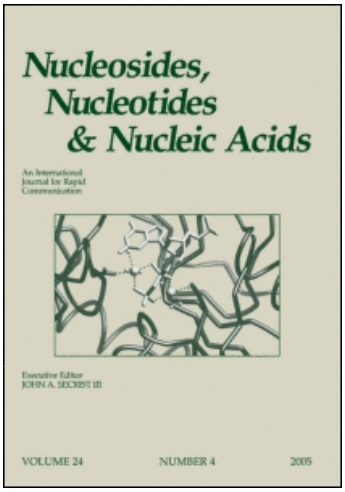

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Synthesis of Fused Cyclopropane-Containing Nucleosides by [1,2]-Hydride Shift Rearrangements and B-Elimination Reactions of Sulfonylated Ribonucleosides

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SYNTHESIS OF FUSED CYCLOPROPANE-CONTAINING NUCLEOSIDES BY [1,2]-HYDRIDE SHIFT REARRANGEMENTS AND β-ELIMINATION REACTIONS OF SULFONYLATED RIBONUCLEOSIDES*

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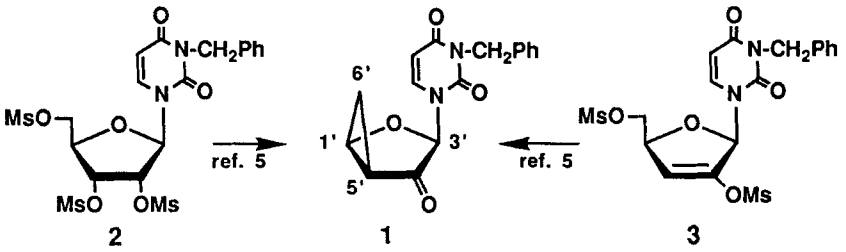
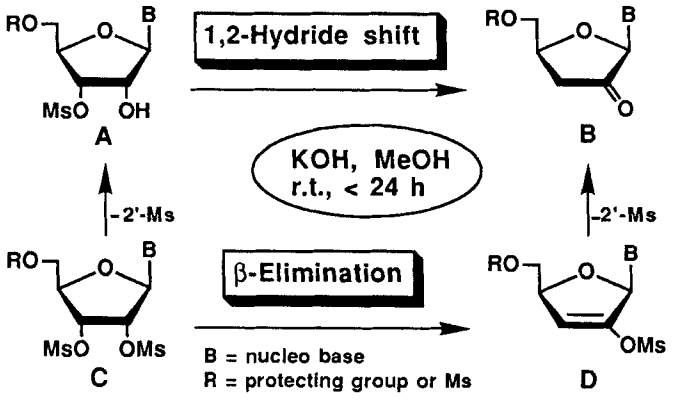
ABSTRACT. (1'R, 3'S and R, 5'S)-4'-Oxo-2'-oxabicyclo[3.1.0]hexan-3'-yl pyrimidines and purines were synthesized from ribonucleosides in 2-5 steps. The configurations of the base moieties in the cyclopropano keto-nucleosides were determined by NOE difference spectroscopy.

The chemistry of naturally occurring and synthetic cyclopropane derivatives are extensively studied, since the cyclopropanes possess unique structures and properties.[1,2] Therefore, compounds that contain the cyclopropane ring conjugated to a reactive carbonyl functions are attractive synthetic targets from chemical[3] and biological[4] viewpoints. Several kinds of cyclopropane-containing nucleosides which were modified in a sugar[5-10] or a base[11-14] moiety have been reported in the field of nucleoside chemistry. In 1973, Sasaki and his co-workers[5] have synthesized for the first time an intriguing uracil nucleoside having a cyclopropane ring fused to a 2'-keto-furanosyl ring at C-3' and 4' (SCHEME 1). They treated N^3-benzylated 2',3',5'-tri-O-mesyl or 3'-deoxy-2',5'-di-O-mesyl-2'-enofuranosyluridine (**2** or **3**) with potassium carbonate in N,N-dimethylformamide (DMF) or DMF-acetone to obtain the N^3-benzylated 4'-oxo-2'-oxabicyclo[3.1.0]hexan-3'-yluracil (**1**) in 6 or

* Dedicated to the memory of the late Professor Tohru Ueda.



SCHEME 1



SCHEME 2

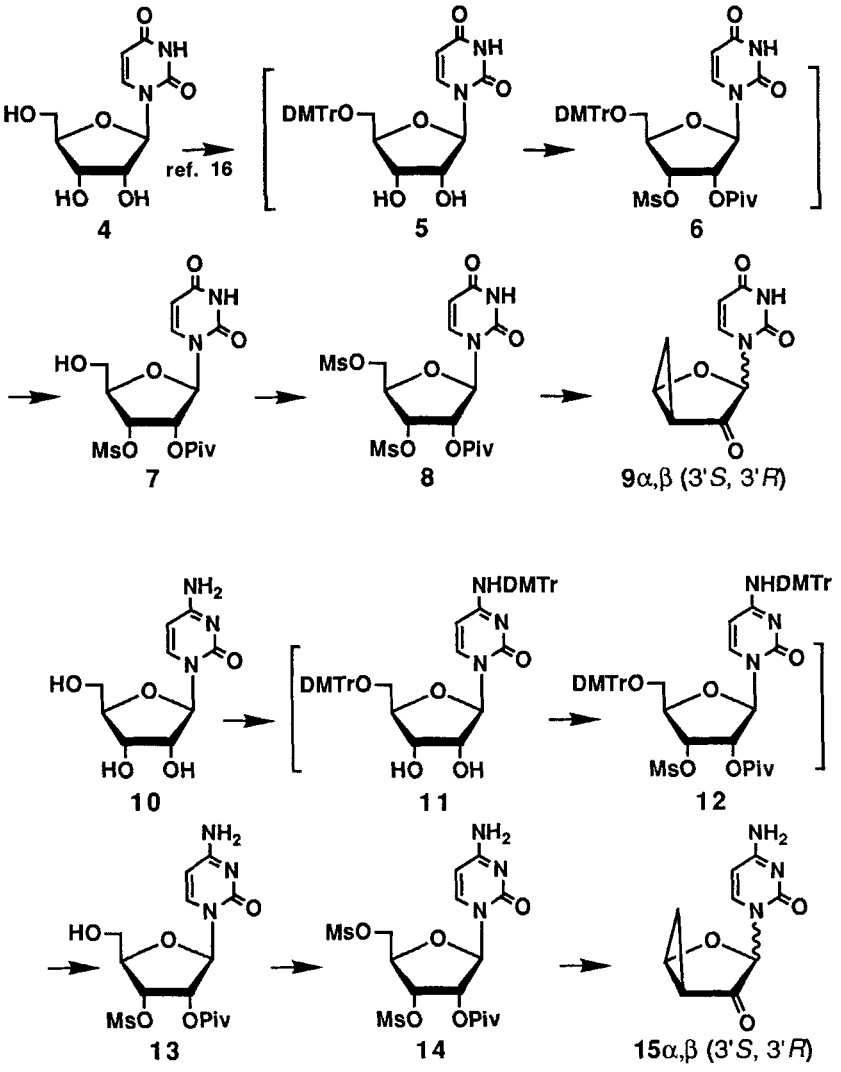
40% yield, respectively. N^3-Benzyl protection was necessary in their reaction sequences to avoid an undesirable intramolecular participation of the uracil carbonyl group (at C-2) to the C-2' bearing the mesyloxy group. They have pointed out that an appropriate protecting group for the N^3 other than the stable benzyl group would be developed in the future in order to obtain a free nucleoside of **1**.

