SYNTHESIS AND BIOLOGICAL EVALUATION OF 4'-C-METHYL NUCLEOSIDES

Toshiaki Waga, Hiroshi Ohru and Hiroshi Meguro

Central Research Laboratory, Asahi Breweries LTD, 2-13-1 Ohmorikita Ohta-ku, Tokyo 143, Japan and Department of Applied Biological Chemistry, Faculty of Agriculture, Tohoku University, 1-1 Tsutsumidori-Amamiya, Sendai 981, Japan

Abstract: A series of 2'-deoxy, 2',3'-unsaturated and 2',3'-dideoxynucleoside analogues, which have an additional methyl group at the 4'-position, have been synthesized. When evaluated for their inhibitory activity against HIV in MT-4 cell, 2'-deoxy-4'-C-methyl nucleosides exhibited potent activity.

Several types of viral infection cause severe diseases, including cancer. The HIV, the causative agent of AIDS, has recently spread all over the world to become a serious life-threatening disease. Therefore, the development of drugs to prevent such diseases is an important research subject. A number of sugar-modified nucleosides, especially since the discovery of AZT, 2',3'-dideoxy nucleosides and 2',3'-didehydro-dideoxy analogs as chemotherapeutic agents for AIDS, have been synthesized to test against such diseases. After conversion to the triphosphate in cells, these analogs may either inhibit HIV reverse transcriptase, or be incorporated by it into the growing chain of DNA, resulting in chain termination or disruption.

Modification of the sugar fragment of 2'-deoxy nucleosides has resulted in some very potent inhibitors. Recently, Magg et al. reported on the synthesis and anti-HIV activity of various 4'-azido- and 4'-methoxynucleosides with electronegative substituents at 4'-position. In the previous paper, we described the preparation of the 4'-modified nucleoside that have an additional C-C linked methyl group. The 4'-C-methyl nucleoside analogs are particularly interesting because the reactivities of 3' and 5'-hydroxyl groups differ from those of natural nucleosides due to the neopentyl character and further the steric effect of the 4'-C-methyl group can be also expected.

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

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In this paper, we report the syntheses and the HIV-inhibitory activity of the 4'-C-methyl-2'-deoxy nucleosides to evaluate the effect of 4'-C-methyl group and also report the preparation of the unsaturated (D4) and dideoxy (DD) derivatives of them which are expected to act as the chain terminators of viral DNA synthesis. Our target nucleosides are shown in Fig. 1.

RESULTS AND DISCUSSION

CHEMISTRY

Since we have reported in detail the preparation of 4-C-methyl-β-ribose derivatives 1, we would like to discuss here the preparation of nucleosides from 1.

The application of Saneyoshi's protocol to the 4-C-methyl ribose derivatives 1 gave an unseparable mixture (50:50) of 9- (2a) and 7-adenyl derivative (2b) in a 26% yield (Fig. 2). The change of the catalyst from stannic chloride to trimethylsilyltrifluoromethanesulfonate (TMSOTf) improved the yield up to 72% but the ratio of 2a and 2b could not be improved (58:42). Since the transition state of this glycosylation reaction can be speculated as shown in Fig. 3, we expected that the ratio of 9 and 7-adenylation could be change by the bulkiness of the 6-substituent of adenine. Thus, the glycosylation reaction was also carried out with N6-benzoyladenine. Condensation of 1 with N6-benzoyladenine in dry acetonitrile in the presence of TMSOTf at 0 °C gave a mixture of 9-adenyl derivative 3a (74%) and 7-adenyl derivative 3b (8.9%). These compounds were separated by silica gel column chromatography.

Treatment of 3a with saturated methanolic ammonia at room temperature for 18 h and subsequent deoxygenation by Robins's protocol gave 2'-deoxy derivative (6) in a 40% yield. Birch reduction of 6 gave 2'-deoxy-4'-C-methyladenosine (7) in an 87% yield (Scheme 1). In the deoxygenation procedure, use of excess phenoxythiocarbonyl chloride gave 4'-C-methyl purine derivative 8 in a 12% yield.

Thymidine derivative was also prepared from 9 by similar procedure to that described for 2'-deoxyadenosine derivative 7 (Scheme 2). The catalytic hydrogenation of 12 gave 13 in a 23% yield. However, the hydrogenolysis of benzyl groups did not proceed completely, due to the presence of a small amount of residual tin compound. Therefore, we chose a different route in which the O-debenzylation was performed before the deoxygenation of 2'-hydroxyl group. Mansui reported the preparation of 3',5'-di-O-acetyl-2'-bromothymidine in a 97% yield by treatment of ribofuranosylthymine with acetyl bromide. Thus, treatment of thymidine derivative 14 with acetyl bromide in dry acetonitrile at reflux gave 15 and subsequent reduction of 15 with tributyltin hydride in toluene-benzene in the presence of 2,2'-azobisisobutyronitrile (AIBN) gave 16 in a 72% yield. The major by-product of this sequence was 2,2'-anhydro derivative 17, which were formed during the reaction with acetyl bromide. Treatment of 16 with saturated methanolic ammonia at room temperature for 18 h gave 4'-C-methylthymidine (13) in a 62% yield (Scheme 3).

The approach to 4'-C-methyl-2'-deoxycytidine utilized a similar procedure to that described for 4'-C-methylthymidine (13). Compound 20, which was prepared from 4'-C-methyluridine
(18) via its bromo acetyl derivative 19, was converted to 2'-deoxy-4'-C-methylcytidine (23) by Reese’s method \(^7\) through 1,2,4-triazolyl derivative 22 in a 68% yield (Scheme 3).

Next we turned our attention to the preparation of D4- and DD-derivatives. One of the methods to prepare D4-derivatives is to convert the vicinal 2',3'-diol to vicinal bromoacetate and reduce it with Zn/Cu reagent. However, treatment of 4'-C-methyladenosine (24)\(^3\) with 2-acetoxyisobutyl bromide (Mattock's bromide) gave a very complex mixture including compound 25. Therefore, in the case of 24, we selected the Corey's direct conversion of vicinal diols to double bond. Reaction of 24 with tert-butylidimethylsilyl chloride (TBDMSI) in N,N-dimethylformamide (DMF) in the presence of imidazole at 60°C gave 5'-O-silyl protected derivative 26 in a 65%
yield. Thionocarbonate 27, which was prepared by the reaction of 26 with thiocarbonyldiimidazole in a 88% yield, was deoxygenated to 28 by treatment with 1,3-dimethyl-2-phenyl-1,3,2-diazaphosphetidline in a 63% yield. Deprotection of 28 with 1M tetrabutylammonium fluoride-tetrahydrofuran (THF) gave the desired D4A analogue (29) in a 74% yield. DDA analogue 30 was prepared by hydrogenation of 29 over Pd-black in methanol in a 68% yield (Scheme 4).

The syntheses of D4T and DDT analogues followed the Mansuri's protocol61. Reaction of 15 with Zn/Cu couple in methanol gave olefinic product 31 in a 28% yield, which was O-
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**SCHEME 3**

a) AcBr/CH₂CN, b) t-Bu₃SnH, AIBN/PhCH₂- PhH, c) NH₃/MeOH, d) CIPh-POCl₂, Tz/pyr.

