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Synthesis of 1- β -L-Arabinofuranosylcytosine (β -L-Ara-C) and 2'-Deoxy-2'-methylene- β -L-cytidine (β -L-DMDC) as Potential Antineoplastic Agents

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SYNTHESIS OF 1- β -L-ARABINOFURANOSYLCYTOSINE (β -L-Ara-C) AND 2'-DEOXY-2'-METHYLENE- β -L-CYTIDINE (β -L-DMDC) AS POTENTIAL ANTINEOPLASTIC AGENTS

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Abstract: 1- β -L-Arabinofuranosylcytosine (β -L-Ara-C, **7**) and 2'-deoxy-2'-methylene- β -L-cytidine (β -L-DMDC, **14**) have been synthesized via a multi-step synthesis from L-arabinose. These compounds were tested in vitro against L1210, P388, Sarcoma 180, and CEM cells, and found not to be active at a concentration up to 100 μ M. β -L-Ara-C and β -L-DMDC were also tested against HSV-1 and HSV-2 and yielded ID₅₀ values of >100 μ M.

L-Nucleosides, the enantiomers of natural D-nucleosides, are believed not to be recognized by normal cellular enzymes and, therefore, are not toxic to the host cells.¹ In addition, it was found that L-ribonucleoside diphosphates interact with bacterial polynucleotide phosphorylase and nucleolytic enzymes.^{2,3} Spadari et al.⁴ reported that L-thymidine is not recognized by human thymidine kinase, but is a substrate for a kinase from the herpes simplex virus (HSV-1) and reduces HSV-1 multiplication in HeLa cells. 2',3'-Dideoxy- β -L-cytidine (ddC) has been shown to be a potent inhibitor of the replication of both human immunodeficiency virus (HIV)⁵ and human hepatitis B virus (HBV)^{6,7} in vitro. However, long-term ddC usage causes delayed toxicity such as peripheral neuropathy in patients, which has been suggested to result from the depletion of mitochondrial DNA (mt DNA) in cells treated with ddC.⁸ Recently, 2',3'-dideoxy- β -L-cytidine (β -L-ddC) and 2',3'-dideoxy- β -L-fluorocytidine (β -L-FddC) have shown much more potent antiviral activity against HBV than their D-counterparts, 2',3'-dideoxy- β -D-cytidine (ddC) and 2',3'-dideoxy- β -D-fluorocytidine (β -D-FddC), with respective ED₅₀

values of 0.01, 0.01, 2.8, and 10 μM , and with negligible inhibition to the host mitochondrial DNA synthesis.^{9,10}