In the course of our work on synthetic utility of a [1,2]-hydride shift rearrangement,[15] we found an efficient method for synthesizing free cyclopropano keto-nucleosides without the final deprotection step. Sasaki et al.[5] have presumed that an important intermediate for the synthesis of **1** would be an *in situ* generated N^3-benzyl-3'-deoxy-2'-keto uracil derivative from **2** or **3**. Our synthetic approach to the key intermediate is shown in SCHEME 2. When a 3'-mesylated ribonucleoside

(**A**) was treated with potassium hydroxide (KOH) in a methanolic solution, a 3'-deoxy-2'-keto nucleoside (**B**) was found to be formed by the [1,2]-hydride shift rearrangement, where the hydrogen atom on C-2' was stereoselectively transferred to the neighboring C-3' with the elimination of the mesyloxy group.[15,16] Under similar conditions a 2',3'-di-O-mesyl purine nucleoside (**C**) also afforded **B** through an enol mesylate (**D**) by the β-elimination.[5,17,18] We have found that the 2'-mesyloxy group of **C** was susceptible to methanolysis under alkaline conditions, giving **A**, which was, in turn, converted into **B**.[17] Therefore, if a compound (**A** or **C**), which has a mesyl group at the C-5' (R=Ms), is treated with KOH in a methanolic solution, the resulting **B** (R=Ms) that corresponds to the anticipated intermediate proposed by Sasaki et al. will give rise to the expected cyclopropano keto-nucleoside.

RESULTS AND DISCUSSION

In a pyrimidine series (SCHEME 3), uridine (**4**) was protected with bis(4-methoxyphenyl)chlorophenylmethane ("4,4'-dimethoxytrityl chloride", DMTrCl) at its 5'-OH group to give 5'-O-(4,4'-dimethoxytrityl)uridine (**5**).[19] Introduction of a mesyl group to the 3'-OH function of **5** was performed by our method,[16] which consisted of consecutive reactions of regioselective pivaloylation[20] and mesylation in a one-pot manner. The resulting 3'-mesyl-2'-pivaloyl derivative (**6**) was, without purification, detritylated with an acid to give 3'-O-mesyl-2'-O-pivaloyluridine (**7**) in 58% overall yield from **4**. The structure of **7** was fully characterized on the basis of its elemental analysis and spectral data (UV and ^{1}H-NMR). Mesylation of **7** provided a 3',5'-di-O-mesyl derivative (**8**) in 94% yield. This product was subjected to the deoxygenative [1,2]-hydride shift rearrangement followed by cyclopropanation in a one-flask reaction. Thus **8** was treated with KOH (10 mol equiv.) in a mixture of MeOH and tetrahydrofuran (THF) at room temperature for 21 h to produce an anomeric mixture of 1-[(1R,3S,5S)- and (1R,3R,5S)-4-Oxo-2-oxabicyclo[3.1.0]hexan-3-yl]uracil [**9α** (3'S) and **9β** (3'R), 94:6] in 58% combined yield after chromatography. The analytically pure α-anomer of **9** could be isolated as crystals, but attempts to obtain its pure β-anomer were unsuccessful.



SCHEME 3

In a similar way, 3',5'-di-O-mesyl-2'-O-pivaloylcytidine (**14**) was synthesized starting from cytidine (**10**) according to a reaction sequence shown in SCHEME 3. A 5'-OH free nucleoside (**13**) was obtained in 27% overall yield from **10** without purification of intermediates (**11** and **12**). Careful mesylation of **13** gave **14** in 74% yield. Upon treatment of **14** with KOH in a methanolic solution, an anomeric mixture of cyclopropano

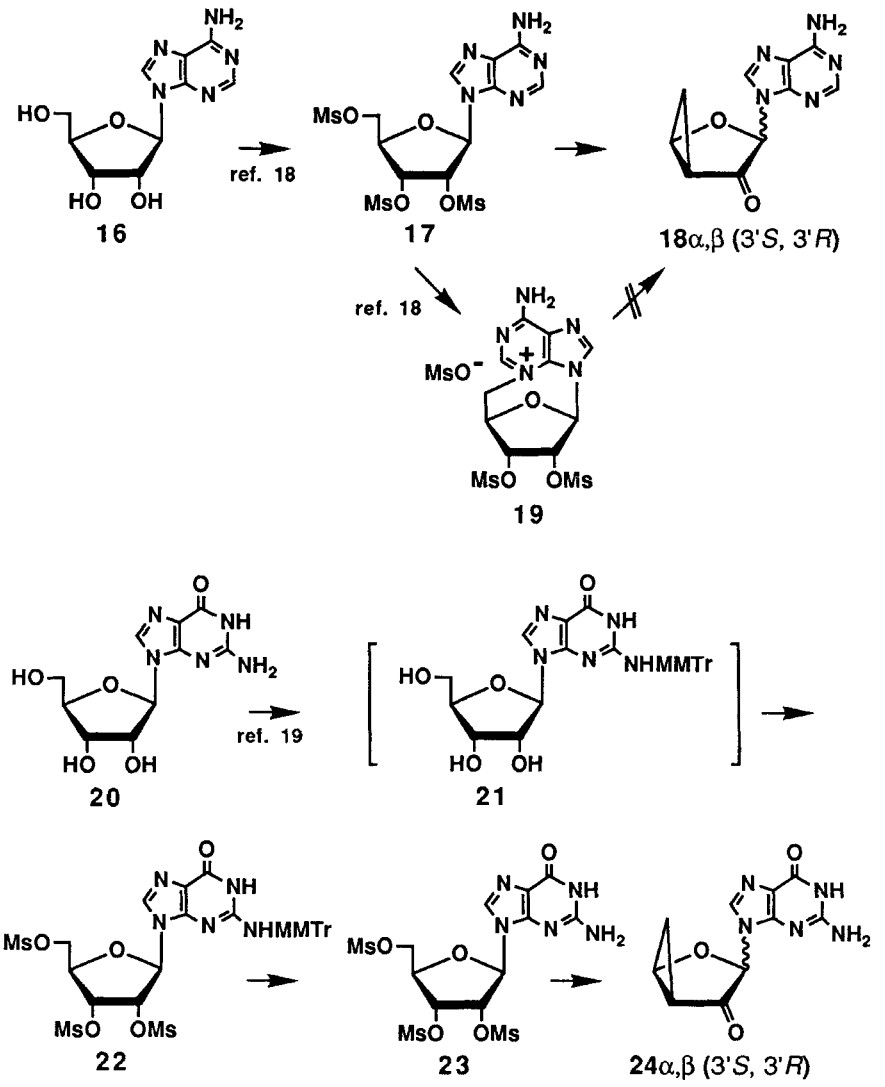
keto-cytosine (**15α** and **15β**, 9:1) could be obtained in 59% combined yield. Here again the α-anomer was isolated as crystals and its structure was fully characterized as described later.