**SCHEME 4**

a) Mattocks-Br/CH₂CN, b) TBDMSCI, Im/DMF, c) Im₂C=S/DMF, d) DMPDAP/THF,

e) Bu₂NF/THF, f) H₂, Pd-black/MeOH
deacetylated to give D4T analogue 32 in a 98% yield. Hydrogenation of 31 over 10% Pd-carbon followed by deacetylation gave DDT analogue 34 in a 81% yield (Scheme 5).

The reaction of cytidine derivative 35 with Mattock’s reagent did not give the desired bromoacetate similar with adenosine derivative 24. The preparation of 2',3'-unsaturated nucleoside via cyclic thionocarbonic acid was also applied to cytidine derivative to give 39 in a 24% yield from 35, which on desilylation with tetrabutylammonium fluoride, followed by N-deacetylation gave D4C analogue 41 in a 69% yield (Scheme 6). However, attempted reduction of 40 to the corresponding saturated cytidine analogue (44) was not successful. Therefore, DDC analogue 44 was synthesized from 43, which was prepared from 4'-C-methyluridine (18) by Mansuri’s protocol via D4U analogue 42 in a 26% overall yield, by the Reese’s method through 1,2,4-triazolyl derivative in a 21% yield (Scheme 5).

The 2,2'-anhydro derivative 21, which was obtained as by-product in the preparation of 20, was converted to ara-C analogue 46 in a 49% yield through 45 (Scheme 7).

**BIOLOGICAL ACTIVITY**

The 4'-C-methyl nucleosides were evaluated for their in vitro inhibitory effect on the cytopathicity of HIV (HTLV-II_B strain) in MT-4 cells with AZT, DDT and DDA as references.

All of the 2'-deoxy derivatives were potent inhibitors of HIV. IC50’s ranged from 0.072 µM for cytidine derivative (23) to 50 µM for purine derivative (8). Thymidine derivative (13) was found to inhibit HIV replication at a concentration that was 14-fold below the cytotoxicity threshold. It was found that, although the cytidine derivative (23) was 100-fold more potent than compound 13, it was also the most cytotoxic compound among the 4'-C-methyl nucleosides tested. Compound 23 was also tested for its ability to inhibit the growth of P388 mouse leukemia cells in vitro and was proved to have markedly effective activity (IC50 = 1.7 µM).

Within the class of dehydro-dideoxy derivatives, D4T analogue (32) was shown a substantial level of anti-HIV activity, and D4A and D4C analogues (29, 41) were inactive.

The arabinoside 46 was higher cytotoxicity than 2'-deoxy derivative 23.

It has been a common knowledge that D4 and DD types of sugar modified nucleosides exhibit a significant anti-HIV activity regardless the difference of nucleobases, and the nucleoside derivatives must be devoid of the 3'-hydroxyl group to be potential anti-HIV.

Some results presented here are in contrast with the general knowledge of the structure-activity relationships. The contrasts are as follows. 1) In the case of adenosine analogues, D4 type was found to be inactive and DD type exhibited good anti-HIV activity. On the other hand, in the thymidine series, DD type was inactive and D4 type showed a significant activity. 2) The 2'-deoxy type was found to be more potent than the corresponding D4 and DD types.

Although the reasons for these results are not clear at the present time, these structure-activity relation is very interesting and useful to design new potential anti viral nucleosides.

Lastly, we also showed that the deletion of the 3'-hydroxyl group is not indispensable for anti-HIV activity as in the case of Magg et al.2)
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SCHEME 5

SCHEME 6
TABLE  
In vitro antiviral activity of 4'-C-methyl nucleosides against HIV-1 in MT-4 cells.

<table>
<thead>
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<th>Comp.</th>
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<th>CC50 (µM)</th>
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<td>14</td>
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EXPERIMENTAL
Melting point (mp) values were taken with a Shibata melting apparatus and are uncorrected. ¹H-NMR spectra were recorded with a JEOL JNMEX-270 spectrometer at 28 °C, in CDCl₃ using Me₃Si or D₂O using DSS as an internal standard. UV spectra were recorded with a Hitachi U-2000 spectrophotometer. Mass spectra were recorded with a Hitachi M-80B spectrometer at 70eV. IR spectra were recorded on with a Shimazu FTIR-8100M spectrometer. Specific rotation values were measured with a JASCO DIP-360 at 589nm. Merck silica gel Art. 9385 was used for column chromatography and Merck silica gel Art. 5554 for analytical thin layer chromatography.
N⁶-Benzoyl-2'-O-acetyl-3',5'-di-O-benzyl-4'-C-methyladenosine (3a). N⁶-
Benzoyleadenine (2.2 g, 9.34 mmol) was suspended in a solution of 1³ (4.0 g, 9.34 mmol) in dry
acetonitrile (200 ml) at 0 °C. A solution of TMSOTf (3.6 ml, 18.7 mmol) in dry acetonitrile
(80 ml) was added and the mixture was stirred at the same temperature. After 1 h, sodium
bicarbonate (2.0 g) was added to a reaction mixture and filtered. The filtrate was evaporated and
the residue was partitioned with CHCl₃ and H₂O. The CHCl₃ layer was dried (MgSO₄) and
evaporated. The residue was purified by silica gel column chromatography, using CHCl₃-MeOH-
AcOEt-hexane (50:1:30:10) as an eluent, to give 3a (5.4 g, 95%) as a pale yellow syrup, [α]D²⁵
+8.9° (c 1.0, CHCl₃), ¹H-NMR (CDCl₃) δ: 9.21 (1 H, br s, NH), 8.76 (1 H, s, 2), 8.36 (1 H, s, 8), 8.02 (2 H, d, J = 7.1 Hz, Bz), 7.52 (3 H, m, Bz), 7.32 (10 H, m, Ph), 6.36 (1 H, d, J = 4.2
Hz, 1''), 5.89 (1 H, dd, J = 4.2, 5.4 Hz, 2''), 4.62 (1 H, d, J = 11 Hz, Bn), 4.55 (1 H, d, J = 5.4
Hz, 3''), 4.51 (1 H, d, J = 11 Hz, Bn), 4.49 (1 H, d, J = 12 Hz, Bn), 4.44 (1 H, d, J = 12 Hz,
Bn), 3.56 (1 H, d, J = 10 Hz, 5''), 3.37 (1 H, d, J = 10 Hz, 5''), 2.10 (3 H, s, Ac), 1.35 (3 H, s,
Me); IR νmax (neat) cm⁻¹: 3200, 3000, 1740, 1700, 1600, 1570, 1500, 1440, 1220, 1090, 1020,
900, 800, 740, 700; EI-MS m/z: 607 (M⁺); HR-MS calcd for C₅₂H₇₃N₅O₄ (M⁺) 607.2429, found
607.2432.