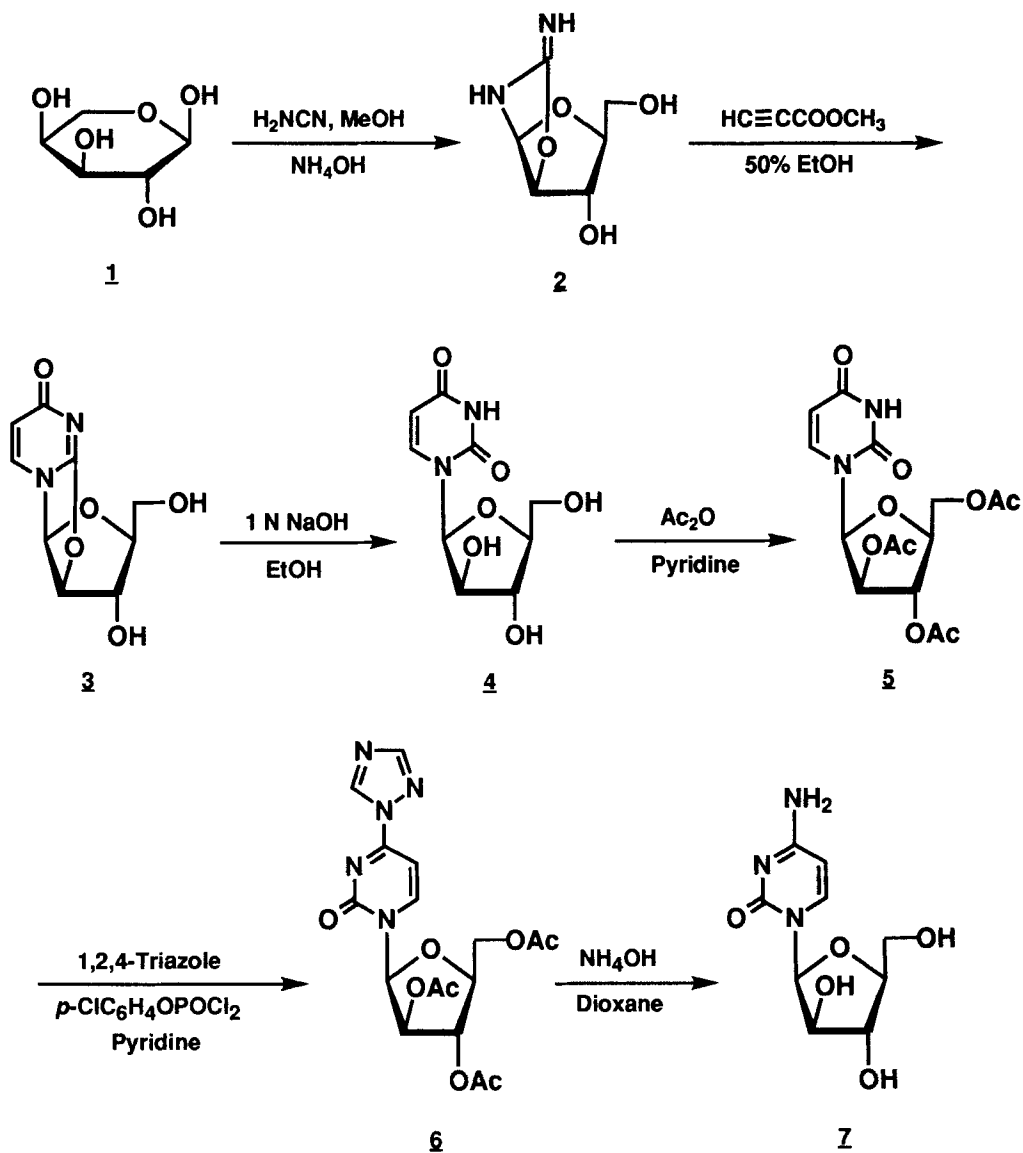
1- β -D-Arabinofuranosylcytosine (Ara-C) is an important chemotherapeutic agent in the treatment of acute myelogenous leukemia,^{11,12} and, recently, 2'-deoxy-2'-methylene- β -D-cytidine (DMDC) was found to have significant anticancer activity in vivo.¹³⁻¹⁵ Based on these findings, the L-counterparts of ara-C and DMDC were synthesized as potential anticancer agents, with the hope that these compounds would retain their anticancer activity with a reduction of the host toxicity.

