, R_F 0.31 (Solvent A) and 0.28 (Solvent B), u.v.: λ_{max} 300 nm (shoulder), 290 nm (ε 21300), and λ_{min} 235 nm (ε 6900), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.33 – 1.83 (6H, m, C-C$\underline{H}_2$ x 3), 3.23 – 3.60 (2H, m, O-C$\underline{H}_2$), 3.66 – 3.93 (5H, m, H-5', 5'', and O-C$\underline{H}_3$), 4.00 – 4.27 (3H, m, H-2', 3', and 4'), 5.02 (1H, br. s, O-C$\underline{H}$-O), 5.83 (1H, d, $J_{1',2'}$ 1.5 Hz, H-1'), 6.95 (2H, d, J 9 Hz, Ph proton x 2), 7.33 (1H, d, $J_{5,6}$ 7 Hz, H-5), 7.93 (2H, d, J 9 Hz, Ph proton x 2), and 8.50 (1H, d, H-6).

Anal. Calcd for $C_{22}H_{27}N_3O_8$: C, 57.26; H, 5.90; N, 9.11. Found: C, 57.22; H, 5.83; N, 9.29.

The more polar isomer of 8f had m.p. 196 – 197°C (from methanol), R_F (Solvent A), u.v.: λ_{max} 288 nm (ε 23900) and λ_{min} 235 nm (ε 7400), ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.33 – 1.83 (6H, m, C-C$\underline{H}_2$ x 3), 3.33 – 4.33 (10H, m, H-2', 3', 4', 5', 5'', O-C$\underline{H}_3$, and O-C$\underline{H}_2$), 4.89 (1H, br. s, O-C$\underline{H}$-O), 6.10 (1H, d, $J_{1',2'}$ 7.5 Hz, H-1'), 6.93 (2H, d, J 9 Hz, Ph proton x 2), 7.35 (1H, d, $J_{5,6}$ 7.5 Hz, H-5), 7.93 (2H, d, J 9 Hz, Ph proton x 2), and 8.42 (1H, d, H-6).

Anal. Calcd for $C_{22}H_{27}N_3O_8$: C, 57.26; H, 5.90; N, 9.11. Found: C, 57.03; H, 5.92; N, 8.86.

2'-O-(Tetrahydropyran-2-yl)ation of 5i (R = Bz; cf. Entry 5 in Table 4): The reaction of 5i (R = Bz; 0.7581 g), followed by O-debenzoylation, gave the less and more polar diastereomers of N^2-iso-

butyryl-2'-O-(tetrahydropyran-2-yl)guanosine (8i) in 17% (0.1006 g) and 58% (0.3425 g) yields, respectively.

The less polar isomer of 8i had m.p. 201 – 202°C (from ethyl acetate), R_F 0.26 (Solvent A) and 0.10 (Solvent B), u.v.: λ_{max} 280 nm (ε 12500), 258 nm (ε 14500), λ_{min} 271 nm (ε 11600), and 226 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD – TMS): δ 1.17 – 1.31 [6H, s x 2, $C(CH_3)_2$], 1.42 – 1.77 (6H, m, C-CH_2 x 3), 2.50 – 2.93 (1H, m, $CHMe_2$), 3.30 – 3.70 (2H, m, O-CH_2), 3.77 – 3.87 (2H, m, H-5' and 5''), 4.03 – 4.17 (1H, m, H-4'), 4.33 – 4.75 (3H, m, H-2', 3', and O-CH-O), 5.93 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), and 8.08 (1H, s, H-2).

Anal. Calcd for $C_{19}H_{27}N_5O_7 \cdot \frac{1}{4}H_2O$: C, 51.64; H, 6.27; N, 15.85. Found: C, 51.89; H, 6.16; N, 15.73.

The more polar isomer of 8i had m.p. 132 – 133°C [Purified by pouring its solution in chloroform (2 mL) into hexane (30 mL) under vigorous stirring], R_F 0.20 (Solvent A) and 0.05 (Solvent B), u.v.: λ_{max} 280 nm (ε 11700), 258 nm (ε 14000), λ_{min} 271 nm (ε 11200), and 225 nm, ^{1}H-n.m.r. (DMSO-d_6 – CD_3OD –TMS): δ 1.17 and 1.28 [6H, s x 2, $C(CH_3)_2$], 1.40 – 1.80 (6H, m, O-CH_2 x 3), 2.43 – 2.97 (1H, m, $CHMe_2$), 3.27 – 3.40 (2H, m, O-CH_2), 3.77 – 3.85 (2H, m, H-5' and 5''), 4.03 – 4.23 (1H, m, H-4'), 4.47 (1H, dd, $J_{2',3'}$ 5 Hz, $J_{3',4'}$ 4 Hz, H-3'), 4.67 (1H, t, H-2'), 4.72 (1H, br. s, O-CH-O), 6.00 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), and 8.10 (1H, s, H-8).