3',5'-Di-O-benzyl-2'-deoxy-4'-C-methyladenosine (6). A solution of 3a (5.4 g,
8.89 mmol) in saturated methanolic ammonia (350 ml) was stirred at room temperature for 18 h
and then evaporated to dryness. The residue was purified by silica gel column chromatography,
using CHCl₃-MeOH-AcOEt-hexane (20:2:15:5) as an eluent, to give 4 (3.5 g, 86%) as crystal. To a
stirred suspension of 4 (4.4 g, 9.53 mmol) and 4-(dimethylamino)pyridine (3.5 g, 28.6 mmol)
in dry acetonitrile (250 ml), phenylchlorothionocarbonate (2.0 ml, 14.3 mmol) was added
dropwise under nitrogen at room temperature. After 22 h, the solvent was evaporated to dryness
in vacuo to give a residue which was partitioned between CHCl₃ and H₂O. The CHCl₃ layer was
dried (MgSO₄) and evaporated. The residue was purified by silica gel column chromatography,
using CHCl₃-MeOH-AcOEt-hexane (50:1:30:10) as an eluent, to give 5 (5.0 g, 90%) as a pale
yellow syrup. A stirred solution of tributyltin hydride (6.6 g, 22.6 mmol) and AIBN (1.4 g,
8.37 mmol) in dry benzene (200 ml) was heated at 60 °C. A solution of 5 (5.0 g, 8.37 mmol) in
dry benzene (150 ml) was added dropwise to an above hot solution. The resulting solution was
heated under reflux for 4 h, and then the solvent was evaporated. The residue was purified by
silica gel column chromatography, using CHCl₃-MeOH-AcOEt-hexane (50:1:30:10) as an eluent,
to give 6 (2.0 g, 52%) as a pale yellow syrup, [α]D²⁵ +9.0° (c 0.6, CHCl₃), ¹H-NMR (CDCl₃) δ:
8.33 (1 H, s, 2), 8.17 (1 H, s, 8), 7.33 (10 H, m, Ph), 6.42 (1 H, dd, J = 5.9, 6.4 Hz, 1''), 5.56
(2 H, br s, NH₂), 4.61 (1 H, d, J = 12 Hz, Bn), 4.56 (1 H, d, J = 12 Hz, Bn), 4.51 (2 H, d,
J = 12 Hz, Bn), 4.41 (1 H, t, J = 5.9 Hz, 3''), 3.59 (1 H, d, J = 10 Hz, 5''), 3.46 (1 H, d, J = 10
Hz, 5''), 2.70 (2 H, m, 2''), 1.33 (3 H, s, Me); IR νmax (neat) cm⁻¹: 3300, 3150, 2900, 2850,
1600, 1470, 1420, 1330, 1300, 1210, 1100, 740, 700; EI-MS m/z: 445 (M⁺); HR-MS calcd for
C₂₅H₂₇N₅O₄ (M⁺) 445.2144, found 445.2173.
2'-Deoxy-4'-C-methyladenosine (7). Sodium (260 mg, 11.2 mmol) was added to a stirred suspension of 6 (1.0 g, 2.24 mmol) in liquid ammonia (100 ml) at -78 °C, and the mixture was stirred for 10 min at the same temperature. Ammonium chloride was added to the mixture, and the mixture was evaporated. The residue was purified by silica gel column chromatography, using CHCl₃-MeOH (5:1) as an eluent, to give 7 (520 mg, 87%) as a crystal, mp 128 °C, \([\alpha]_D^{25}\) -5.2° (c 1.0, MeOH), \(^1\)H-NMR (D₂O) 8: 8.29 (1 H, s, 2'), 8.17 (1 H, s, 8), 6.41 (1 H, t, J = 6.6 Hz, 1'), 4.62 (1 H, dd, J = 5.3, 5.9 Hz, 3'), 3.66 (2 H, s, 5'), 2.93 (1 H, s, 5'), 2.64 (1 H, ddd, J = 5.3, 6.6, 14 Hz, 2'), 2.45 (1 H, ddd, J = 5.3, 6.6, 14 Hz, 2'), 1.29 (3 H, s, Me); IR \(\nu\) max (KBr) cm⁻¹: 3400, 3250, 1650, 1620, 1590, 1500, 1440, 1350, 1320, 1260, 1220, 1060, 980, 810; EI-MS m/z: 265 (M⁺); HR-MS calcd for C₁₇H₁₉N₄O₄ (M⁺) 265.1175, found 265.1170; UV \(\lambda\) max (H₂O) nm (ε): 260 (11900), 209 (13900).

9-(2-Deoxy-4-C-methyl-β-D-ribofuranosyl)purine (8). Compound 8 was prepared from crude 6 in a 12% yield by the similar procedure to that described for 7. 8: mp 170-171 °C, \([\alpha]_D^{25}\) +3.1° (c 0.6, MeOH), \(^1\)H-NMR (D₂O) 8: 9.13 (1 H, s, 2), 8.95 (1 H, s, 8), 8.71 (1 H, s, 6), 6.59 (1 H, t, J = 6.3 Hz, 1'), 4.70 (1 H, dd, J = 5.6, 6.3 Hz, 3'), 3.67 (2 H, s, 5'), 3.05 (1 H, dt, J = 6.3, 14 Hz, 2'), 2.71 (1 H, ddd, J = 5.6, 6.3, 14 Hz, 2'), 1.31 (3 H, s, Me); IR \(\nu\) max (KBr) cm⁻¹: 3320, 3080, 1600, 1500, 1410, 1300, 1220, 1150, 1090, 1070, 1040, 950, 760, 740; EI-MS m/z: 250 (M⁺); HR-MS calcd for C₁₈H₁₄N₄O₃ (M⁺) 250.1065, found 250.1071; UV \(\lambda\) max (H₂O) nm (ε): 263 (8380), 197 (26200).

