extracted with ether (10 mL). The combined organic extract was washed with brine, dried, and evaporated. The residue purified by chromatography on silica gel (1:9 ethyl acetate–hexane) yielded keto aldehyde (+)-**29** (52 mg, 50%) as a colorless liquid, a by-product, i.e., 2-hydroxy-4-methyl-4-(4-methylphenyl)-5,5-dimethyltetrahydrofuran (**33**) (22 mg, 20%) as an unseparable mixture of diastereoisomers, and starting material (−)-**32** (28 mg, 30%). Spectral data of (+)-**29** were identical with those reported above.

Data of **33**: ^{1}H NMR ($CDCl_3$) δ in 2:1 *a*/b mixture, 7.35–7.05 (m, 4 H), *5.70*/5.67 (X part of ABX system, 1 H, *a*/b), 3.80–3.55 (br s, OH, a/b), 2.54 [AB part of ABX system of b isomer, $\Delta\nu_{AB}$ = 165.6 Hz, 2.95 (A part, J_{AB} = 13.8 Hz, J_{AX} = 6.5 Hz, 0.33 H), 2.12 (B part, J_{AB} = 13.8 Hz, J_{BX} = 2.3 Hz, 0.33 H)], 2.54 [AB part of ABX system of a isomer, $\Delta\nu_{AB}$ = 100 Hz, 2.78 (A part, J_{AB} = 13.1 Hz, J_{AX} = 6.2 Hz, 0.66 H), 2.29 (B part, J_{AB} = 13.1 Hz, J_{BX} = 6.0 Hz, 0.66 H)], 2.35 (s, 6 H, 2 Me, tolyl a/b), 1.56 (s, 3 × 0.33 H, Me, b), 1.52 (s, 3 × 0.33 H, Me, b), 1.43 (s, 3 × 0.66 H, Me, a), 1.37 (s, 3 × 0.66 H, Me, a), 1.03 (s, 3 × 0.66 H, Me, a), 0.79 (s, 3 × 0.33 H, Me, b).

Supplementary Material Available: ^{1}H NMR spectra for obtained compounds (26 pages). Ordering information is given on any current masthead page.

Syntheses of the Anti-AIDS Drug 2′,3′-Dideoxycytidine from Cytidine

Percy S. Manchand,* Peter S. Belica, Michael J. Holman, Tai-Nang Huang, Hubert Maehr, Steve Y.-K. Tam, and Roxana T. Yang

Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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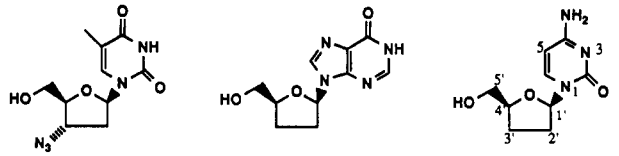
Two efficient syntheses of the anti-AIDS drug 2′,3′-dideoxycytidine (**3**) from N^4-acetylcytidine (**4**) are described. In one, silylation of the C-5′ hydroxyl group of **4** with *tert*-butyldimethylsilyl chloride followed by treatment with 1′,1′-(thiocarbonyl)diimidazole gave the cyclic thionocarbonate **7**, which on reaction with 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine gave the crystalline alkene **8**. Hydrogenation of **8**, followed by desilylation with tetrabutylammonium fluoride and hydrolysis, gave **3** in 27% overall yield from **4**. In the other synthesis, **4** was converted into a regioisomeric mixture of bromo acetates **11** with 2-acetoxy-2-methylpropanoyl bromide. Reductive elimination of **11** with zinc–copper couple in acetic acid or electrochemically gave the crystalline alkene **15**, whose stereostructure was established by a single-crystal X-ray analysis. Hydrogenation of **15**, followed by hydrolysis, gave ddC (**3**). In a through process, which is suitable for large-scale work, this second synthesis gave **3** in over 40% overall yield from **4**. The use of (*S*)-(−)-2-acetoxypropanoyl bromide, of 2-acetoxybenzoyl bromide, and of hydrogen bromide/acetic acid in the bromoacetylation of **4** is also described.