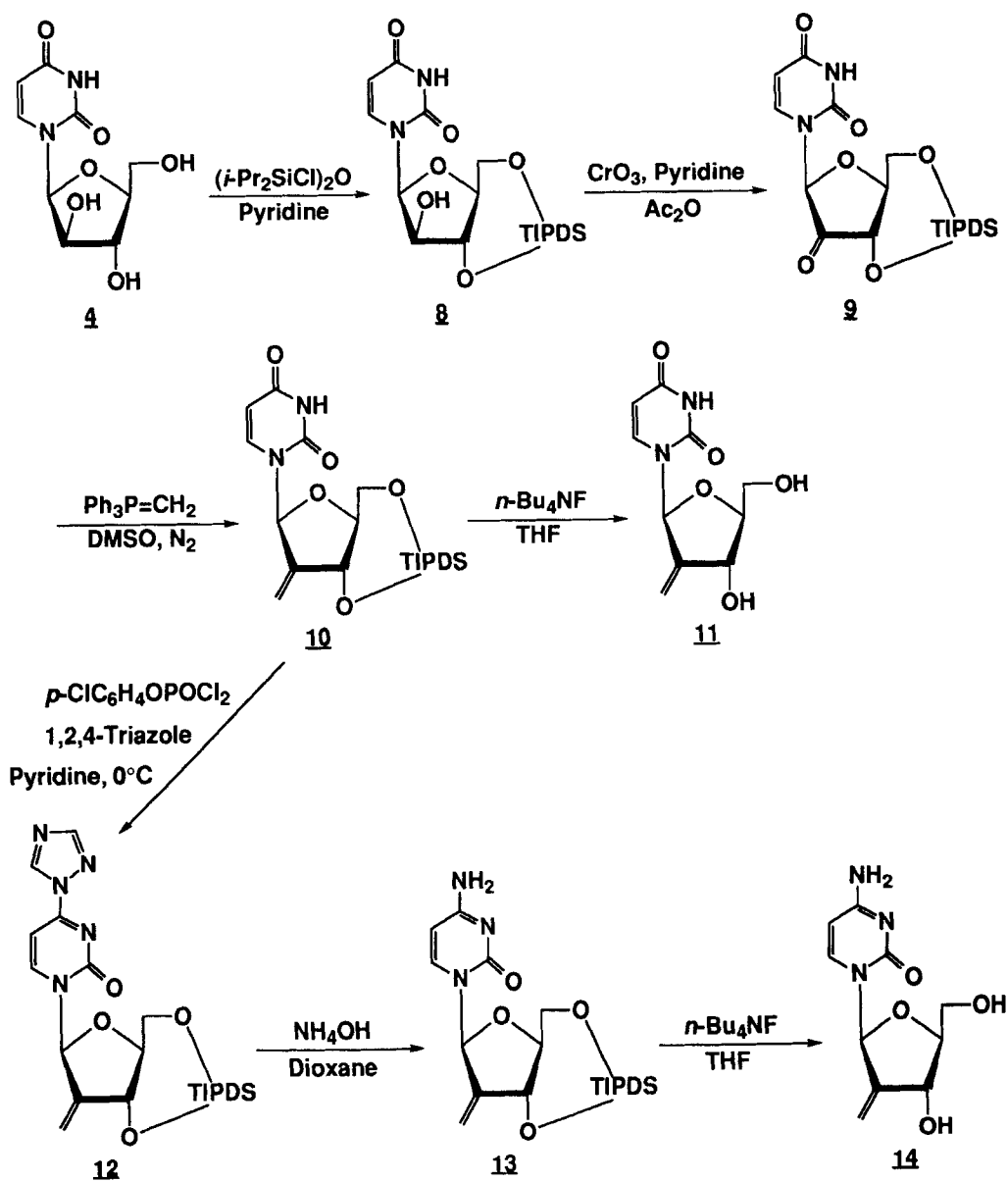
The syntheses of 1- β -L-arabinofuranosylcytosine (β -L-Ara-C, **7**) and 2'-deoxy-2'-methylene- β -L-cytidine (β -L-DMDC, **14**) are described in Schemes 1 and 2. The anhydro derivative **3** was synthesized from L-arabinose by the methodology of Holy.¹⁶ Reaction of compound **3** with 1 N NaOH in ethanol yielded 1- β -L-arabinofuranosyluracil (**4**). Acetylation of compound **4** with acetic anhydride, followed by treatment^{17,18} of the acetate **5** with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole in anhydrous pyridine at room temperature yielded the 4-triazolylpyrimidinone derivative **6**. Subsequent treatment of compound **6** with a mixture of ammonium hydroxide/dioxane (2:1, v/v) gave the desired product **7** (Scheme 1). Treatment¹⁹ of 1- β -L-arabinofuranosyluracil (**4**) with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane in dry pyridine gave the corresponding 3',5'-O-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl) derivative **8**. Oxidation²⁰ of compound **8** with chromium trioxide/pyridine/acetic anhydride complex, followed by reaction²¹ with methylenetriphenylphosphorane in anhydrous dimethyl sulfoxide produced the 2'-methylene analog **10** via the intermediate **9**. Deprotection¹⁹ of compound **10** with tetra-*n*-butylammonium fluoride in THF yielded 2'-deoxy-2'-methylene- β -L-uridine (**11**). Compound **10** was also converted to the corresponding cytidine derivative **13** via the intermediate **12** by a similar procedure as previously described for the synthesis of compound **7**. Treatment of compound **13** with tetra-*n*-butylammonium fluoride in THF gave the desired product **14**.