Anal. Calcd for $C_{19}H_{27}N_5O_7$: C, 52.17; H, 6.22; N, 16.01. Found: C, 52.07; H, 6.05; N, 15.81.

Derivatization of the 3'- (7) and 2'-O-(Tetrahydropyran-2-yl)ribonucleosides (8) to the Corresponding 2',5'- (9) and 3',5'-Diacetates (10): General Procedure. Compound 7 or 8 (0.5 mmol) was treated with acetic anhydride (0.48 mL, 5 mmol) in dried pyridine (1.5 mL) according to the usual manner for acetylation; as a criterion, at room temperature for 6 h. When completion of the reactions was confirmed by t.l.c., the resulting mixture was quenched with methanol (1 mL) and evaporated. The residue was coevaporated with water and, then, with ethanol. The product thus obtained was subjected to ^{1}H-n.m.r. spectral determination.

2',5'-Di-O-acetyl-3'-O-(tetrahydropyran-2-yl)uridine (9a):

The less polar isomer of 9a had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.40 – 1.77 (6H, m, C-CH_2 x 3), 2.16 (6H, s, CH_3CO x 2), 3.53 – 3.73 (2H, m, O-CH_2), 4.17 – 4.50 (4H, m, H-3', 4', 5', and 5''), 4.68 (1H, br. s,

O-CH-O), 5.30 (1H, t, H-2'), 5.72 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.89 (1H, d, $J_{1',2'}$ 4.5 Hz, H-1'), and 7.37 (1H, d, H-6).

The more polar isomer of 9a had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.40 – 1.70 (6H, m, C-CH_2 x 3), 2.12 (6H, s, CH_3CO x 2), 3.50 – 3.73 (2H, m, O-CH_2), 4.25 – 4.47 (4H, m, H-3', 4', 5', and 5''), 4.58 (1H, br. s, O-CH-O), 5.28 (1H, dd, $J_{1',2'}$ 3.5 Hz, $J_{2',3'}$ 1 Hz, H-2'), 5.72 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.97 (1H, d, H-1'), and 7.43 (1H, d, H-6).

2',5'-Di-O-acetyl-3'-O-(tetrahydropyran-2-yl)adenosine (9b):

The less polar isomer of 9b had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.40 – 1.87 (6H, m, C-CH_2 x 3), 2.07 and 2.17 (6H, s x 2, CH_3CO x 2), 3.50 – 3.90 (2H, m, O-CH_2), 4.30 – 4.57 (3H, m, H-4', 5', and 5''), 4.67 – 4.93 (2H, m, H-3' and O-CH-O), 5.88 (1H, dd, $J_{1',2'}$ 4 Hz, $J_{2',3'}$ 5 Hz, H-2'), 6.10 (1H, d, H-1'), 6.37 (2H, br. s, NH_2), 7.88 (1H, s, H-8), and 8.25 (1H, s, H-2).

The more polar isomer of 9b had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.33 – 1.75 (6H, m, C-CH_2 x 3), 2.07 and 2.12 (6H, s x 2, CH_3CO x 2), 3.53 – 3.80 (2H, m, O-CH_2), 4.17 – 4.83 (5H, m, H-3', 4', 5', 5'', and O-CH-O), 5.75 (1H, dd, $J_{1',2'}$ 3.5 Hz, $J_{2',3'}$ 5 Hz, H-2'), 6.13 (1H, d, H-1'), 6.37 (2H, br. s, NH_2), 7.92 (1H, s, H-8), and 7.88 (1H, s, H-2).

2',5'-Di-O-acetyl-N^4-anisoyl-3'-O-(tetrahydropyran-2-yl)cytidine (9f):

The less polar isomer of 9e had ^{1}H-n.m.r. ($CDCl_3$ –TMS): δ 1.37 – 1.73 (6H, m, C-CH_2 x 3), 2.13 (6H, s, CH_3CO x 2), 3.40 – 3.57 (2H, m, O-CH_2), 3.83 (3H, s, O-CH_3), 4.27 – 4.40 (4H, m, H-3', 4', 5', and 5''), 4.63 (1H, br. s, O-CH-O), 5.47 (1H, t, H-2'), 5.95 (1H, d, $J_{1',2'}$ 3 Hz, H-1'), 6.88 (2H, d, J 9 Hz, Ph proton x 2), 7.41 (1H, d, $J_{5,6}$ 7 Hz, H-5), 7.83 (2H, d, J 9 Hz, Ph proton x 2), and 7.88 (1H, d, H-6).