In a purine series (SCHEME 4), the method for the synthesis of the cyclopropano nucleosides was straightforward and simple to use, because no protection at the 2'-positions of the ribonucleosides was required (**C** → **B**, SCHEME 2). In particular, adenosine (**16**) was converted, in a two-step reaction, into cyclopropano keto-nucleosides (**18α** and **18β**, 85:15) by the reaction of a trimesylated adenosine (**17**)[21] with KOH (5 mol equiv.) at room temperature for 1.5 h in 69% overall yield. In this case, we could not isolate neither pure α- nor β-anomer. However, recrystallization of the solid mixture from EtOH gave analytically pure mixtures of 51:49 and 93:7 of **18α** and **18β**. The solubility of the former mixture in EtOH was less than that of the latter.

In a route for the synthesis of a trimesylated guanosine (**23**), $\underline{N}^2$-protection of guanosine (**20**) with "4-monomethoxytrityl chloride" (MMTrCl) was required. When the protected guanosine (**21**)[22] was mesylated by a conventional method, overmesylation[23] at the guanine base occurred to some extent, but brief treatment of the permesylated nucleoside with KOH gave **22** in 55% overall yield from **20**. Final cyclopropanation of a deprotected trimesylate (**23**) proceeded very nicely under conditions analogous to those for the synthesis of **18**. A crude mixture of **24α** and **24β** (86:14, 89%) was precipitated out from the reaction mixture. However, attempts to obtain an analytically pure sample of **24α** or **24β** were unsuccessful, because of their extremely low solubility[24] in water and common organic solvents except for dimethyl sulfoxide (DMSO) and DMF.

Finally, we examined if there was some possibility that the cyclopropanation of **17** would undergo through $\underline{N}^3$,5'-cyclonucleosides, which were known to be easily formed from 5'-sulfonylated nucleosides of pentofuranosides.[25] The trimesylate **17** was converted into its $\underline{N}^3$,5'-cycloadenosine (**19**)[21] according to the method reported earlier. Treatment of **19** under the present conditions for the cyclopropanation gave no formation of **18** at all.

The structures of the newly synthesized cyclopropano keto-nucleosides were established on the basis of their analytical and/or spectroscopic data. The ^{1}H-NMR spectra (TABLE 1) of the all compounds



SCHEME 4

showed five signals [H-1', 3', 5', 6'a (exo), and 6'b (endo)] characteristic to the 4-oxo-2-oxabicyclo[3.1.0]hexyl system,[5] together with signals due to the base protons. Clear differences in chemical shifts by the deshielding effect of the base moiety between the α- and β-anomers in a pair of the nucleoside were observed: (1) the signal due to H-1' of the α-anomers appeared at a field lower by ca. 0.2 ppm than

TABLE 1. ^{1}H-NMR [DMSO-d_6, δ (J, Hz)] of the cyclopropano nucleosides[a]

Compd.	H-1' (m)	H-3' (s)	H-5' (ddd)	H-6'a (ddd)	H-6'b (m)	H-2(s) H-5(d)	H-6(d) H-8(s)	NH NH_2
9α	4.80	5.55 (br)	2.19 (4.1, 4.5, 10.5)	1.36 (4.5, 4.9, 10.5)	1.62	5.63 (dd) (1.9, 7.9)	7.55 (7.9)	11.5 (s)
9β	4.60	5.70	2.25 (dddd) (1.1, 4.5, 4.5, 10.4)	1.41 (4.8, 4.8, 11.2)	2.11	5.65 (7.9)	7.60 (7.8)	11.5 (br s)
15α	4.68 (br s)	5.28	2.15 (4.6, 4.6, 10.7)	1.27 (5.3, 5.3, 10.4)	1.43 (br s)	5.70 (7.3)	7.46 (7.3)	7.35 (d) (5.9)
15β	4.51 (ddd) (2.4, 2.4, 4.4)	5.48	2.14 (m)	1.31 (4.4, 4.4, 11.1)	2.32 (ddd) (2.0, 2.0, 4.4)	5.72 (7.5)	7.51 (7.5)	7.38 (br d) (6)
18α	4.97 (br s)	6.16 (4.3, 4.3, 10.7)	2.38	1.50 (4.9, 6.1, 10.7)	1.94	8.12	8.18	7.31 (s)
18β	4.75	6.35 (1.1, 4.3, 4.6, 11.6)	2.43 (dddd)	1.57 (4.9, 5.6, 11.3)	2.73	8.13	8.20	7.36 (s)
24α	4.91	5.92 (4.4, 4.4, 10.6)	2.30	1.48 (4.8, 5.9, 10.6)	1.88	7.68 (s, H-8)	6.48 (br s, NH_2)	10.8 (br s)
24β	4.69	6.14	2.37 (m)	1.48 (m)	2.60	7.70 (s, H-8)	6.51 (br s, NH_2)	10.7 (br s)

a) The numbering of the bicyclo[3.1.0] system was adopted.

TABLE 2. NOE difference spectral data (%)[a] for the cyclopropno keto-nucleosides

Irradiated protons	Observed protons	9α	9β	15α	15β	18α	18β	24α	24β
H-1'	H-3'	0	2	0	1	*	3	0	2
	H-8	-	-	-	-	0	0	1	0
H-3'	H-1'	*	3	0	2	0	2	0	2
	H-5'	*	0	0	0	0	0	0	0
	H-6'a	5	0	4	0	5	0	3	0
H-5'	H-3'	0	1	0	0	*	2	*	0
	H-8	-	-	-	-	*	0	*	0
H-6'b	H-3'	11	*	7	0	11	0	13	0
	H-6	0	2	0	0	-	-	-	-
	H-8	-	-	-	-	0	4	0	3

a) Measured in DMSO-d_6 (ca. 0.06M solution) at 27 °C. * 0.5-0.8% enhancement.

that for the β-anomers, this phenomenon being observed in the case of 3'-deoxy-2'-keto nucleosides;[26] (2) the signal attributable to H-6'b (endo) of the β-anomers revealed at a field lower by ca. 0.7 ppm than that of the α-anomers. The shielding effect responsible for the cyclopropane ring was also observed: the signal due to H-3' of the α-anomers resonated at a field higher by ca. 0.2 ppm than that for the β-anomers. Spin-spin decoupling experiments indicated that H-5' in **9β** or **18β** was coupled to the respective H-3' (J=1.1 Hz) because of their W-shaped arrangement,[27] although the signal due to the H-3' was observed as a slightly broad singlet.