β -L-Ara-C (**7**) and β -L-DMDC (**14**) were tested in vitro against L1210, P388, Sarcoma 180, and CEM cells and found not to be active at a concentration up to 100 μM . β -L-Ara-C and β -L-DMDC were also tested against HSV-1 and HSV-2 and yielded ID₅₀ values of >100 μM . The results suggest that these compounds are not the substrates for the relevant enzyme(s).

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian EM-390 (90 MHz) NMR

**Scheme 1**

**Scheme 2**

spectrometer. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer Model 241 polarimeter at 25 °C. The UV spectra were recorded on a Beckman-25 spectrophotometer. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT.

1- β -L-Arabinofuranosyluracil (4). A suspension of 2,2'-anhydro-L- β -uridine (**3**, 5.0 g, 22 mmol), 1 N NaOH (20 mL), and 50% ethanol (130 mL) was stirred at room temperature until a clear solution was obtained. The reaction mixture was stirred for an additional hour and then neutralized with HOAc/EtOH (1:1, v/v) to ~pH 7. The resulting solution was evaporated in vacuo to a small volume, and the precipitated white solid was collected by filtration, washed with water, dried, and recrystallized from ethanol to give 4.6 g (84%) of product: mp 202-204 °C; R_f 0.6 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$, 2:1, v/v); ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 3.50-4.10 (m, 6 H, 2'-H, 3'-H, 4'-H, 5'-H and 5'-OH, D_2O exchangeable), 5.30-6.30 (br s, 2 H, 2'-OH and 3'-OH, D_2O exchangeable), 5.45-5.55 (d, 1 H, 5-H), 5.95 (m, 1 H, 1'-H), 7.60 (d, 1 H, 6 H). Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_6\cdot\text{H}_2\text{O}$: C, 41.18; H, 5.38; N, 10.68. Found: C, 41.06; H, 5.08; N, 10.28.

2',3',5'-Tri-*O*-acetyl-1- β -L-arabinofuranosyluracil (5). Acetyl anhydride (15 mL) was added dropwise to a stirred solution of compound **4** (3.0 g, 12 mmol) in dry pyridine (100 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. The solution was evaporated to dryness in vacuo to give an oil, which was dissolved in 70 mL of methylene chloride, washed with water (2 x 25 mL), and dried (MgSO_4). The solvent was removed under reduced pressure to give a residue which was then chromatographed on a silica gel column ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 4:1, v/v, R_f 0.56) to yield 3.9 g (87%) of white solid: mp 130-131 °C; ^1H NMR (CDCl_3) δ 2.00 (s, 3 H, COCH_3), 2.10 (s, 6 H, 2 x COCH_3), 4.21 (m, 1 H, 4'-H), 4.36 (m, 2 H, 5'-H), 5.02 (m, 1 H, 3'-H), 5.42 (m, 1 H, 2'-H), 5.72 (d, 1 H, 5-H), 6.23 (d, 1 H, 1'-H), 7.35 (d, 1 H, 6-H), 9.42 (s, 1 H, 3-NH, D_2O exchangeable). Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_9$: C, 48.65; H, 4.90; N, 7.57. Found: C, 48.47; H, 4.63; N, 7.53.