1-(2-O-Acetyl-3,5-di-O-benzyl-4-C-methyl-β-D-ribofuranosyl)thymine (9). A mixture of thymine (1.2 g, 9.34 mmol), hexamethyldisilazane (2.0 ml) and trimethylchlorosilane (0.5 ml) was refluxed overnight and then concentrated. To a solution of the silylated thymine and 1′(2.0 g, 4.67 mmol) in 1,2-dichloroethane (20 ml) was added TMSOTf (1.4 ml, 7.00 mmol) in 1,2-dichloroethane (5 ml). The mixture was stirred for 1 h at room temperature and diluted with CHCl₃. The mixture was washed with water, dried over MgSO₄ and evaporated. The residue was purified by silica gel column chromatography, using CHCl₃-MeOH-AcOEt-hexane (50:1:20:10) as an eluent. Evaporation of the appropriate fractions and crystallization of the residue from AcOEt-hexane yielded 2.2 g (95%) of 9 as crystal, mp 156 °C, \([\alpha]_D^{35}\) +51.6° (c 1.0, CHCl₃), \(^1\)H-NMR (CDCl₃) 8: 8.49 (1 H, br s, NH), 7.52 (1 H, s, 6), 7.33 (10 H, m, Ph), 6.20 (1 H, d, J = 4.6 Hz, 1'), 5.38 (1 H, dd, J = 4.6, 5.9 Hz, 2'), 4.63 (1 H, d, J = 12 Hz, Bn), 4.48 (3 H, m, Bn), 4.31 (1 H, d, J = 5.9 Hz, 3'), 3.61 (1 H, d, J = 10 Hz, 5'), 3.38 (1 H, d, J = 10 Hz, 5'), 2.11 (3 H, s, Ac), 1.51 (3 H, s, Me), 1.28 (3 H, s, 4'Me); IR \(\nu\) max (KBr) cm⁻¹: 3150, 3050, 2850, 1750, 1710, 1680, 1460, 1370, 1280, 1230, 1100, 1060, 1010, 750, 700; EI-MS m/z: 494 (M⁺); Calcd for C₂₂H₃₆N₂O₄: C, 65.58; H, 6.12; N, 5.67, Anal. Found: C, 65.39; H, 5.96; N, 5.73.
3',5'-Di-O-benzyl-4'-C-methylthymidine (12). Employing conditions analogous to those used for the preparation of 6, 9 (810 mg, 1.80 mmol) gave 12 (250 mg, 32%) as a pale yellow syrup via 10 and 11. 12: $[\alpha]_D^{25} +50.6^\circ$ (c 1.0, CHCl$_3$). $^1$H-NMR (CDCl$_3$) $\delta$: 8.27 (1 H, br s, NH), 7.66 (1 H, d, $J = 1.2$ Hz, 6), 7.32 (10 H, m, Ph), 6.27 (1 H, t, $J = 6.1$ Hz, 1'), 4.62 (1 H, d, $J = 12$ Hz, Bn), 4.56 (1 H, d, $J = 12$ Hz, Bn), 4.52 (1 H, d, $J = 12$ Hz, Bn), 4.46 (1 H, d, $J = 12$ Hz, Bn), 4.29 (1 H, dd, $J = 5.6, 6.6$ Hz, 3'), 3.65 (1 H, d, $J = 10$ Hz, 5'), 3.49 (1 H, d, $J = 10$ Hz, 5'), 2.51 (1 H, ddd, $J = 5.6, 6.6, 14$ Hz, 2'), 2.26 (1 H, ddd, $J = 5.9, 6.6, 14$ Hz, 2'), 1.55 (3 H, d, $J = 1.2$ Hz, Me), 1.26 (3 H, s, 4'Me); IR $\nu_{max}$ (neat) cm$^{-1}$: 3150, 3050, 2900, 1690, 1460, 1360, 1290, 1200, 1100, 860, 750, 700; El-MS m/z: 436 (M$^+$); HR-MS calcd for C$_{31}$H$_{33}$N$_2$O$_5$ (M$^+$) 436.1997, found 436.1981.

4'-C-Methylthymidine (13): From 3',5'-di-O-benzyl-4'-C-methylthymidine (12). A solution of 12 (220 mg, 0.50 mmol) in MeOH (40 ml) was shaken under hydrogen with Pd-black (100 mg) for 3 h. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was purified by silica gel column chromatography, using CHCl$_3$-MeOH (7:1) as an eluent, to give 13 (30 mg, 23%) as a crystal and starting material 12 (65 mg).

From 3',5'-Di-O-acetyl-4'-C-methylthymidine (16). A solution of 16 (640 mg, 1.88 mmol) in saturated methanolic ammonia (40 ml) was stirred at room temperature for 18 h and then evaporated to dryness. The residue was recrystallized from MeOH-Et$_2$O to give 13 (300 mg, 62%) as a crystal, mp 167 °C, $[\alpha]_D^{25} +33.6^\circ$ (c 1.1, MeOH). $^1$H-NMR (D$_2$O) $\delta$: 7.70 (1 H, d, $J = 1.3$ Hz, 6), 6.24 (1 H, t, $J = 6.3$ Hz, 1'), 4.48 (1 H, t, $J = 6.3$ Hz, 3'), 3.65 (2 H, s, 5'), 2.48 (2 H, t, $J = 6.3$ Hz, 2'); IR $\nu_{max}$ (KBr) cm$^{-1}$: 3500, 3200, 2950, 1700, 1470, 1400, 1290, 1200, 1130, 1070, 1010, 960, 850, 820, 780; El-MS m/z: 256 (M$^+$); HR-MS calcd for C$_{12}$H$_{18}$N$_2$O$_5$ (M$^+$) 256.1057, found 256.1061; UV $\lambda_{max}$ (MeOH) nm (e): 267 (9030).

3',5'-Di-O-acetyl-4'-C-methylthymidine (16) and 2,2'-Anhydro-3',5'-di-O-acetyl-4'-C-methylthymidine (17). Acetyl bromide (1.7 ml, 21.3 mmol) was added dropwise over 0.5 h to a suspension of 1-(4-methyl- p-D-ribofuranosyl)thymine (14) (1.0 g, 3.67 mmol) in acetonitrile (45 ml) heated at reflux. On completion of addition, the solution was allowed to cool and then concentrated. The residue was dissolved in methylene chloride (100 ml) and washed with water. The organic phase was dried (Na$_2$SO$_4$) and concentrated to leave crude 15. The solution of crude 15 in dry benzene (10 ml) was added dropwise over 0.5 h to a suspension of 1-(4-methyl- $\beta$-D-ribofuranosyl)thymine (14) (1.0 g, 3.67 mmol) in acetonitrile (45 ml) heated at reflux. On completion of addition, the solution was allowed to cool and then concentrated. The residue was dissolved in methylene chloride (100 ml) and washed with water. The organic phase was dried (Na$_2$SO$_4$) and concentrated to leave crude 15. The solution of crude 15 in dry benzene (10 ml) was added dropwise to a stirred hot mixture of tributyltin hydride (2.1 g, 7.35 mmol) and AIBN (600 mg) in dry toluene (20 ml) at 60 °C. The resulting mixture was refluxed for 4 h and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography, using CHCl$_3$-MeOH-AcOEt-hexane (40:1:30:10) as an eluent, to give two fractions. The first-eluted fraction gave 16 (900 mg, 72%) as a colorless syrup, $[\alpha]_D^{25} +15.7^\circ$ (c 0.7, CHCl$_3$). $^1$H-NMR (CDCl$_3$) $\delta$: 9.35 (1 H, br s, NH), 7.34 (1 H, d, $J = 1.3$ Hz, 6), 6.29 (1 H, dd, $J = 6.3, 7.3$ Hz, 1'), 5.33 (1 H, dd, $J = 3.6, 6.9$ Hz, 3'), 4.21 (1 H, d, $J = 12$ Hz, 5'), 3.46 (1 H, J = 12 Hz, 5'), 2.46 (1 H, ddd, $J = 3.6, 6.3$, 1020, 990, 960, 920, 890, 860, 830, 800, 770, 740, 710, 680, 650, 620, 590, 560, 530, 500, 470, 440, 410, 380, 350, 320, 290, 260, 230, 200, 170, 140, 110, 80, 50, 20, 10, 5, 2, 1, a, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z.
14 Hz, 2'), 2.34 (1 H, ddd, J = 6.9, 7.3, 14 Hz, 2'), 2.14 (6 H, s, Ac), 1.94 (3 H, d, J = 1.3 Hz, Me), 1.28 (3 H, s, 4'Me); IR νmax (neat) cm−1: 3190, 3050, 1750, 1690, 1470, 1380, 1240, 1120, 1050, 960; EI-MS m/z: 340 (M+); HR-MS calcd for C14H20N4O7 (M+) 340.1268, found 340.1240. The second fraction gave 17 (220 mg, 18%) as a crystal, mp 199–200°C, [α]D25 -61.0° (c 1.0, CHCl3). 1H-NMR (CDCl3) δ: 7.19 (1 H, d, J = 1.3 Hz, 6), 6.17 (1 H, d, J = 6.3 Hz, 1'), 5.57 (1 H, br s, 3'), 5.34 (1 H, dd, J = 6.3, <1 Hz, 2'), 4.15 (1 H, d, J = 12 Hz, 5'), 3.86 (1 H, d, J = 12 Hz, 5'), 2.19 (3 H, s, Ac), 2.00 (3 H, s, Ac), 1.98 (3 H, d, J = 1.3 Hz, Me), 1.26 (3 H, s, 4'Me); IR νmax (KBr) cm−1: 3070, 1750, 1670, 1620, 1560, 1490, 1380, 1450, 1220, 1070, 1040, 1030, 1000, 790; EI-MS m/z: 338 (M+); HR-MS calcd for C14H18N2O7 (M+) 338.1111, found 338.1111.