It has been demonstrated that nuclear Overhauser effect (NOE) difference spectroscopy is extremely useful for determining the anomeric configurations of nucleosides.[28] In our case, the unambiguous assignment of configuration of the cyclopropano derivatives could be accomplished by means of their NOEs (TABLE 2). Some of the data are

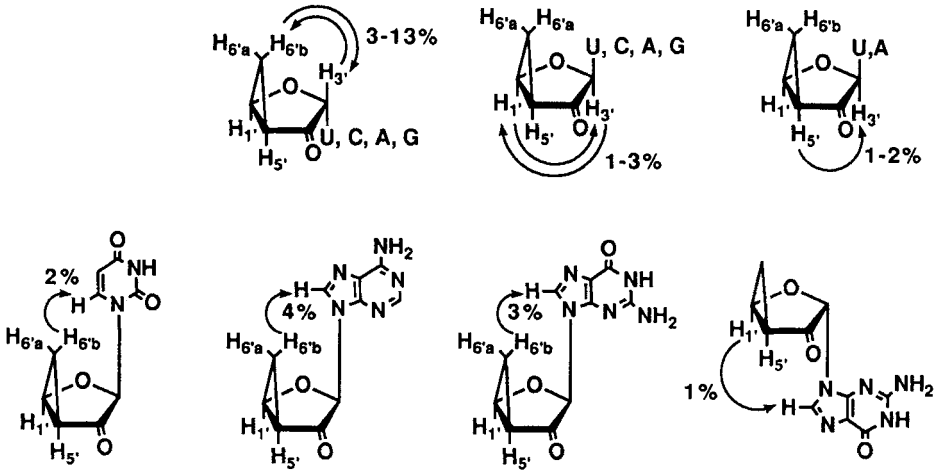


FIGURE 1

depicted as in FIGURE 1. Great enhancement (7-13%) of H-3' in all the α-anomers upon irradiation of the respective H-6'b (endo) was consistent with the assigned configurations.

Other spectral data (IR and UV, see Experimental Section) were compatible with the proposed structures of the fused cyclopropano keto-nucleosides.

The investigation of scope and limitation of our cyclopropanation as well as the biological evaluation of the prepared cyclopropano-keto nucleosides are now in progress and will be reported elsewhere.

EXPERIMENTAL SECTION

Melting points were determined with a Yamato micro melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241MC polarimeter. IR spectra were obtained with a Shimadzu FTIR-8100M spectrophotometer, and UV spectra were recorded using a Varian Cary 2200 instrument. ^{1}H-NMR and NOE difference spectra were obtained on JEOL JNM-GX 400 and 500 spectrometers, respectively, using Me_4Si as the internal standard. High resolution mass spectra were measured with a JEOL SX-102 spectrometer. Analytical HPTLC plates (Silica Gel 60, F_{254}) and silica gel (Silica Gel 60, 70-230 mesh) were purchased from Merck. A neutral silica gel (SilicAR, 100-200 mesh) was

purchased from Mallinckrodt. Detection of TLC was done by UV (254 nm) or spraying the plates with a solution of MeOH-sulfuric acid-p-anisaldehyde (85:15:5, v/v/v), followed by heating them on an electric plate. Elemental analyses were performed by the Microanalytical Laboratory of this Institute. Analytical samples were dried in vacuo over phosphorus pentaoxide (P_2O_5) for 4 h at 60 °C, except that the cyclopropano nucleosides were dried at room temperature. All ribonucleosides, DMTrCl, and MMTrCl were purchased from Dojin Chemical Co. (Japan), and used without purification. Reagent quality solvents were dried over molecular sieves 4A and used without further purification.

3'-O-Mesyl-2'-O-pivaloyluridine (7). To a solution of **4** (4.88 g, 20 mmol) in dry pyridine (80 ml) was added DMTrCl (7.12 g, 21 mmol) at room temperature, after which the mixture was stirred at this temperature for 17 h. After the mixture had been cooled to 5 °C, pivaloyl chloride (3.71 ml, 30 mmol) was added, and the mixture was stirred at this temperature for 20 min. Mesyl chloride (6.2 ml, 80 mmol) was then added, and the mixture was stirred at room temperature for 1.8 h. After the mixture had been cooled, 50% aq. pyridine (5 ml) was added followed by addition of iced water (50 ml). The mixture was extracted with Et_2O (400 ml) and the extract was washed successively with H_2O, aq. $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated. The pyridine was removed by repeated co-evaporation with toluene. The residue was dissolved in CH_2Cl_2 and the solution was concentrated to dryness to give crude **6** (15.6 g) as a foam.

To a stirred solution of a portion (7.8 g) of this foam in $CHCl_3$ (95 ml) was added a solution of p-toluenesulfonic acid monohydrate (2.85 g, 15 mmol) in MeOH (10 ml) at room temperature. The mixture was allowed to stand at this temperature for 1 h, after which time it was washed with H_2O (50 ml). The organic layer was dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column with $CHCl_3$-MeOH (97:3 → 95:5) to give **7** (2.37 g, 58% from **4**). An analytically pure sample was prepared by precipitation from CH_2Cl_2-n-pentane:[17] amorphous powder; $[\alpha]^{25}$ (589 nm) +15.7° (c=1.05, DMSO); UV λ_{max} (MeOH) (ε 11000); ^{1}H-NMR (DMSO-d_6) δ 1.15 (9H, s, t-Bu), 3.27 (3H, s, SMe), 3.71 (2H, dd, J=3.2 and 4.7 Hz, H-5' and 5''), 4.31 (1H, dd, J=3.0 and 5.6 Hz, H-4'), 5.25 (1H, dd, J=2.8 and 5.6 Hz, H-3'), 5.40 (1H, dt, J=5.6

and 6.7 Hz, H-2'), 5.46 (1H, t, J=4.8 Hz, OH), 5.72 (1H, dd, J=2.1 and 7.8 Hz, H-5), 6.00 (1H, d, J=6.7 Hz, H-1'), and 7.89 (1H, d, J=7.8 Hz, H-6).

Anal. Calcd. for $C_{15}H_{22}N_2O_9S \cdot 0.3C_5H_{12}$ (428.1): C, 46.30; H, 6.03; N, 6.54; S, 7.49. Found: C, 46.58; H, 5.78; N, 6.77; S, 7.46.