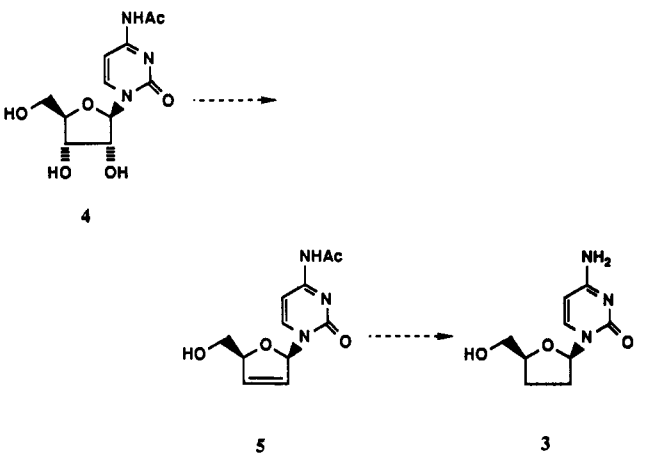
The recognition that the human immunodeficiency virus (HIV) is responsible for the etiology of acquired immune deficiency syndrome (AIDS) has prompted an enormous effort to find agents that would combat this disease.[1] For its early phase of replication, HIV, a retrovirus, requires the viral specific reverse transcriptase to transcribe its RNA into viral DNA. Of the various compounds tested to inhibit this process, 2′,3′-dideoxynucleosides have been the most successful.[2] Two of these, 3′-azido-3′-deoxythymidine (**1**, AZT) and 2′,3′-dideoxyinosine (**2**, ddI), have



1 (AZT) 2 (ddI) 3 (ddC)

been approved by the Food and Drug Administration for the treatment of AIDS, while 2′,3′-dideoxycytidine (**3**, ddC) is in the late stages of clinical trials.[1,2] These 2′,3′-dideoxynucleotides, after cytoplasmic phosphorylation to their 5′-triphosphates, have a higher affinity for HIV reverse transcriptase than for cellular DNA polymerases and are therefore incorporated into the growing viral DNA chain; however, since they lack a hydroxyl group at the C-3′ position, formation of the 5′,3′-phosphodiester linkage is not possible, resulting in termination of viral DNA synthesis.

Scheme I



4 5 3

Previous syntheses of ddC followed two principal routes. In one, the starting material is a nucleoside that is subjected to a number of transformations giving **3**, usually in low overall yields.[3] In the other, a protected form of 2′,3′-dideoxyribose is coupled to a cytosine derivative in

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(2) DeClercq, E.; Ed. *Design of Anti-AIDS Drugs*; Elsevier, New York, 1990.

(3) (a) Horwitz, J. P.; Shua, J.; Noel, N.; Donatti, J. T. *J. Org. Chem.* **1967**, *32*, 817. (b) Marumoto, R.; Honjo, M. *Chem. Pharm. Bull.* **1974**, *22*, 128. (c) Samukov, V. V.; Ofitserov, V. I. *Bioorg. Khim (USSR)* **1983**, *9*, 132; *Chem. Abstr.* **1983**, *98*, 161014X. (d) Prisbe, E. J.; Martin, J. C. *Synth. Comm.* **1985**, *15*, 401. (e) Kawana, M.; Yamasaki, N.; Nishikawa, M.; Kuzuhara, H. *Chem. Lett.* **1987**, 2419. (f) Lin, T.-S.; Chen, M. S.; McLaren, C.; Gao, Y. S.; Ghazzouli, L.; Prusoff, W. H. *J. Med. Chem.* **1987**, *30*, 440. (g) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; VanRoey, P. *J. Org. Chem.* **1989**, *54*, 2217. (h) Kaskar, B.; Markovac, A. *J. Heterocycl. Chem.* **1989**, *26*, 1531.