1-(2,3,5-Tri-*O*-acetyl- β -L-arabinofuranosyl)-4-(1,2,4-triazole-1-yl)-1H-pyrimidine-2-one (6). To a stirred solution of compound **5** (2.2 g, 6.0 mmol) in dry pyridine was added dropwise 4-chlorophenyl phosphorodichloridate (1.96 mL, 12.0 mmol) at 0-5 °C (ice/water bath), followed by the addition of 1,2,4-triazole (1.68 g, 24 mmol). The reaction mixture was stirred at room temperature for 3 days and then concentrated to dryness under reduced pressure. The residue was co-evaporated with

toluene (30 mL) and then chromatographed on a silica gel column ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 1:2, v/v) to afford 1.2 g (48%) of product as a foam: R_f 0.43 (EtOAc); ^1H NMR (CDCl_3) δ 1.95 (s, 3 H, COCH_3), 2.10 (s, 3 H, COCH_3), 2.13 (s, 3 H, COCH_3), 4.28 (m, 1 H, 4'-H), 4.40 (s, 2 H, 5'-H), 5.09 (m, 1 H, 3'-H), 5.53 (d, 1 H, 2'-H), 6.34 (d, 1 H, 1'-H), 7.05 (d, 1 H, 5-H), 8.04 (s, 1 H, triazolyl 3-H), 7.35 (d, 1 H, 6-H), 9.42 (s, 1 H, 3-NH, D_2O exchangeable). Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_9$: C, 48.46; H, 4.54; N, 16.62. Found: C, 48.17; H, 4.63; N, 16.24.

1- β -L-Arabinofuranosylcytosine (7). Compound **6** (1.2 g, 2.9 mmol) was dissolved in 80 mL of NH_4OH /dioxane (1:3, v/v) and the reaction mixture was stirred for 2 days at room temperature. The solvent was removed in vacuo to give a residue, which was purified on a silica gel column (EtOAc/MeOH, 2:1, v/v) to yield 0.6 g (87%) of a white solid: mp 209–210 °C; $[\alpha]_D -111^\circ$ ($c = 0.20$, MeOH); ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 3.45–4.00 (m, 5 H, 2'-H, 3'-H, 4'-H, and 5'-H), 4.95 (m, 1 H, 5'-OH, D_2O exchangeable), 5.35 (m, 2 H, 2'-OH and 3'-OH, D_2O exchangeable), 5.63 (d, 1 H 5-H), 6.00 (m, 1 H, 1'-H), 6.98 (m, 2 H, NH_2 , D_2O exchangeable), 7.58 (d, 1 H, 6 H). Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_5 \cdot \text{H}_2\text{O}$: C, 44.44; H, 5.70; N, 17.28. Found: C, 44.25; H, 5.39; N, 16.99.

1-[3,5-*O*-(1,1,3,3-Tetraisopropylidisiloxane-1,3-diyl)- β -L-arabinofuranosyl]uracil (8). A mixture of compound **4** (5.4 g, 22 mmol) and 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (7.2 g, 23 mmol) in 80 mL of dry pyridine was stirred at room temperature for 3 days. The reaction mixture was evaporated in vacuo to dryness, and co-evaporated twice with methylene chloride. The residue was dissolved in methylene chloride (100 mL), washed with water, and dried (MgSO_4). The filtrate was evaporated to dryness in vacuo and the residue was chromatographed on a silica gel column ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1, v/v) to afford 8.6 g (80%) of product as a foam: R_f 0.78 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1, v/v); ^1H NMR (CDCl_3) δ 1.05 (m, 28 H, CHMe_2), 3.70–4.50 (m, 5 H, 2'-H, 3'-H, 4'-H and 5'-H), 4.40–4.70 (m, 1 H, 2'-OH, D_2O exchangeable), 5.50–5.65 (d, 1 H, 5-H), 6.00–6.10 (d, 1 H, 1'-H), 7.70–7.80 (d, 1 H, 6-H), 10.4 (br s, 1 H, 3-NH, D_2O exchangeable).