The more polar isomer of 9e had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.33 – 1.67 (6H, m, C-CH_2 x 3), 2.12 (6H, s, CH_3CO x 2), 3.47 – 3.73 (2H, m, O-CH_2), 3.83 (3H, s, O-CH_3), 4.17 – 4.63 (5H, m, H-3', 4', 5', 5'', and O-CH-O), 5.37 – 5.47 (1H, m, H-2'), 6.02 (1H, d, $J_{1',2'}$ 2 Hz, H-1'), 6.90 (2H, d, J 9 Hz, Ph proton x 2), 7.43 (1H, d, $J_{5,6}$ 8 Hz, H-5) 7.85 (2H, d, J 9 Hz, Ph proton x 2), and 7.98 (1H, d, H-6).

2',5'-Di-O-acetyl-N^2-isobutyryl-3'-O-(tetrahydropyran-2-yl)guanosine (9i):

The less polar isomer of 9i had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.18 and 1.28 [6H, s x 2, $C(CH_3)_2$], 1.37 – 1.87 (6H, m, C-CH_2 x 3), 2.07 and 2.10 (6H, CH_3CO x 2), 2.67 – 2.97 (1H, m, $CHMe_2$), 3.47 – 3.80 (2H, m, O-CH_2), 4.07 – 4.80 (5H, m, H-3', 4', 5', 5'', and O-CH-O), 5.71 (1H, t, H-2'), 5.97 (1H, d, $J_{1',2'}$ 4.5 Hz, H-1'), and 7.85 (1H, s, H-8).

The more polar isomer of 9i had ^{1}H-n.m.r. ($CDCl_3$ – TMS): 1.17 and 1.27 [6H, s x 2, $C(CH_3)_2$], 1.37 – 1.73 (6H, m, C-CH_2 x 3), 2.03 and 2.07 (6H, s x 2, CH_3CO x 2), 2.58 – 2.95 (1H, m, $CHMe_2$), 3.47 – 3.77 (2H, m, O-CH_2), 4.13 – 4.70 (5H, m, H-3', 4', 5', 5'', and O-CH-O), 5.66 (1H, dd, $J_{1',2'}$ 3.5 Hz, $J_{2',3'}$ 4.5 Hz, H-2'), 5.97 (1H, d, H-1'), and 7.79 (1H, s, H-8).

3',5'-Di-O-acetyl-2'-O-(tetrahydropyran-2-yl)uridine (10a):

The less polar isomer of 10a had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.35 – 1.77 (6H, m, C-CH_2 x 3), 2.12 (6H, s, CH_3CO x 2), 3.38 – 3.70 (2H, m, O-CH_2), 4.28 – 4.38 (3H, m, H-4', 5', and 5''), 4.45 (1H, dd, $J_{1',2'}$ 4 Hz, $J_{2',3'}$ 5.5 Hz, H-2'), 4.80 (1H, br. s, O-CH-O), 4.95 – 5.17 (1H, m, H-3'), 5.72 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.92 (1H, d, H-1'), and 7.48 (1H, d, H-6).

The more polar isomer of 10a had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.35 – 1.70 (6H, m, C-CH_2 x 3), 2.10 (6H, s, CH_3CO x 2), 3.38 – 3.67 (2H, m, O-CH_2), 4.28 – 4.48 (4H, m, H-2', 4', 5', and 5''), 4.55 (1H, br. s, O-CH-O), 5.07 – 5.27 (1H, m, H-3'), 5.70 (1H, d, $J_{5,6}$ 8 Hz, H-5), 5.92 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), and 7.32 (1H, d, H-6).

3',5'-Di-O-acetyl-2'-O-(tetrahydropyran-2-yl)adenosine (10b):

The less polar isomer of 10b had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.31 – 1.68 (6H, m, C-CH_2 x 3), 2.10 and 2.15 (6H, s x 2, CH_3CO x 2), 3.27 – 3.70 (2H, m, O-CH_2), 4.35 – 4.47 (3H, m, H-4', 5', and 5''), 4.60 (1H, br. s, O-CH-O), 5.07 (1H, t, H-2'), 5.30 – 5.47 (1H, m, H-3'), 6.10 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), 6.60 (2H, br. s, NH_2), 7.94 (1H, s, H-8), and 8.23 (1H, s, H-2).