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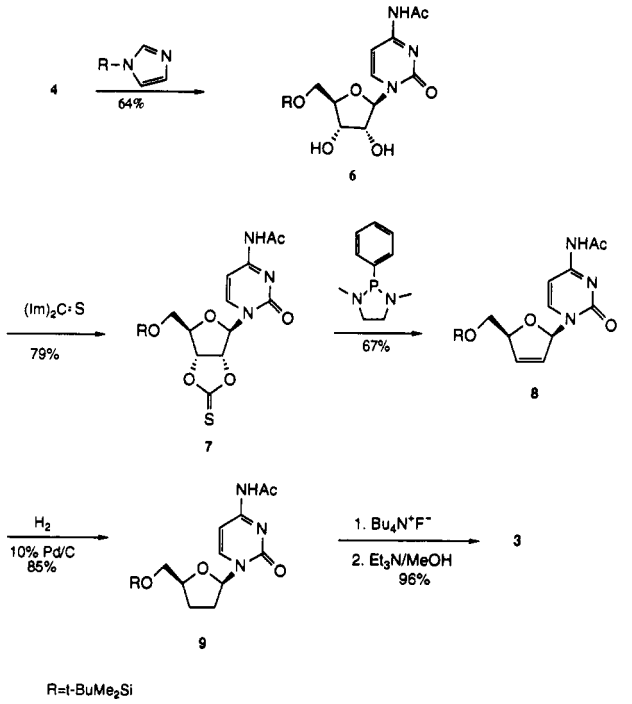
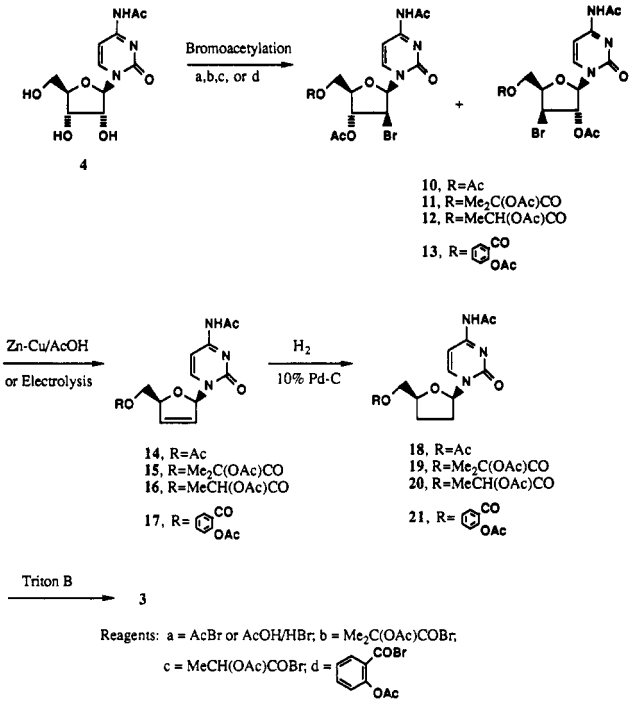
Scheme II



Scheme III



the presence of a Lewis acid (Hilbert-Johnson coupling)[4] to give the nucleoside as a mixture of α- and β-anomers, which has to be separated.[5] In the present report, we describe two syntheses of ddC by deoxygenation of the readily available N^4-acetylcytidine (4) followed by hydrogenation of the resulting alkene and hydrolysis (Scheme I). One of these syntheses employed the Corey–Hopkins deoxygenation[6] and provided ddC in 27% overall yield (Scheme II), while the other employed the Moffatt–Mattocks[7] bromoacetylation using 2-acetoxy-2-methylpropanoyl bromide and gave ddC in over 40% overall yield with a purity >99.7% without the use of chromatography at any stage of the synthesis (Scheme III).