3',5'-*O*-(1,1,3,3-Tetraisopropylidisiloxane-1,3-diyl)-2'-keto- β -L-uridine (9). A mixture of CH_2Cl_2 (16 mL), CrO_3 (0.6 g), pyridine (1 mL), and acetic anhydride (0.6 mL) was stirred for 3 min then compound **8** (1.0 g, 2 mmol) was added to the mixture and stirred at room temperature for 1 h. The dark brown solution was poured into 130 mL of ethyl acetate with stirring and the resulting mixture was filtered. The filtrate was evaporated and the residue was co-evaporated with toluene and methylene chloride to

give 0.95 g of product, which was immediately used for the next reaction without further purification.

3',5'-O-(1,1,3,3-Tetraisopropylidisiloxane-1,3-diyl)-2'-deoxy-2'-methylene- β -L-uridine (10). A suspension of NaH (1.85 g, 80% dispersion in mineral oil, 62 mmol) in 71 mL of DMSO was heated at 65 °C under nitrogen until all the sodium hydride had dissolved. The reaction mixture was cooled to room temperature after which methyltriphenylphosphonium bromide (22.2 g, 62 mmol) was added. After stirring for 45 min, compound **9** (8.5 g, 18 mmol) was added to the reaction mixture and stirred for 2 more hours at 50-60 °C. The resulting solution was poured into ice-water (800 mL) and the pH value of the solution was adjusted to pH 7 with acetic acid. The solution was extracted with methylene chloride (4 x 100 mL), and the combined extracts were washed with water, dried (MgSO₄), and filtered. The filtrate was evaporated in vacuo to a small volume and purified by chromatography on a silica gel column (CH₂Cl₂/EtOAc, 1:1, v/v) to give 5.8 g (69%) of product as a white foam: *R*_f 0.83 (CH₂Cl₂/EtOAc, 1:1, v/v); ¹H NMR (CDCl₃) δ 1.05 (m, 28 H, CHMe₂), 3.60-3.80 (m, 1 H, 4'-H), 4.05-4.20 (m, 2 H, 5'-H), 4.75-4.95 (m, 1 H, 3'-H), 5.40-5.60 (m, 2 H, methylene), 5.60-5.75 (d, 1 H, 5-H), 6.50-6.60 (d, 1 H, 1'-H), 7.35-7.50 (d, 1 H, 6-H), 9.50-9.65 (s, 1 H, 3-NH, D₂O exchangeable). Anal. Calcd. for C₂₂H₃₈N₂O₆Si₂·0.1CH₂Cl₂: C, 54.03; H, 7.84; N, 5.70. Found: C, 53.81; H, 8.32; N, 5.32.

2'-Deoxy-2'-methylene- β -L-uridine (11). A mixture of compound **10** (0.8 g, 1.7 mmol) and *n*-Bu₄NF (5 mL, 5 mmol) in THF (100 mL) was stirred at room temperature until the starting material had disappeared (~1.5 h, followed by TLC: CH₂Cl₂/EtOAc, 1:1, v/v). The reaction mixture was then evaporated in vacuo to dryness and the residue was partitioned between water (30 mL) and methylene chloride (40 mL). The methylene chloride layer was extracted with water, and the combined water layers were co-evaporated with 5 g of silica gel under reduced pressure. The resulting residue was chromatographed on a silica gel column (CH₂Cl₂/EtOH, 5:1, v/v) to afford 0.32 g (79%) as a white solid: mp 162-164 °C; ¹H NMR (Me₂SO-*d*₆) δ 3.40-3.50 (m, 1 H, 4'-H), 3.60-3.80 (m, 1 H, 4'-H), 3.60-3.80 (m, 2 H, 5'-H), 4.40-4.60 (m, 1 H, 3'-H), 4.90-5.05 (m, 1 H, 3'-OH, D₂O exchangeable), 5.25-5.45 (m, 2 H, methylidene), 5.55-5.75 (m, 2 H, 5-H and 5'-OH, D₂O exchangeable), 6.40-6.50 (m, 1 H, 1'-H), 7.50-7.60 (d, 1 H, 6-H), 9.40-9.55 (s, 1 H, 3-NH, D₂O exchangeable). Anal. Calcd. for C₁₀H₁₂N₂O₅: C, 50.00; H, 5.04; N, 11.76. Found: C, 49.99; H, 5.34; N, 11.29.