3',5'-Di-O-acetyl-2'-deoxy-4'-C-methyluridine (20) and 2,2'-Anhydro-3',5'-di-O-acetyl-2'-deoxy-4'-C-methyluridine (21). Employing conditions analogous to those used for the preparation of 16, 181) (1.08 g, 4.18 mmol) gave 20 (910 mg, 67%) as crystal and 21 (300 mg, 22%) as crystal via 19. 20: mp 141°C, [α]D25 +39.0° (c 1.0, CHCl3), 1H-NMR (CDCl3) δ: 8.29 (1 H, br s, NH), 7.55 (1 H, d, J = 7.9 Hz, 6), 6.25 (1 H, t, J = 6.6 Hz, 1'), 5.76 (1 H, dd, J = 2.0, 7.9 Hz, 5), 5.32 (1 H, dd, J = 3.6, 6.6 Hz, 3'), 4.19 (1 H, d, J = 12 Hz, 5'), 4.14 (1 H, d, J = 12 Hz, 5'), 2.52 (1 H, dd, J = 3.6, 6.6, 14 Hz, 2'), 2.35 (1 H, dt, J = 6.6, 14 Hz, 2'), 2.13 (3 H, s, Ac), 2.11 (3 H, s, Ac), 1.29 (3 H, s, Me); IR νmax (KBr) cm−1: 3040, 1740, 1700, 1670, 1620, 1560, 1490, 1380, 1240, 1060, 1030, 860; EI-MS m/z: 326 (M+); HR-MS calcd for C14H18N2O7 (M+) 326.0956, found 326.0958.

2'-Deoxy-4'-C-methylcytidine (23). A solution of 20 (1.0 g, 3.06 mmol) and 4-chlorophenylphosphorodichloridate (1.1 ml, 6.44 mmol) in dry pyridine (20 ml) was stirred at 0°C for 2 min. 1,2,4-Triazole (1.6 g, 23.0 mmol) was then added to the solution, and the mixture was stirred for 48 h at room temperature. The mixture was concentrated under reduced pressure to give a syrup residue, which was purified by silica gel column chromatography, using CHCl3-MeOH-AcOEt (40:1:30) as an eluent, to give 22 (830 mg, 72%) as crystal. Compound 22 (500 mg, 1.32 mmol) was dissolved in NH4OH-dioxane (1:3, v/v, 20 ml), and then the mixture was stirred for 3 h at room temperature and concentrated under reduced pressure to give a syrup. This syrup was dissolved in saturated manethanol ammonia (20 ml), and stirred for 16 h at room temperature and concentrated to give another syrup. The syrup was purified by silica gel column
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chromatography, using CHCl₃-MeOH (5:1) as an eluent. Evaporation of the appropriate fractions and crystallization of the residue from EtOH-Et₂O yielded 300 mg (94%) of 23 as crystal, mp 188 °C, [α]D₂⁵ +81.6° (c 1.0, MeOH). ¹H-NMR (D₂O) δ: 7.88 (1 H, d, J = 7.6 Hz, 6'), 6.21 (1 H, t, J = 6.6 Hz, 1'), 6.05 (1 H, d, J = 7.6 Hz, 5), 4.42 (1 H, t, J = 5.9 Hz, 3'), 3.64 (2 H, s, 5'), 2.52 (1 H, ddd, J = 5.9, 6.6, 14 Hz, 2'), 2.43 (1 H, ddd, J = 5.9, 6.6, 14 Hz, 2'), 1.25 (3 H, s, Me); IR νmax (KBr) cm⁻¹: 3430, 3340, 3220, 1650, 1620, 1540, 1480, 1410, 1370, 1290, 1060, 970; CI-MS m/z: 242 (M⁺+H); Calcd for C₁₁H₁₁N₂O₂: C, 49.79; H, 6.27; N, 17.42; Anal. Found: C, 49.69; H, 6.20; N, 17.13; UV λmax (H₂O) nm (c): 272 (10700), 198 (23000).

5′-O-(tert-Butyldimethylsilyl)-4′-C-methyladenosine (26).

To a stirred suspension of 4′-C-methyladenosine (24)[3] (2.0 g, 7.11 mmol) and imidazole (1.2 g, 17.8 mmol) in DMF (70 ml) was added tert-butyldimethylsilyl chloride (1.2 g, 7.82 mmol). The reaction mixture was heated at 60 °C with the exclusion of moisture for 3 h. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography, using CHCl₃-MeOH (20:1) as an eluent, to give 26 (1.8 g, 65%) as a crystal, mp 183 °C, [α]D₀⁻²⁵ -24.4° (c 0.6, CHCl₃). ¹H-NMR (CDCl₃) δ: 8.29 (1 H, s, 2), 8.06 (1 H, s, 8), 5.93 (1 H, d, J = 6.3 Hz, 1'), 5.73 (2 H, br s, NH₂), 4.73 (1 H, dd, J = 5.3, 6.3 Hz, 2'), 4.28 (1 H, d, J = 5.3 Hz, 3'), 3.62 (1 H, d, J = 11 Hz, 5'), 3.57 (1 H, d, J = 11 Hz, 5'), 1.40 (3 H, s, 4'Me), 0.74 (9 H, s, Bu'), -0.01 (3 H, s, Me), -0.08 (3 H, s, Me); IR νmax (KBr) cm⁻¹: 3340, 3220, 2930, 1660, 1650, 1600, 1490, 1420, 1330, 1300, 1260, 1210, 1100, 840, 780; EI-MS m/z: 395 (M⁺); HR-MS calcd for C₁₁H₁₅N₂O₂Si (M⁺) 395.1934, found 395.1960.