Results and Discussion

Although numerous methods are known to effect deoxygenation of vicinal diols,[8] we concentrated on those that were considered mild and practical since the derived allylic glycosidic bond is somewhat labile. An attempt to effect direct vicinal deoxygenation of 4 with NaI/Me_3SiCl[9] led to deacylation with no 2′,3′-alkene formation. The Corey–Hopkins deoxygenation[6] was then examined. The C-5′ hydroxyl group in N^4-acetylcytidine was protected as the *tert*-butyldimethyl silyl derivative 6, which was then treated with 1,1′-(thiocarbonyl)diimidazole at room temperature to give the cylic thionocarbonate 7 in 79% yield. Treatment of 7 with 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine in CH_3CN gave the crystalline 2′,3′-alkene 8 in 67% yield, which on hydrogenation over 10% Pd/C followed by desilylation with tetrabutylammonium fluoride and hydrolysis (Et_3N/CH_3OH) gave ddC in 81.6% yield from 8. It should be noted that, in a contemporaneous investigation, Chu and co-workers reported[3g] that they were unable to convert the thionocarbonate 7 into the alkene 8 due to the instability of the former substance.

Although the synthesis proceeding through the cyclic thionocarbonate 7 was suitable for small-scale preparations of ddC, it was considered impractical for the preparation of the large quantities of material needed for clinical and toxicological studies. Attention was therefore directed to an approach involving bromoacetylation of N^4-acetylcytidine (4) followed by reductive elimination of the derived bromo acetate to give the corresponding 2′,3′-alkene (Scheme III). In contrast to uridine,[10] bromoacetylation of 4 (or cytidine) with acetyl bromide gave low yields (ca. 30%) of the desired regioisomeric mixture of bromo acetates 10. These yields could be increased to 81% using HBr in acetic acid but scale-up was extremely troublesome. 2-Acetoxy-2-methylpropanoyl bromide (Mattock's bromide),[7] a reagent known to effect the conversion of vicinal diols into a regioisomeric mixture of trans bromo acetates, was next examined. Whereas cytidine gave a complex mixture of products when treated with Mattock's bromide, N^4-acetylcytidine in CH_3CN or CH_2Cl_2 was smoothly converted to a mixture of the two pairs of regioisomeric bromides 10 and 11. HPLC analysis of the mixture indicated 85.28% of the bromo acetates 11 and 10.89% of 10. Since the weight of the crude reaction product was quantitative and there was negligible amount of base-line material as judged by TLC, the yield of bromo acetates that can be converted subsequently into ddC was a remarkable 96%.

Reductive elimination of the bromo acetate mixture 10 and 11 was readily accomplished with zinc–copper couple in acetic acid (ca. 75% yield) or by the electrochemical

(4) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234 and references cited therein.

(5) (a) Farina, V.; Benigni, D. A. *Tetrahedron Lett.* **1988**, *29*, 1239. (b) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. T.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780. (c) Motawia, M. S.; Pedersen, E. B. *Liebigs Ann. Chem.* **1990**, 599.

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(8) See, for example: (a) Eastwood, F. W.; Harrington, K. J.; Josan, J. S.; Para, J. L. *Tetrahedron Lett.* **1970**, 5223. (b) Hanessian, S.; Bargiotti, A.; LaRue, M. *Ibid.* **1978**, 737. (c) Barrett, A. G.; Barton, D. H. R.; Bielski, R. *J. Chem. Soc., Perkins Trans. 1* **1979**, 2378.

(9) Sarma, J.; Barua, N. C.; Sharma, R. P.; Barua, J. N. *Tetrahedron* **1983**, *39*, 2843.

(10) Mansuri, M. M.; Starrett, J. E.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780. Cf. ref 3b.

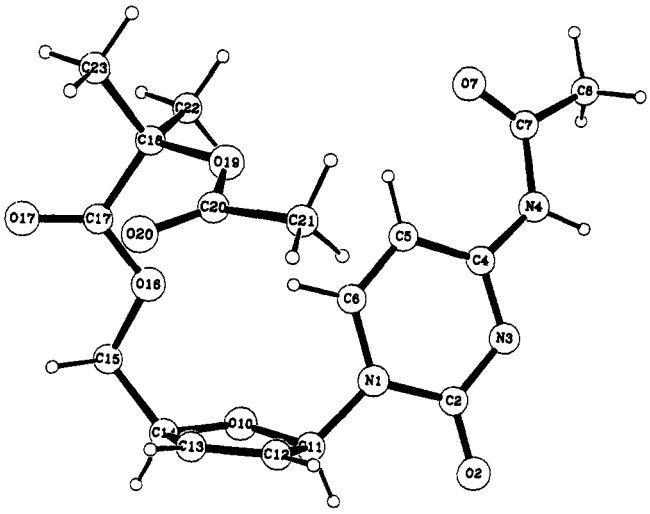


Figure 1. ORTEP perspective drawing of compound **15**.