The more polar isomer of 10b had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.27 – 1.67 (6H, m, C-CH_2 x 3), 2.08 and 2.15 (6H, s x 2, CH_3CO x 2), 3.05 – 3.23 (2H, m, O-CH_2), 4.33 – 4.48 (3H, m, H-4', 5', and 5''), 4.57 (1H, br. s, O-CH-O), 5.07 (1H, t, H-2'), 5.45 (1H, dd, $J_{2',3'}$ 6 Hz, $J_{3',4'}$ 3 Hz, H-3'), 6.10 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), 6.68 (2H, br. s, NH_2), 7.92 (1H, s, H-8), and 8.27 (1H, s, H-2).

3',5'-Di-O-acetyl-N^4-anisoyl-2'-O-(tetrahydropyran-2-yl)cytidine (10f):

The less polar isomer of 10f had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.23 – 1.70 (6H, m, C-CH_2 x 3), 2.09 (6H, sm CH_3CO x 2), 3.23 – 3.47 (2H, m, O-CH_2), 3.83 (3H, s, O-CH_3), 4.23 – 4.70 (5H, m, H-2', 4', 5', 5". and O-CH-O), 5.10 – 5.27 (1H, m, H-3'), 6.00 (1H, d, $J_{1',2'}$ 4.5 Hz, H-1'), 6.87 (2H, d, J 9 Hz, Ph proton x 2), 7.37 (1H, d, $J_{5,6}$ 7.5 Hz, H-5), 7.80 (1H, d, H-6), and 7.85 (2H, d, J 9 Hz, Ph proton x 2).

The more polar isomer of 10f had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.20 – 1.70 (6H, m, C-CH_2 x 3), 2.08 and 2.13 (6H, s x 2, CH_3CO x 2), 3.40 – 3.52 (2H, m, O-CH_2), 3.80 (3H, s, O-CH_3), 4.27 – 4.63 (4H, m, H-2', 4', 5', and 5"), 4.83 – 5.07 (2H, m, H-3' and O-CH-O), 5.90 (1H, d, $J_{1',2'}$ 1.5 Hz, H-1'), 6.88 (2H, d, J 8.5 Hz, Ph proton x 2), 7.48 (2H, d, $J_{5,6}$ 7.5 Hz, H-5), 7.88 (2H, d, J 8.5 Hz, Ph proton x 2), and 8.05 (1H, d, H-6).

3',5'-Di-O-acetyl-N^2-isobutyryl-2'-O-(tetrahydropyran-2-yl)guanosine (10i):

The less polar isomer of 10i had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.18 and 1.28 [6H, s x 2, $C(CH_3)_2$], 1.43 – 1.67 (6H, m, C-CH_2 x 3), 2.06 and 2.14 (6H, s x 2, CH_3CO x 2), 2.58 – 3.00 (1H, m, $CHMe_2$), 3.40 – 3.67 (2H, m, O-CH_2), 4.33 – 4.50 (3H, m, H-4', 5', and 5"), 4.60 (1H, br. s, O-CH-O), 4.97 (1H, t, H-2'), 5.27 – 5.43 (1H, m, H-3'), 5.88 (1H, d, $J_{1',2'}$ 5 Hz, H-1'), and 7.79 (1H, s, H-8).

The more polar isomer of 10i had ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.18 and 1.28 ([6H, s x 2, $C(CH_3)_2$], 1.36 – 1.67 (6H, m, C-CH_2 x 3), 2.07 and 2.12 (6H, s x 2, CH_3CO x 2), 2.58 – 3.00 (1H, m, $CHMe_2$), 3.03 – 3.30 (2H, m, O-CH_2), 4.33 – 4.50 (3H, m, H-4', 5', and 5"), 4.57 (1H, br. s, O-CH-O), 4.97 (1H, t, H-2'), 5.27 – 5.43 (1H, m, H-3'), 5.88 (1H, d, $J_{1',2'}$ 6 Hz, H-1'), and 7.80 (1H, s, H-8).

This paper is dedicated to Professor Morio Ikehara for the occasion of his retirement from Osaka University in March, 1986.

ACKNOWLEDGEMENT

The authors thank Mrs. N. Hasegawa, Department of Chemistry, Tokyo Institute of Technology, for the elemental analyses, and Ministry of Education, the Japanese Government, for Scientific Grant-in-aid (No. 5943006 and 61111004).

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Received September 1, 1986.