3',5'-O-(1,1,3,3-Tetraisopropylidisiloxane-1,3-diyl)-2'-methylene- β -L-cytidine (13). 4-Chlorophenylphosphodichloridate (7.2 mL, 43.8 mmol) was added dropwise to a cooled (ice-water) solution of compound **10** (4.8 g, 10 mmol) and triazole (9.1 g, 0.13 mol) in 75 mL of anhydrous pyridine. The reaction mixture was stirred at room temperature for 2 days and then evaporated in vacuo to dryness. The residue was dissolved in methylene chloride, washed with water, dried (MgSO_4), and filtered. The filtrate was concentrated to a small volume and purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 4:1, v/v) to afford 3.3 g (62.3%) of compound **12**, which was used immediately without further purification.

To a solution of compound **12** (3.0 g, 5.6 mmol) in 60 mL of dioxane was added 20 mL of NH_4OH and the mixture was stirred at room temperature overnight. The solution was evaporated in vacuo to dryness and the residue was chromatographed on a silica gel column, using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10:1, v/v) as eluting solvent. The desired fractions with a R_f of 0.45 were collected and concentrated to afford 2.4 g (89%) of product as a foam: ^1H NMR (CDCl_3) δ 1.05 (m, 28 H, CHMe_2), 3.75 (m, 1 H, 4'-H), 4.10 (d, 2 H, 5'-H), 4.75 (d, 1 H, 3'-H), 5.40 (d, 1 H, methylene- H_A), 5.55 (m, 1 H, methylene- H_B), 5.80 (d, 1 H, 5-H), 6.70 (s, 1 H, 1'-H), 7.50 (d, 1 H, 6-H), 8.30 (s, 2 H, 4- NH_2 , D_2O exchangeable). Anal. Calcd. for $\text{C}_{22}\text{H}_{39}\text{N}_3\text{O}_5\text{Si}\cdot 0.5\text{H}_2\text{O}$: C, 53.84; H, 8.21; N, 8.56. Found: C, 53.52; H, 7.93; N, 8.39.

2'-Deoxy-2'-methylene- β -L-cytidine (14) and its hydrochloride salt.

A mixture of compound **13** (1.9 g, 4.0 mmol) and 12 mL (12 mmol) of 1 M *n*-BuNF/THF in 150 mL of THF was stirred at ambient temperature until TLC showed that the starting material had disappeared (~1.5 h). The reaction mixture was evaporated in vacuo to dryness and the residue was then partitioned between water (50 mL) and methylene chloride (60 mL). The water layer was washed with methylene chloride and evaporated in vacuo to dryness. The residue was chromatographed on a silica gel column using EtOAc/EtOH (6:1, v/v) as eluting solvent to afford 0.6 g (63%) of product as a white foam, which was converted to its hydrochloride salt as white crystals: mp darkened at 160 °C and decomposed at 300 °C; $[\alpha]_D^{+5}$ ($c = 0.23$, MeOH) for the free nucleoside **14**; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 3.58 (m, 2 H, 5'-H), 3.65 (m, 1 H, 4'-H), 4.46 (m, 1 H, 3'-H), 4.90 (t, 1 H, 5'-OH, D_2O exchangeable), 5.15 (d, 1 H, methylene- H_A), 5.25 (d, 1 H, methylene- H_B), 5.50 (d, 1 H, 3'-OH, D_2O exchangeable), 5.70 (d, 1 H, 5-H), 6.40 (d, 1 H, 1'-H), 7.00 (d, 2 H, 4- NH_2 , D_2O exchangeable), 7.40 (d, 1 H, 6-H). Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{N}_3\text{O}_4\text{Cl}\cdot 0.4\text{H}_2\text{O}$: C, 42.45; H, 5.25; N, 14.85. Found: C, 42.62; H, 5.51; N, 14.68.