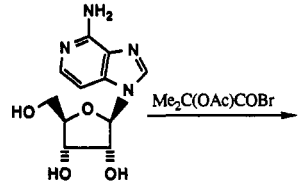
method developed by Inoue[11a] (42% yield), to give the alkenes **14** and **15**, respectively, from which the latter was obtained by crystallization.

Hydrogenation of **15** at room temperature and atmospheric pressure over 10% palladium on charcoal gave **19** in 95% yield accompanied by some cleavage (ca. 5%) of the anomeric C–N bond. Of the two compounds produced by this cleavage, N^4-acetylcytosine was easily removed, together with the catalyst, by filtration and the other compound, the 2',3'-deoxyribose derivative, was removed in the next step. It should be noted that an attempt to obtain **19** by the direct hydrogenolysis[12] of **11** was unsuccessful.

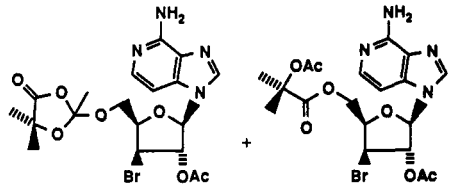
Careful hydrolysis of **19** with *N*-benzyltrimethylammonium hydroxide (Triton B) in methanol at room temperature afforded pure ddC in 50–60% yield. In a through process, without isolation of the intermediates **10**, **11**, **14**, **15**, **18** and **19**, we were able to prepare pure ddC in over 40% overall yield from N^4-acetylcytidine (**4**). The stereostructure of ddC was confirmed by a single-crystal X-ray analysis.[13]

Despite the excellent results obtained with Mattock's bromide, the relatively high cost of this reagent made its replacement desirable. (*S*)-(−)-2-Acetoxypropanoyl bromide, derived from (*S*)-lactic acid, and 2-acetoxybenzoyl bromide[14] were investigated as possible replacements for Mattock's bromide. However, the yields of the bromo acetates produced with these reagents were only 64% for **12** and 54% for **13**. Conversion of **12** and **13** into ddC was accomplished by the sequence described previously, i.e., reductive elimination using zinc–copper couple in acetic acid, hydrogenation of the derived alkenes (**16** and **17**), and finally hydrolysis.

There is some ambiguity concerning the nature of the functional group at C-5' when certain nucleosides are treated with Mattock's bromide. It has been reported that, depending on the heterocyclic base and solvent used, either a dioxolanone or acetoxyisobutyrate substituent is produced at C-5' in the uridine,[7a] adenosine,[7b,15] tubercidin, and formycin[7c] series. The evidence for the dioxolanone formulation was based on the strong IR absorption observed at ca. 1800 cm^{-1} and on ^1H NMR data. More recently, Serafinowski proposed[16] that 3-deazaadenosine (**22**) when treated with Mattock's bromide gave the dioxolanone **23** as the kinetic product, which was then slowly converted (48 h) by acid into the 5'-*O*-acetoxyisobutyrate derivative **24**. At equilibrium the mixture of **23** and **24** was found to be 1:6. No IR data were given for these products, and the possibility of regioisomerism was not discussed.