3',5'-Di-O-mesyl-2'-O-pivaloyluridine (**8**). The mesylate **7** (2.2 g, 5.4 mmol) was dried by co-evaporation with CH_2Cl_2-toluene to remove traces of H_2O, after which it was dissolved in dry pyridine (20 ml). To this solution was added MsCl (0.51 ml, 6.5 mmol) at room temperature and the mixture was stirred at room temperature for 70 min. After the mixture had been cooled, the reaction was quenched with iced water, and it was extracted with Et_2O-$CHCl_3$ (8:2). The extract was washed twice with a small amount of water, and evaporated. The pyridine was removed by repeated co-evaporation with toluene to give almost pure **8** (2.45 g, 94%) as amorphous solids. An analytically pure sample was obtained by crystallization from MeOH: mp 168-169 °C; $[\alpha]^{25}$ (589 nm) +20.6° (c=1.12, DMSO); UV λ_{max} (MeOH) 257 nm (ε 10100); ^{1}H-NMR (DMSO-d_6) δ 1.17 (9H, s, t-Bu), 3.27 and 3.33 (6H, each s, 2 x SMe), 4.48-4.58 (3H, m, H-4', 5', and 5''), 5.31 (1H, dd, J=4.9 and 6.0 Hz, H-3'), 5.49 (1H, t, J=5.8 Hz, H-2'), 5.72 (1H, dd, J=2.1 and 8.2 Hz, H-5), 5.92 (1H, d, J=5.2 Hz, H-1'), 7.72 (1H, d, J=8.2 Hz, H-6), and 11.5 (1H, s, NH).

Anal. Calcd. for $C_{16}H_{24}N_2O_{11}S_2$ (484.5): C, 39.67; H, 4.99; N, 5.79; S 13.23. Found: C 39.69,; H, 5.03; N, 5.81; S, 13.26.

1-[(1R,3S,5S)- and (1R,3R,5S)-4-Oxo-2-oxabicyclo[3.1.0]hexan-3-yl]uracil (**9α** and **9β**). To a stirred solution of **8** (484 mg, 1 mmol) in a mixture of MeOH (4 ml) and THF (6 ml) was added a solution of KOH (560 mg, 10 mmol) in MeOH (4 ml) at 0-5 °C, after which the mixture was stirred at room temperature for 21 h. After the mixture had been cooled to 5 °C, it was neutralized to pH ca. 8 with a mixture of concd. HCl-MeOH (1:4, v/v). The precipitates were filtered and washed with cold MeOH (10 ml). The combined filtrate and washings were concentrated to 2-3 ml at 20-25 °C under reduced pressure. The residue was chromatographed on a neutral silica gel column with $CHCl_3$-MeOH (95:5) to afford a mixture (94:6, 58%) of **9α** and **9β** as solids. An analytically pure, crystalline **9α** was obtained from MeOH: mp 194-195 °C; $[\alpha]^{26}$ (589) -5.1, (578) -9.2, (546) -21.6, (435) -169, (365 nm) -803° (c=0.68,

DMSO); IR (KBr) 1748 cm^{-1} (C=O at 4'-position); UV λ_{max} (MeOH) 257 nm (ε 10200); ^{1}H-NMR (see TABLES 1 and 2).

Anal. Calcd. for $C_9H_8N_2O_4$ (208.2): C, 51.93; H, 3.87; N, 13.46. Found: C, 51.93; H, 3.85; N, 13.61.

3'-O-Mesyl-2'-O-pivaloylcytidine (13). To a solution of **10** (14.6 g, 60 mmol) in dry DMSO (180 ml) was added dry pyridine (90 ml), immediately after which DMTrCl (42.7 g, 126 mmol) was added. The mixture was stirred at room temperature for 45 h. After the mixture had been cooled to 5 °C, the reaction was quenched with 50% aq. pyridine (12 ml), and extracted with $CHCl_3$. The extract was washed successively with H_2O, aq. $NaHCO_3$, and H_2O (three times), dried ($MgSO_4$), and evaporated. The pyridine was removed by repeated co-evaporation with toluene. The residue (62.5 g) containing **11** was dissolved in dry pyridine (300 ml). To this stirred solution was added pivaloyl chloride (22 ml, 180 mmol) at 0-5 °C, after which the mixture was stirred at this temperature for 30 min. Mesyl chloride (18.5 ml, 240 mmol) was then added, and the mixture was stirred first at 0-5 °C for 1 hr and then at room temperature for 4 h. After the mixture had been cooled, the reaction was carefully quenched with 50% aq. pyridine (11 ml). The mixture was extracted with a mixture of Et_2O and $CHCl_3$ (8:2), and the extract was washed successively with H_2O, aq. $NaHCO_3$, and H_2O (three times), dried ($MgSO_4$), and evaporated. The pyridine was removed by repeated co-evaporation with toluene to give an amorphous solid (73.3 g) containing **12**.

A portion (6.0 g) of this solid was dissolved in acetic acid (32 ml) at 60-65 °C (bath temperature) under stirring. To this solution was added H_2O (15 ml), and the stirring was continued at this temperature for 45 min. The mixture was concentrated, and the acetic acid was removed by co-evaporation with a mixture of EtOH and H_2O. The resulting syrup was dissolved in MeOH (10 ml), and the solution was poured into a stirred mixture of Et_2O (80 ml) and n-hexane (20 ml). The mixture was allowed to stand at room temperature overnight. The resulting syrupy product was separated by decantation, and triturated with a mixture of Et_2O (40 ml) and n-hexane (40 ml) to give a solid, which was collected by filtration. The solid products were chromatographed on a silica gel column with $CHCl_3$-MeOH (9:1) to give **13** (541 mg, 27% from **10**) as a foam. An analytically pure sample was obtained by precipitation from CH_2Cl_2-n-

pentane: amorphous powder; $[\alpha]^{25}$ (589 nm) +25.6° (c=0.5, DMSO); UV λ_{max} 242, 269 nm (ε 9200, 8900); ^{1}H-NMR (DMSO-d_6) δ 1.15 (9H, s, t-Bu), 3.24 (3H, s, SMe), 3.70 (2H, m, H-5' and 5''), 4.23 (1H, dd, J=3.4 and 7.0 Hz, H-4'), 5.23 (1H, dd, J=3.8 and 5.3 Hz, H-3'), 5.35 (1H, t, J=5.0 Hz, OH), 5.41 (1H, t, J=5.6 Hz, H-2'), 5.76 (1H, d, J=7.3 Hz, H-5), 5.98 (1H, d, J=5.8 Hz, H-1''), 7.27 (2H, br d, J=24 Hz, NH_2), and 7.79 (1H, d, J=7.3 Hz, H-6).

Anal. Calcd. for $C_{15}H_{23}N_3O_8S$ (405.4): C, 44.44; H, 5.72; N, 10.37; S, 7.91. Found: C, 44.64; H, 5.73; N, 10.09; S, 7.67.