5′-O-(tert-Butyldimethylsilyl)-2′, 3′-didehydro-2′, 3′-dideoxy-4′-C-methyladenosine (28).

To a solution of 26 (1.8 g, 4.65 mmol) in DMF (25 ml) was added 1,1′-thionocarboxyldiimidazole (1.0 g, 5.58 mmol), and the mixture was heated at 80 °C for 1 h. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography, using CHCl₃-MeOH (20:1) as an eluent. Evaporation of the appropriate fractions and crystallization of the residue from CHCl₃-hexane yielded 1.8 g (88%) of 27 as crystal. To an ice-cooled solution of 27 (1.5 g, 3.43 mmol) in dry THF (15 ml) was added dropwise 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (2.0 g, 10.3 mmol). The reaction mixture was stirred under nitrogen at 0 °C for 10 min and then at room temperature for 3 h. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography, using CHCl₃-MeOH (30:1) as an eluent. Evaporation of the appropriate fractions and crystallization of the residue from benzene-hexane yielded 780 mg (63%) of 28 as a crystalline product, mp 142 °C, [α]D₀⁻²⁵ +1.3° (c 0.6, CHCl₃). ¹H-NMR (CDCl₃) δ: 8.38 (1 H, s, 2), 8.09 (1 H, s, 8), 7.11 (1 H, d, J = 1.3, 1.7 Hz, 1'), 6.35 (1 H, d, J = 1.7, 5.9 Hz, 2'), 5.98 (1 H, d, J = 1.3, 5.9 Hz, 3'), 5.68 (2 H, br s, NH₂), 3.65 (2 H, s, 5'), 1.37 (3 H, s, 4'Me), 0.89 (9 H, s, Bu'), 0.05 (3 H, s, Me), 0.03 (3 H, s, Me); IR νmax (KBr) cm⁻¹: 3180,
2',3'-Didehydro-2',3'-dideoxy-4'-C-methyladenosine (29). To a solution of 28 (730 mg, 2.20 mmol) in dry THF (10 ml), cooled in an ice bath, was added a 1M solution of tetramethylammonium fluoride in THF (4.0 ml, 4.04 mmol). The mixture was stirred for 40 min at room temperature and concentrated. The resulting residue was purified by silica gel column chromatography, using CHCl₃-MeOH (10:1) as an eluent. Evaporation of the appropriate fractions and crystallization of the residue from MeOH yielded 370 mg (74%) of 29 as a crystalline product, mp 164 °C, [α]D 25 +94.2° (c 0.6, MeOH), ¹H-NMR (DMSO-d₆) δ: 8.18 (1 H, s, 2), 8.14 (1 H, s, 8), 7.23 (2 H, br s, NH₂), 6.95 (1 H, dd, J = 1.3, 2.0 Hz, 1'), 6.40 (1 H, dd, J = 2.0, 5.9 Hz, 2'), 6.06 (1 H, dd, J = 1.3, 5.9 Hz, 3'), 5.10 (1 H, t, J = 5.6 Hz, OH), 3.49 (1 H, dd, J = 5.6, 12 Hz, 5'), 3.43 (1 H, dd, J = 5.6, 12 Hz, 5'), 1.26 (3 H, s, Me); IR ν max (KBr) cm⁻¹: 3330, 3180, 1660, 1600, 1480, 1420, 1370, 1330, 1290, 1240, 1200, 1080, 970, 840; EI-MS m/z: 247 (M⁺); HR-MS calcd for C₁₅H₁₇N₂O₂ (M⁺) 247.1067, found 247.1048.

2',3'-Dideoxy-4'-methyladenosine (30). A solution of 29 (250 mg, 1.01 mmol) in MeOH (60 ml) was hydrogenated at 1.0 kg/cm² in the presence of Pd-black (100 mg) for 3 h. The reaction mixture was filtered and the filtrate was evaporated. Crystallization of the crude product from MeOH-Et₂O gave 30 (170 mg, 68%) as crystal, mp 180-181 °C, [α]D 25 -8.8° (c 0.5, MeOH), ¹H-NMR (DMSO-d₆) δ: 8.20 (1 H, s, 2), 8.20 (1 H, s, 8), 6.34 (1 H, dd, J = 4.6, 6.3 Hz, 1'), 3.63 (1 H, d, J = 12 Hz, 5'), 3.57 (1 H, d, J = 12 Hz, 5'), 2.33 (1 H, dt, J = 8.3, 13 Hz, 3'), 2.02 (1 H, ddd, J = 5.6, 8.3, 13 Hz, 3'), 1.32 (3 H, s, Me); IR ν max (KBr) cm⁻¹: 3320, 3180, 1660, 1570, 1470, 1420, 1370, 1340, 1300, 1250, 1210, 1080, 1000, 940; EI-MS m/z: 249 (M⁺); HR-MS calcd for C₁₅H₁₃N₂O₂ (M⁺) 249.1225, found 249.1233, UV λ max (MeOH) nm (ε): 260 (18000), 207 (25500).

5'-O-Acetyl-2',3'-didehydro-3'-deoxy-4'-C-methylthymidine (31). Acetyl bromide (5.0 ml, 60.1 mmol) was added dropwise over 0.5 h to a suspension of 1-(4-methyl-β-D-ribofuranosyl)thymine (14) (2.82 g, 10.4 mmol) in acetonitrile (120 ml) heated at reflux. On completion of addition, the solution was allowed to cool and then concentrated. The residue was dissolved in methylene chloride and washed with water. The organic phase was dried (Na₂SO₄) and concentrated to leave crude 15. The Zn/Cu couple (ca. 14 g) was suspended in methanol (100 ml), and crude 15 (4.34 g, 10.4 mmol) was added, and the mixture was stirred for 0.5 h. The mixture was filtered and concentrated. The residue was purified by silica gel column chromatography, using CHCl₃-MeOH-AcOEt-hexane (40:1:30:10) as an eluent. Evaporation of the appropriate fractions and crystallization of the residue from AcOEt-hexane yielded 810 mg (28%) of 31 as crystal, mp 158 °C, [α]D 25 -10.0° (c 1.0, CHCl₃), ¹H-NMR (CDCl₃) δ: 7.33 (1 H, d, J = 1.2 Hz, 6), 6.99 (1 H, dd, J = 1.2, 2.0 Hz, 1'), 6.23 (1 H, dd, J = 2.0, 5.9 Hz, 3'),...
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5.82 (1 H, dd, J = 1.2, 5.9 Hz, 2'), 4.36 (1 H, d, J = 12 Hz, 5'), 4.06 (1 H, d, J = 12 Hz, 5'), 2.09 (3 H, s, Ac), 1.92 (3 H, d, J = 1.2 Hz, Me), 1.38 (3 H, s, 4'Me); IR \( \upsilon_{\text{max}} \) (KBr) cm\(^{-1}\): 3150, 3000, 2800, 1740, 1680, 1460, 1420, 1360, 1250, 1220, 1110, 1080, 1020, 890, 830, 770; EI-MS \( m/z \): 280 (M'); Caled for C\(_{13}\)H\(_{18}\)N\(_2\)O\(_5\): C, 55.71; H, 5.75; N, 10.00, Anal. Found: C, 55.51; H, 5.65; N, 10.04.