22



23 **24**

In the case of N^4-acetylcytidine, the bromo acetates **11** formed from Mattock's bromide gave IR absorptions (1740–1750 cm^{-1}) indicative of an ester group, with no absorption in the 1800 cm^{-1} region, which would be indicative of a dioxolanone structure. Although we were unable to obtain suitable crystals of one of the bromo acetates **11**, an X-ray crystallographic analysis of the derived alkene **15** confirmed the presence of an acetoxyisobutyrate function at C-5'. An ORTEP perspective drawing of **15** is given in Figure 1. By conjecture, we tentatively assign C-5' ester formulations of **12** and **13**, corroborative evidence being their strong IR absorptions in the 1740–1750 cm^{-1} region; there was no absorption in the 1800 cm^{-1} region. It should, however, be emphasized that until a more detailed study of the chemical behavior of Mattock's bromide is undertaken, no definite conclusions can be made concerning the apparent dichotomous behavior of this unusual bromide.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Unless otherwise indicated, infrared (IR) and ultraviolet (UV) spectra were determined in $CHCl_3$ and EtOH, respectively. Assignments of the ^{13}C NMR are based on chemical shifts, off-resonance, and DEPT spectra and are tentative. Thin-layer chromatography was carried out on silica gel plates (Merck, PF-254), and reversed-phase liquid chromatography (HPLC) was performed on a Waters μ-Bondapak C_{18} column (30 cm × 3.9 mm) with a flow rate of 1.3 mL/min; detection was at 270 nm.

N^4-Acetyl-5'-*O*-(*tert*-butyldimethylsilyl)cytidine (6). Powdered *N*-acetylcytidine (**4**)[17] (2.33 g, 8.18 mmol) was added to a solution of (*tert*-butyldimethylsilyl)imidazole in DMF, prepared by adding imidazole (1.36 g, 20.0 mmol) to a stirred solution of *tert*-butyldimethylsilyl chloride (1.37 g, 9.09 mmol) in dry DMF (10 mL, dried over molecular sieves 4A) at room temperature for 1 h. The suspension was stirred at room temperature overnight under argon, and the resulting solution was evaporated. The

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(13) (a) Silverton, J. V.; Quinn, F. R.; Haugwitz, R. D.; Todaro, L. J. *Acta Crystallogr.* **1988**, *C44*, 321. (b) Birbaum, G. I.; Lin, T. S.; Prusoff, W. H. *Biochem. Biophys. Res. Commun.* **1988**, *151*, 608.
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(15) Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, *25*, 367.
(16) Serafinowski, P. *Nucleic Acids Res.* **1987**, *15*, 1121.
(17) Watanabe, K. A.; Fox, J. J. *Angew. Chem.* **1966**, *78*, 589.

product was isolated by flash column chromatography with ethyl acetate and then 5% MeOH in ethyl acetate. Evaporation gave 2.099 g (64% yield) of **6** as a sticky foam: UV (EtOH) 213 (ε 20620), 247 (ε 15800), 298 (ε 8250) nm; IR (KBr) 3100–3600, 1722, 1658 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.09 (3 H, s, CH_3Si), 0.10 (3 H, s, CH_3Si), 0.90 (9 H, s, *t*-BuSi), 2.10 (3 H, s, CH_3CO), 3.72 (1 H, d, J = 11 Hz, H_A-5′), 3.94 (3 H, br s, H-2′ + H-3′ + H-4′), 3.96 (1 H, d, J = 11 Hz, H_B-5′), 5.07 (1 H, br d, J = 2 Hz, O*H*), 5.58 (1 H, br d, J = 2 Hz, O*H*), 5.75 (1 H, s, H-1′), 7.18 (1 H, d, J = 7 Hz, H-5), 8.30 (1 H, d, J = 7 Hz, H-6), 10.95 (1 H, s, N*H*); MS m/z 384 ($M^+ - CH_3$); MS (FAB) m/z 422 (M^+ + Na), 400 (M + H). This material was used immediately for the next step.