3',5'-Di-O-mesyl-2'-O-pivaloylcytidine (**14**). A solution of **13** (391 mg, 0.97 mmol) in dry pyridine was evaporated to remove traces of H_2O. The residue was dissolved in dry pyridine (4 ml) and MsCl (0.12 ml, 1.5 mmol) was added at 0-5 °C. The mixture was stirred at this temperature for 25 min, after which time iced water was added. The mixture was extracted with $CHCl_3$. The extract was washed with H_2O and evaporated. The pyridine was removed by repeated co-evaporation with CH_2Cl_2-toluene. The residue was chromatographed on a silica gel column with $CHCl_3$-MeOH (95:5) to give **14** (346 mg, 74%). An analytically pure sample was obtained by precipitation from CH_2Cl_2-n-pentane: amorphous powder; $[\alpha]^{25}$ (589 nm) +25.3° (c=0.74, DMSO); UV λ_{max} (MeOH) 240, 270 (sh) nm (ε 10800, 9900); ^{1}H-NMR (DMSO-d_6) δ 1.17 (9H, s, t-Bu), 3.22 and 3.28 (6H, each s, 2 x SMe), 4.41 (1H, m, H-4'), 4.55 (1H, dd, J=3.4 and 11.3 Hz, 5'), 4.49 (1H, dd, J=5.5 and 11.3 Hz, 5''), 5.38 (1H, t, H=6.0 Hz, H-3'), 5.50 (1H, dd, J=4.4 and 6.0 Hz, H-2'), 5.76 (1H, d, J=7.3 Hz, H-5), 5.82 (1H, d, J=4.3 Hz, H-1''), 7.36 (2H, br d, J=14 Hz, NH_2), and 7.64 (1H, d, J=7.3 Hz, H-6).

Anal. Calcd. for $C_{16}H_{25}N_3O_{10}S_2 \cdot 0.3C_5H_{12}$ (505.2): C, 41.60; H, 5.71; N, 8.32; S, 12.69. Found: C, 41.62; H, 5.58; N, 8.15; S, 12.34.

1-[(1R,3S,5S)- and (1R,3R,5S)-4-Oxo-2-oxabicyclo[3.1.0]hexan-3-yl]cytosine (**15α** and **15β**). The trimesylate **14** (484 mg, 1 mmol) was treated under the same conditions as described for the synthesis of **9**. After neutral silica gel column chromatography with $CHCl_3$-MeOH (93:7 → 9:1), a mixture (9:1, 122 mg) of **15α** and **15β** in 59% combined yield. An analytically pure **15a** was obtained from crystallization from MeOH: mp 195-200 °C (sintered); $[\alpha]^{26}$ (589) -8.0, (578) -9.6, (546) -21.7, (435) -135, (365 nm) -620° (c=0.54, DMSO); IR (KBr) 1748 cm^{-1} (C=O at 4'-

position); UV λ_{max} (MeOH) 240, 265 (sh) nm (ε 8000, 6800); ^{1}H-NMR (see TABLES 1 and 2).

Anal. Calcd. for $C_9H_9N_3O_3 \cdot 0.8MeOH \cdot 0.4H_2O$ (240.0): C, 49.04; H, 5.46; N, 17.51. Found: C, 48.81; H, 5.16; N, 17.29.

Preparation of Tri-O-mesyladenosine (17).[21] The method of Sasaki et al.[21] was slightly modified.

To a stirred suspension of **16** (8.01 g, 30 mmol) in dry pyridine (150 ml) was added MsCl (7.5 ml, 96 mmol) at 0-5 °C and the mixture was stirred at room temperature for 5 h. After the mixture was cooled, it was poured gradually into a stirred saturated solution of NaCl in H_2O (2000 ml) containing $NaHCO_3$ (40 g). After 30 min, ice was added and syrupy materials were scratched on a wall of a beaker to give crystals. The stirring was continued for another 4 h, after which time the crystalline materials were collected by filtration, washed successively with H_2O and cold MeOH (100 ml), and dried first at room temperature and then at 60 °C in vacuo for 1 h over P_2O_5 to provide **17** (12.4 g, 82%). This product could be used for the next reaction without further purification. A portion of the product was dissolved in acetonitrile at room temperature and the solvent was allowed to evaporate at this temperature from an open vessel to deposit crystals on a wall of the vessel. The crystals were collected and washed a small amount of acetonitrile to give an analytically pure **17**: mp ca. 170 °C (sintered); $[\alpha]^{25}$ (589 nm) -24.2° (c=0.8, DMSO); UV λ_{max} (MeOH) 258 nm (ε 14500); ^{1}H-NMR (DMSO-d_6) δ 3.15, 3.30, and 3.41 (9H, each s, 3 x SMe), 4.62 (3H, m, H-4', 5', and 5''), 5.74 (1H, dd, J=3.7 and 5.4 Hz, H-3'), 6.11 (1H, t, J=5.5 Hz, H-2'), 6.37 (1H, d, J=5.5 Hz, H-1'), 7.39 (2H, br s, NH_2), 8.18 (1H, s, H-2), and 8.35 (1H, s, H-8).

Anal. Calcd. for $C_{13}H_{19}N_5O_{10}S_3$ (501.5): C, 31.14; H, 3.82; N, 13.97; S, 19.18. Found: C, 31.22; H, 3.78; N, 13.91; S, 19.06.

9-[(1R,3S,5S)- and (1R,3R,5S)-4-Oxo-2-oxabicyclo[3.1.0]hexan-3-yl]adenine (**18α** and **18β**). To a stirred suspension of **17** (3.01 g, 6 mmol) in a mixture of MeOH (30 ml) and THF (35 ml) was added a solution of KOH (3.36 g, 60 mmol) in MeOH (40 ml) at 0-5 °C, and the mixture was stirred at room temperature for 1.5 h. After the mixture had been cooled, it was neutralized with a mixture of concd. HCl and MeOH (1:4, v/v) to pH 7-8. The undissolved materials were removed by filtration through a Celite pad, and washed with cold MeOH (40 ml). The combined

filtrate and washings were concentrated to ca. 8 ml. The residue was chromatographed on a silica gel column with $CHCl_3$-MeOH (99:1 → 97:3 → 95:5) to provide a mixture of **18α** and **18β** (85:15, 1.18 g, 84%) as crystalline solids. Recrystallization from EtOH gave an analytically pure sample of a mixture of **18α** and **18β** (51:49, by ^{1}H-NMR): mp >174 °C (dec.); $[\alpha]^{26}$ (589) +46.4, (578) +48.2, (546) +42.3, (435) -12.8, (365 nm) -379° (c=0.39, DMSO); IR (KBr) 1750 cm^{-1} (C=0); UV λ_{max} (MeOH) 258 nm (ε 14700); ^{1}H-NMR (see TABLES 1 and 2).

Anal. Calcd. for $C_{10}H_9N_5O_2 \cdot 0.04EtOH \cdot 0.1H_2O$ (234.9): C, 51.55; H, 4.05; N, 29.82. Found: C, 51.55; H, 3.97; N, 29.59.

The mother liquor was concentrated to provide another crop of an analytically pure sample of a mixture (**18α** and **18β**, 93:7, by ^{1}H-NMR): mp 155.0-155.5 °C (dec.); $[\alpha]^{25}$ (589) +41.4, (578) +40.2, (546) -11.5, (435) -41.4, (365 nm) -454° (c=0.1, DMSO); IR (KBr) 1750 cm^{-1} (C=0); UV λ_{max} (MeOH) 258 nm (ε 15300); ^{1}H-NMR (see TABLES 1 and 2).