2', 3'-Didehydro-3'-deoxy-4'-C-methylthymidine (32). Compound 32 (330 mg) was prepared from 31 in a 98% yield by the similar procedure to that described for 13. 32: mp 140 °C, [\( \alpha \)]\(_D\)\(^{25}\) +83.5° (c 1.0, MeOH), \(^1\)H-NMR (D\(_2\)O) \( \delta \): 7.67 (1 H, s, 6), 6.95 (1 H, br s, 1'), 6.43 (1 H, dd, J = 1.7, 6.1 Hz, 3'), 5.91 (1 H, brd, J = 3.7), 3.71 (1 H, d, J = 13 Hz, 5'), 3.57 (1 H, d, J = 13 Hz, 5'), 1.85 (3 H, s, Me), 1.31 (3 H, s, 4'Me); IR \( \upsilon_{\text{max}} \) (KBr) cm\(^{-1}\): 3400, 3150, 3000, 1680, 1640, 1460, 1390, 1250, 1070, 980, 900, 820, 770; EI-MS \( m/z \): 238 (M'); Caled for C\(_{11}\)H\(_{14}\)N\(_2\)O\(_4\); C, 54.63; H, 6.00; N, 11.58; Anal. Found: C, 54.37; H, 5.73; N, 11.48; UV \( \lambda_{\text{max}} \) (MeOH) nm (E): 266 (7460), 210 (7590).

5'-O-AcetyI-3'-deoxy-4'-C-methylthymidine (33). A solution of 31 (500 mg, 1.78 mmol) in methanol (20 ml) was stirred under hydrogen with 10% Pd-carbon (250 mg) for 1 h. The catalyst was removed by filtration and the filtrate was evaporated to give crude crystal, which were recrystallized from AcOEt-hexane to give 33 (460 mg, 91%) as crystal, mp 130 °C, [\( \alpha \)]\(_D\)\(^{10}\) +10.9° (c 1.0, CHCl\(_3\)), \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 8.34 (1 H, br s, NH), 7.42 (1 H, d, J = 1.3 Hz, 6), 6.13 (1 H, t, J = 5.9 Hz, 1'), 4.26 (1 H, d, J = 12 Hz, 5'), 4.11 (1 H, d, J = 12 Hz, 5'), 2.47-2.57 (1 H, m, 2'), 2.14 (3 H, s, Me), 1.80-2.10 (3 H, m, 2', 3'), 1.94 (3 H, d, J = 1.3 Hz, Me), 1.32 (3 H, s, 4'Me); IR \( \upsilon_{\text{max}} \) (KBr) cm\(^{-1}\): 3190, 3060, 1740, 1690, 1480, 1380, 1270, 1230, 1120, 1070, 1040, 960, 900, 850; EI-MS \( m/z \): 282 (M'); HR-MS calcd for C\(_{13}\)H\(_{18}\)N\(_2\)O\(_5\) (M') 282.1214, found 282.1204.

3'-Deoxy-4'-C-methylthymidine (34). Compound 34 (280 mg) was prepared from 33 in a 89% yield by the similar procedure to that described for 13. 34: mp 125-126 °C, [\( \alpha \)]\(_D\)\(^{25}\) +29.6° (c 1.0, MeOH), \(^1\)H-NMR (D\(_2\)O) \( \delta \): 7.76 (1 H, d, J = 1.0 Hz, 6), 6.18 (1 H, dd, J = 4.3 Hz, 6.9, 1'), 3.67 (1 H, d, J = 12 Hz, 5'), 3.63 (1 H, d, J = 12 Hz, 5'), 2.49-2.64 (1 H, m, 2'), 2.10-2.23 (2 H, m, 2', 3'), 1.90 (3 H, d, J = 1.0 Hz, Me), 1.84-1.94 (1 H, m, 3'), 1.26 (3 H, s, 4'Me); IR \( \upsilon_{\text{max}} \) (KBr) cm\(^{-1}\): 3370, 2920, 1710, 1650, 1460, 1410, 1280, 1260, 1140, 1110, 1080, 1060, 1000, 930, 860, 840; EI-MS \( m/z \): 240 (M'); HR-MS calcd for C\(_{13}\)H\(_{16}\)N\(_2\)O\(_4\) (M') 240.1109, found 240.1109, UV \( \lambda_{\text{max}} \) (H\(_2\)O) nm (E): 268 (10800), 207 (10800).

\( N^4 \)-Acetyl-1', 4'-C-methylcytidine (36). A mixture of 4'-C-methylcytidine (35)\(^3\) (1.9 g, 7.39 mmol) and acetic anhydride (2 ml) in methanol (90 ml) was heated under reflux with stirring. At hourly intervals, acetic anhydride (2 ml x 2) was added to a mixture. After 4 h, the reaction mixture cooled at room temperature and evaporated. The residue was purified by silica gel column
chromatography, using CHCl₃-MeOH (5:1) as an eluent, to give 36 (1.5 g, 66%) as crystal, mp 191 °C. [α]D²⁵ +18.4° (c 0.9, MeOH). ¹H-NMR (D₂O) δ: 8.32 (1 H, d, J = 7.6 Hz, 6), 7.35 (1 H, d, J = 7.6 Hz, 5), 6.01 (1 H, d, J = 4.9 Hz, 1'), 4.47 (1 H, dd, J = 4.9, 5.9 Hz, 2'), 4.24 (1 H, d, J = 5.9 Hz, 3'), 3.68 (2 H, s, 5'), 2.25 (3 H, s, Ac). 1.33 (3 H, s, Me); IR νmax (KBr) cm⁻¹: 3530, 3270, 1720, 1650, 1490, 1430, 1390, 1320, 1310, 1190, 1100, 1060, 810, 790; EI-MS m/z: 299 (M⁺); HR-MS calcd for C₁₃H₁₅N₂O₂ (M⁺) 299.1116, found 299.1113.

N⁴'-Acetyl-2',3'-didehydro-2',3'-dideoxy-4'-C-methylcytidine (40). Employing conditions analogous to those used for the preparation of 29, compound 36 (1.6 g, 5.18 mmol) gave 40 (410 mg, 33%) as an amorphous. [α]D +65.8° (c 0.3, CHCl₃), ¹H-NMR (CDCl₃) δ: 8.09 (1 H, d, J = 7.6 Hz, 6), 7.40 (1 H, d, J = 7.6 Hz, 5), 6.93 (1 H, dd, J = 1.3, 1.7 Hz, 1'), 6.13 (1 H, dd, J = 1.7, 5.9 Hz, 3'), 6.04 (1 H, dd, J = 1.3, 5.9 Hz, 3'), 4.43 (1 H, d, J = 12 Hz, 5'), 4.04 (1 H, d, J = 12 Hz, 5'), 2.27 (3 H, s, Ac), 1.41 (3 H, s, Me); IR νmax (neat) cm⁻¹: 3090, 2980, 1750, 1660, 1560, 1500, 1470, 1400, 1370, 1310, 1240, 1090, 1050, 990, 850, 790; EI-MS m/z: 265 (M⁺); HR-MS calcd for C₁₉H₂₁N₂O₂ (M⁺) 265.1062, found 265.1061.