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REFERENCES

- (1) Jurovcik, M.; Holy, A. *Nucl. Acids Res.*, **1976**, *3*, 2143-2154.
- (2) Holy, A.; Sorm, F. *Collect. Czech. Chem. Commun.*, **1971**, *36*, 3282-3299.
- (3) Simuth, J.; Holy, A. *Nucl. Acids Res., Spec. Publ. I*, **1975**, s165-s168.
- (4) Spadari, S.; Maga, G.; Focher, F.; Ciarrocchi, G.; Manservigi, R.; Arcamone, F.; Capobianco, M.; Carcuro, A.; Colonna, F.; Iotti, S.; Garbesi, A. *J. Med. Chem.*, **1992**, *35*, 4214-4220.
- (5) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science*, **1990**, *249*, 1533-1543.
- (6) Yokota, T.; Mochizuki, S.; Konno, K.; Mori, S.; Shigeta, S.; De Clercq, E. *Antimicrob. Agents Chemother.*, **1991**, *35*, 394-397.
- (7) Ueda, K.; Tsurimoto, T.; Nagahata, T.; Chisaka, O.; Matsubara, K. *Virology*, **1989**, *169*, 213-216.
- (8) Chen, C. H.; Cheng, Y. C. *J. Biol. Chem.*, **1989**, *264*, 11934-11937.
- (9) Lin, T. S.; Luo, M. Z.; Liu, M. C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y. C. *Biochem. Pharmacol.*, **1994**, *47*, 171-174.
- (10) Lin, T. S.; Luo, M. Z.; Liu, M. C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y. C. *J. Med. Chem.*, **1994**, *37*, 798-803.
- (11) Dowling, M. D.; Gee, T. S.; Lee, B. J.; Clarkson, B. D.; Burchenal, J. H. *Proc. Am. Assoc. Cancer Res.*, **1972**, *13*, 21.
- (12) Clarkson, B. D. *Cancer*, **1972**, *30*, 1572-1582.
- (13) Takenuki, K.; Matsuda, A.; Ueda, T.; Sasaki, T.; Fujii, A.; Yamagami, K. *J. Med. Chem.*, **1988**, *31*, 1063-1064.
- (14) Matsuda, A.; Takenuki, K.; Tanaka, M.; Sasaki, T.; Fujii, A. *J. Med. Chem.*, **1991**, *34*, 812-819.
- (15) Lin, T. S.; Luo, M. Z.; Liu, M. C.; Clarke-Katzenburg, R. H.; Cheng, Y. C.; Prusoff, W. H.; Mancini, W. R.; Birnbaum, G. I.; Gabe, E. J.; Giziewicz, J. *J. Med. Chem.*, **1991**, *34*, 2607-2615.
- (16) Holy, A. *Coll. Czech. Chem. Commun.*, **1972**, *37*, 4072-4086.
- (17) Sung, W. L. *J. Chem. Soc. Chem. Commun.*, **1981**, No. 19705, 1089.

- (18) Lin, T. S.; Gao, Y. S.; Mancini, W. R. *J. Med. Chem.*, **1983**, *26*, 1691-1696.
- (19) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059-4065.
- (20) Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125-135.
- (21) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.*, **1963**, *28*, 1128-1129.

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