Anal. Calcd. for $C_{10}H_9N_5O_2 \cdot 0.5EtOH \cdot 0.2H_2O$ (257.9): C, 51.24; H, 4.85; N, 27.16. Found: C, 51.27; H, 4.55; N, 27.37.

Preparation of 2',3'-Di-O-mesyl-N^3,5'-cycloadenosine salt (**19**).[21] The method of Sasaki et al.[21] was modified. A solution of **17** (400 mg, 0.8 mmol) in a mixture of 1,4-dioxolane (10 ml) and acetonitrile (4 ml) was refluxed for 24 h and the mixture was then allowed to stand at room temperature overnight. The resulting crystals were collected by filtration, washed with 1,4-dioxolane, and dried at room temperature for 4 h in vacuo over P_2O_5 to give **19** (352 mg, 88%). An analytically pure sample was obtained by recrystallization from a small amount of MeOH: mp 175-180 °C (sintered), 215-218 °C (dec.) [lit.[21] mp 185-195 °C]; $[\alpha]^{25}$ (589 nm) -37.9° (c=1.22, DMSO); UV λ_{max} (MeOH) 275 nm (ε 16000) [lit.[21] 274 nm (ε 12500)]; ^{1}H-NMR (DMSO-d_6) δ 2.30 (3H, s, SMe of mesyloxy anion), 3.32 and 3.41 (6H, each s, 2 x SMe), 4.73 (1H, dd, J=2.5 and 4.6 Hz, H-5'), 5.00 (1H, br dd, J=2 and 5 Hz, H-5''), 5.30 (1H, br m, H-4'), 5.35 (1H, d, J=5.7 Hz, H-2'), 5.54 (1H, dd, J=4.1 and 5.7 Hz, H-3'), 6.97 (1H, s, H-1'), 8.45 and 8.84 (2H, each s, H-2 and 8), and 9.48 (2H, br d, J=57 Hz, NH_2).

Anal. Calcd. for $C_{13}H_{19}N_5O_{10}S_3 \cdot 0.5MeOH \cdot 0.5H_2O$ (526.5): C, 30.80; H, 4.21; N, 13.30. Found: C, 30.76; H, 4.22; N, 13.06.

2',3',5'-Tri-O-mesyl-N^2-(4-methoxytrityl)guanosine (**22**). Commercially available **20** was dried at 100 °C in vacuo for 6 h over

P_2O_5. A suspension of the dry **20** (11.1 g, 35 mmol) in dry DMSO (80 ml) was stirred at room temperature. To this mixture was added dry triethylamine (16 ml) followed by addition of MMTrCl (13.3 g, 43 mmol).[22] The mixture was vigorously stirred at room temperature for 6 h, after which time, it was poured into a stirred, saturated brine (1500 ml) containing ice cubes. The resulting precipitates were collected by filtration, washed first with H_2O and then with Et_2O, air-dried overnight, and finally dissolved in a mixture of MeOH and $CHCl_3$. The solution was concentrated to dryness to give crude **21**[22] (18.8 g, 85%) as a foam.

A portion (5.06 g) of this foam was dissolved in a mixture of CH_2Cl_2 and benzene, and the solvents were evaporated to remove traces of H_2O. The residue was again dissolved in dry CH_2Cl_2 (45 ml). To this solution was added dry triethylamine (11 ml), followed by addition of MsCl (4.4 ml, 57 mmol) at 0-5 °C and the mixture was stirred at this temperature for 5 h. The reaction was quenched with iced water and the mixture was extracted with $CHCl_3$ (250 ml). The extract was washed successively with H_2O (100 ml), aq. $NaHCO_3$ (100 ml), and H_2O (100 ml). After the extract had been cooled to 0-5 °C, a solution of KOH (342 mg, 6.1 mmol) in MeOH (3 ml), the mixture was stirred at this temperature for 20 min, after which time the mixture was washed successively with brine (2 x 100 ml) and H_2O (4 x 100 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column with $CHCl_3$-MeOH (98:2 → 95:5 → 9:1 → 1:1) to give **22** (4.07 g, 55% from **20**) as a foam. An analytically pure sample was obtained by precipitaion from CH_2Cl_2-*n*-pentane: amorphous powder; $[\alpha]^{25}$ (589 nm) -24.8° (c=0.3, DMSO); UV λ_{max} (MeOH) 262, 235 (sh), 277 (sh) nm (ε 21100, 20200, 19600); ^{1}H-NMR (DMSO-d_6) δ 3.00, 3.19, and 3.37 (9H, each s, 3 x SMe), 3.73 (3H, s, OMe), 4.43 (3H, m, H-4', 5', and 5''), 5.25 (1H, d, *J*=7.3 Hz, H-1'), 5.30 (1H, dd, *J*=2.1 and 5.6 Hz, H-3'), 5.49 (1H, dd, *J*=5.6 and 7.3 Hz, H-2'), 6.8-7.4 (14H, m, Arom.), 7.64 (1H, s, N^2-H), 7.94 (1H, s, H-8), 10.7 (1H, s, N^6-H).

Anal. Calcd. for $C_{33}H_{35}N_5O_{12}S_3 \cdot 0.7H_2O$ (802.5): C, 49..39; H, 4.57; N, 8.73; S, 11.99. Found: C, 49.68; H, 4.47; N, 8.69; S, 11.71.

2',3',5'-Tri-O-mesylguanosine (**23**). To a stirred solution of **22** (3.6 g, 4.6 mmol) in acetic acid (40 ml) was added H_2O (10 ml) at 65 °C. The mixture was stirred at this temperature for 1 h, after which time it

was concentrated to about 5 ml. The acetic acid was removed by co-evaporation twice with EtOH (70 ml)-H_2O (30 ml), then with EtOH (70 ml). The residue was triturated with Et_2O (80 ml) to afford solid materials, which were collected by filtration and washed with Et_2O to give almost pure **23** (2.15 g, 90%). A portion (100 mg) of the product was dissolved in a mixture of EtOH (45 ml) and H_2O (1 ml) under refluxing and the resulting solution was allowed to stand at room temperature overnight to give an analytically pure **23** as amorphous solids: $[\alpha]^{25}$ (589 nm) -12.3° (c=0.53, DMSO); UV λ_{max} 255, 250 (sh) nm (ε 15600, 15100); ^{1}H-NMR (DMSO-d_6) δ 3.21, 3.27, and 3.40 (9H, each s, 3 x SMe), 4.59 (3H, s, H-4', 5', and 5''), 5.55 (1H, dd, J=3.1 and 5.2 Hz, H-3'), 5.84 (1H, t, J=5.7 Hz, H-2'), 6.13 (1H, d, J=5.9 Hz, H-1'), 6.51 (2H, br s, NH_2), 7.94 (1H, s, H-8), and 10.8 (1H, s, NH).