2',3'-Didehydro-2',3'-dideoxy-4'-C-methylcytidine (41). Compound 41 (100 mg) was prepared from 40 (150 mg, 0.57 mmol) in a 79% yield by the similar procedure to that described for 13. 41: mp 161 °C. [α]D₂⁵ +90.7° (c 0.5, MeOH), ¹H-NMR (D₂O) δ: 7.78 (1 H, d, J = 7.3 Hz, 6), 6.95 (1 H, br d, J <1 Hz, 1'), 6.40 (1 H, dd, J = 5.9, <1 Hz, 2'), 5.98 (1 H, d, J = 7.3 Hz, 5), 3.68 (1 H, d, J = 12 Hz, 5'), 3.57 (1 H, d, J = 13 Hz, 5'), 1.32 (3 H, s, Me); IR νmax (KBr) cm⁻¹: 3410, 1650, 1590, 1520, 1470, 1400, 1360, 1290, 1230, 1090, 1060, 1030, 850; CI-MS m/z: 224 (M⁺+H); HR-MS calcd for C₁₀H₁₄N₂O₅ (M⁺) 223.0956, found 223.0958, UV λmax (MeOH) nm (ε): 271 (7930).

5'-O-Acetyl-2',3'-dideoxy-4'-C-methyluridine (43). Employing conditions analogous to those used for the preparation of 33, compound 18 (1.7 g, 6.39 mmol) gave 43 (440 mg, 26%) as a pale yellow syrup. [α]D₂⁵ +21.7° (c 1.0, CHCl₃), ¹H-NMR (CDCl₃) δ: 9.50 (1 H, br s, NH), 7.68 (1 H, d, J = 8.2 Hz, 6), 6.11 (1 H, dd, J = 4.6, 6.3 Hz, 1'), 5.73 (1 H, d, J = 8.2 Hz, 5), 4.23 (1 H, d, J = 12 Hz, 5'), 4.11 (1 H, d, J = 12 Hz, 5'), 2.51-2.66 (1 H, m, 2'), 2.12 (3 H, s, Ac), 1.97-2.11 (2 H, m, 2', 3'), 1.89-1.91 (1 H, m, 3'), 1.32 (3 H, s, Me); IR νmax (neat) cm⁻¹: 3200, 3050, 1730, 1700, 1680, 1650, 1470, 1280, 1240, 1100, 1050, 950, 810; EI-MS m/z: 268 (M⁺); HR-MS calcd for C₁₀H₁₆N₂O₅ (M⁺) 268.1058, found 268.1091.

2',3'-Dideoxy-4'-C-methylcytidine (44). Employing conditions analogous to those used for the preparation of 23, compound 43 (400 mg, 1.49 mmol) gave 44 (70 mg, 21%) as an amorphous, [α]D₂⁵ +67.6° (c 1.0, MeOH), ¹H-NMR (D₂O) δ: 7.93 (1 H, d, J = 7.6 Hz, 6), 6.14 (1 H, dd, J = 3.6, 6.6 Hz, 1'), 6.03 (1 H, d, J = 7.6 Hz, 5), 3.68 (1 H, d, J = 12 Hz, 5'), 3.48
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(1 H, d, J = 12 Hz, 5'), 2.55-2.64 (1 H, m, 2'), 2.01-2.14 (2 H, m, 2', 3'), 1.82-1.92 (1 H, m, 3'), 1.27 (3 H, s, Me); IR νmax (neat) cm⁻¹: 3350, 3200, 1650, 1490, 1360, 1290, 1190, 1070, 1010, 950, 790; SI-MS m/z: 226 (M+H); HR-MS calcd for C₁₀H₁₅N₃O₄ (M⁺) 225.1112, found 225.1152, UV λmax (MeOH) nm (ε): 273 (7400).

1-(2',3',5'-Tri-O-acetyl-4'-C-methyl-β-D-arabinofuranosyl)uracil (45). A mixture of 21 (1.2 g, 3.70 mmol) and 1N NaOH (18 mL) in 50% ethanol (150 mL) was stirred at room temperature for 2 h. The solution was neutralized with AcOH/EtOH (1:1, v/v) to pH 7. The solvent was removed under vacuum and the residue was dissolved in pyridine (20 mL). Acetic anhydride (2.5 mL, 26.3 mmol) was added to a pyridine solution and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated to give another syrup. The syrup was purified by silica gel column chromatography, using CHCl₃-MeOH-AcOEt-hexane (20:2:15:5) as an eluent, to give 45 (760 mg, 53%) as crystal, mp 154 °C, [α]D₂⁰ +82.1° (c 0.7, CHCl₃), ¹H-NMR (CDCl₃) δ: 8.28 (1 H, br s, NH), 7.52 (1 H, d, J = 8.3 Hz, 6), 6.32 (1 H, d, J = 4.6 Hz, 1'), 5.73 (1 H, dd, J = 8.3 Hz, 1'), 5.47 (1 H, dd, J = 3.0, 4.6 Hz, 2'), 5.31 (1 H, d, J = 3.0 Hz, 3'), 4.27 (1 H, d, J = 12 Hz, 5'), 4.23 (1 H, d, J = 12 Hz, 5'), 2.15 (3 H, s, Ac), 2.14 (3 H, s, Ac), 2.04 (3 H, s, Ac), 1.31 (3 H, s, Me); IR νmax (KBr) cm⁻¹: 3030, 1750, 1710, 1680, 1380, 1280, 1240, 1120, 1050, 910, 810; CI-MS m/z: 385 (M⁺+H); HR-MS calcd for C₁₆H₂₀N₅O₇ (M⁺) 384.1167, found 384.1149.

1-(4'-C-Methyl-β-D-arabinofuranosyl)cytosine (46). Employing conditions analogous to those used for the preparation of 23, compound 45 (730 mg, 1.90 mmol) gave 46 (450 mg, 92%) as crystal, mp 205-206 °C (dec.), [α]D₂⁰ +91.0° (c 1.1, MeOH), ¹H-NMR (D₂O) δ: 7.88 (1 H, d, J = 7.6 Hz, 6), 6.24 (1 H, d, J = 5.9 Hz, 1'), 6.04 (1 H, d, J = 7.6 Hz, 5), 4.54 (1 H, t, J = 5.9 Hz, 2'), 4.14 (1 H, d, J = 5.9 Hz, 3'), 3.70 (2 H, s, 5'), 1.24 (3 H, s, Me); IR νmax (KBr) cm⁻¹: 3180, 1650, 1510, 1290, 1250, 1190, 1140, 1100, 1060, 820, 790; CI-MS m/z: 258 (M⁺+H); Calcd for C₁₀H₁₅N₃O₄; C, 46.69; H, 5.88; N, 16.33, Anal. Found: C, 46.45; H, 5.93; N, 15.92; UV λmax (H₂O) nm (ε): 272 (10200), 197 (22400).

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REFERENCES