Anal. Calcd. for $C_{13}H_{19}N_5O_{11}S_3 \cdot 0.5H_2O$ (526.5): C, 29.66; H, 3.83; N, 13.30; S, 18.27. Found: C, 29.57; H, 3.58; N, 13.04; S, 18.05.

9-[(1R,3S,5S)- and (1R,3R,5S)-4-Oxo-2-oxabicyclo[3.1.0]hexan-3-yl]guanine (**24α** and **24β**). To a stirred suspension of **23** (259 mg, 0.5 mmol) in a mixture of MeOH (4 ml) and THF (6 ml) was added a solution of KOH (140 mg, 2.5 mmol) in MeOH (2 ml) at room temperature, and the mixture was stirred at this temperature for 2.5 h. The mixture was neutralized under the conditions as described for the synthesis of **18**. The undissolved materials were collected by filtration, washed successively with cold MeOH (5 ml) and H_2O (10 ml), dried at room temperature in vacuo over P_2O_5 for 24 h to give a crude mixture (86:14, 110 mg, 89%) of **24α** and **24β** as solids with >80% purity by judging from ^{1}H-NMR and TLC analysis. The crude product (75 mg) was dissolved in DMSO (0.7 ml) at room temperature, while neutral silica gel (20 ml) column packed with $CHCl_3$-MeOH (95:5) was prepared. DMSO (0.7 ml) was applied first to the column and then the solution of the product was charged. Elution with $CHCl_3$-MeOH (95:5 → 8:2 → 7:3) gave a mixture of **24α** and **14β** (88:12, 27 mg) with >90% purity: amorphous powder; mp >180 °C (dec.); ^{1}H-NMR (see TABLES 1 and 2); HRMS (m/z) 248.0783 (MH^+) [required for $C_{10}H_{10}N_5O_3$ 248.0782].

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REFERENCES

1. H. N. C. Wong, M.-Y. Hon, C.-W. Tse, and Y.-C. Yip, Chem. Rev., **1989**, 89, 165.
2. J. Salaün, Chem. Rev., **1989**, 89, 1247; I. Wagner and H. Musso, Angew. Chem. Int. Ed. Engl., **1983**, 22, 816.
3. T. Cohen and M. Myers, J. Org. Chem., **1988**, 53, 457 and references cited therein; K. Ramig, M. Bhupathy, and T. Cohen, J. Am. Chem. Soc., **1988**, 110, 2678.
4. C. J. Suckling, Angew. Chem. Int. Ed. Engl., **1988**, 27, 537.
5. T. Sasaki, K. Minamoto, and H. Suzuki, J. Org. Chem., **1973**, 38, 598.
6. T. Adachi, T. Iwasaki, M. Miyashi, and I. Inoue, J. Chem. Soc. Chem. Commun., **1977**, 247.
7. J. R. Sufrin, A. J. Spiess, J. F. Karny, D. L. Kramer, R. G. Hughes, Jr., R. J. Bernacki, and C. W. Porter, Nucleosides, Nucleotides, **1989**, 8, 505.
8. M. Okabe and R.-C. Sun, Tetrahedron Lett., **1989**, 30, 2203.
9. J.-C. Wu and J. Chattopadhyaya, Tetrahedron, **1989**, 45, 4522; ibid., **1990**, 46, 2587.
10. T. Watanabe, S. Ueki, T. Nobukuni, S. Nishiyama, S. Yamamura, K. Kato, M. Nagai, and T. Takita, Nucleic Acids Res. Symp. Ser., **1990**, No. 22, p. 131.
11. T. Kunieda and B. Witkop, J. Am. Chem. Soc., **1969**, 91, 7751; ibid., **1971**, 93, 3478.
12. M. Ohno, N. Yagisawa, S. Shibahara, S. Kondo, K. Maeda, and H. Umezawa, J. Am. Chem. Soc., **1974**, 96, 4326.
13. H. P. M. Thiellier, G. J. Koomen, and U. K. Pandit, Tetrahedron, **1977**, 33, 1493.
14. V. E. Marquez, K. V. B. Rao, J. V. Silverton, and J. A. Kelley, J. Org. Chem., **1984**, 49, 912.
15. M. Kawana and S. Emoto, Tetrahedron Lett., **1975**, 3395; Chem. Lett., **1977**, 597; Bull. Chem. Soc. Jpn., **1980**, 53, 222; F. Hansske, and M.

J. Robins, J. Am. Chem. Soc., **1983**, 105, 6736; B. Nawrot, K. W. Pankiewicz, R. A. Zepf, and K. A. Watanabe, J. Carbohydr. Chem., **1988**, 7, 95.

16. M. Kawana, N. Yamasaki, M. Nishikawa, and H. Kuzuhara, Chem. Lett., **1987**, 2419; M. Kawana, M. Nishikawa, N. Yamasaki, and H. Kuzuhara, J. Chem. Soc. Perkin Trans. 1, **1989**, 1593.
17. M. Kawana and H. Kuzuhara, Tetrahedron Lett., **1987**, 28, 4075; Carbohydr. Res., **1989**, 189, 87; P. Herdewijn, Tetrahedron, **1989**, 45, 6563.
18. H. Paulsen and D. Stoye, Chem. Ber., 1969, **102**, 834; J. Hildesheim, A. Gaudemer, and S. D. Géro, Chem. Ind. (London), 1970, 94.
19. G. H. Hakimelahi, Z. A. Proba, and K. K. Ogilvie, Can. J. Chem., **1982**, 60, 1106.
20. K. Kamaike, F. Uemura, S. Yamakage, S. Nishino, and Y. Ishido, Nucleosides, Nucleotides, **1987**, 6, 699; K. Haraguchi, H. Tanaka, T. Miyasaka, Nucleic Acids Symp. Ser., No. 22, **1990**, p. 3.
21. T. Sasaki, K. Minamoto, and S. Tanizawa, J. Org. Chem., **1973**, 38, 2896.
22. K. K. Ogilvie, A. L. Schifman, and C. L. Penney, Can. J. Chem., **1979**, 57, 2230.
23. P. K. Bridson, W. T. Markiewicz, and C. B. Reese, J. Chem. Soc. Chem. Commun., **1977**, 791.
24. R. Zou and M. J. Robins, Can. J. Chem.., **1987**, 65, 1436.
25. M. Ikehara and T. Ueda, Yuki Gosei Kagaku Kyokai Shi, **1974**, 32, 402.
26. M. Kawana, K. Takeuchi, T. Ohba, and H. Kuzuhara, Nucleic Acids Res. Symp. Ser., **1986**, No. 17, p. 37.
27. T. Ito, Can. J. Chem., **1966**, 44, 94.
28. H. Rosemeyer, G. Tóth, and F. Seela, Nucleosides, Nucleotides, **1989**, **8**, 587.

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