N^4-Acetyl-5′-*O*-(*tert*-butyldimethylsilyl)cytidine Cyclic 2′,3′-Thionocarbonate (7). 1,1′-(Thiocarbonyl)diimidazole (0.85 g, 4.77 mmol) was added to a solution of 1.58 g (3.95 mmol) of **6** in 10 mL of dry dichloromethane, and the solution was stirred under argon at room temperature for 16 h. The product was isolated by flash chromatography with 1:1 and 7:3 ethyl acetate–hexane. Evaporation gave 1.37 g (79%) of **7** as a colorless, unstable solid that was difficult to purify further: UV (EtOH) 212 (ε 22700), 243 (ε 27300) 296 (ε 7400) nm; IR (KBr) 1722, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (6 H, s, Me_2Si), 0.86 (9 H, s, *t*-BuSi), 2.27 (3 H, s, CH_3CO), 3.86 (1 H, dd, J = 11 and 3 Hz, H_A-5′), 3.94 (1 H, dd, J = 11 and 3 Hz, H_B-5′), 4.60 (1 H, m, H-4′), 5.55 (1 H, m, H-3′), 5.75 (1 H, d, J = 7 Hz, H-2′), 5.80 (1 H, s, H-1′), 7.49 (1 H, d, J = 7 Hz, H-5), 7.75 (1 H, d, J = 7 Hz), 8.78 (1 H, s, N*H*); MS (HR, FAB) calcd for $C_{18}H_{27}N_3O_6SiS$: 442.1468 (M^+ + H), found 442.1492 (M^+ + H). This material was used immediately for the next step.

N^4-Acetyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxycytidine (8). A solution of the cyclic thionocarbonate **7** (0.710 g, 1.61 mmol) in 8 mL of dry acetonitrile was treated with 0.40 mL (2.20 mmol) of 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine, and the solution was stirred at room temperature under argon for 7.5 h. The resulting crystalline suspension was concentrated to a small volume, and 5 mL of diethyl ether was added. The crystals were collected by filtration and washed well with small portions of diethyl ether to give 0.303 g of **8**; the mother liquor was evaporated and flash chromatographed with 4:1 ethyl acetate–hexane followed by ethyl acetate to furnish an additional crop of **8** (0.0887 g) as colorless crystals. The total amount of **8** obtained was 0.392 g (66.7%): mp 168–170 °C (lit.[3g] mp 168–170 °C), $[\alpha]^{25}_D$ −84.81° ($CHCl_3$, c = 0.350); UV (EtOH) 214 (ε 19510), 247 (ε 15400), 299 (ε 7300); IR (KBr) 3200 (br), 1718, 1668, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3 H, s, CH_3Si), 0.05 (3 H, s, CH_3Si), 0.96 (9 H, s, *t*-BuSi), 2.20 (3 H, s, CH_3CO), 3.80 (1 H, d, J = 11 Hz, H_A-5′), 3.93 (1 H, d, J = 11 Hz, H_B-5′), 4.93 (1 H, s, H-4′), 5.99 (1 H, d, J = 6 Hz, H-2′), 6.16 (1 H, d, J = 6 Hz, H-3′), 7.00 (1 H, s, H-1′), 7.30 (1 H, d, J = 7 Hz, H-5), 8.31 (1 H, d, J = 7 Hz, H-6), 8.64 (1 H, s, N*H*); MS (FAB) m/z 388 (M^+ + Na), 366 (M^+ + H). Anal. Calcd for $C_{17}H_{27}N_3O_4Si$: C, 55.86; H, 7.45; N, 11.50. Found: C, 55.79; H, 7.64; N, 11.53.

N^4-Acetyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-dideoxycytidine (9). The alkene **8** (0.384 g, 1.05 mmol) in 6 mL of methanol and 3 mL of THF was hydrogenated over 200 mg of 10% Pd/C at atmospheric pressure until hydrogen uptake ceased (35 min). The mixture was filtered through Celite, and the Celite was washed well with methanol. The combined filtrate and washings were evaporated, and the residue obtained was redissolved in acetonitrile. A trace of insoluble material was removed by filtration, and the filtrate was evaporated to give 0.327 g (85%) of **9**[3g] as a colorless gum, which was used in the next step without further purification.

A small sample of crude **9** was purified by preparative-scale TLC on silica gel with ethyl acetate as eluent to give **9** as an amorphous solid: UV (EtOH) 214 (ε 16600), 245 (ε 12000), 298 (ε 6210) nm; IR ($CHCl_3$) 3405, 1718, 1660, 838 cm^{-1}; ^1H NMR ($CDCl_3$) 0.05 (3 H, s, CH_3Si), 0.07 (3 H, s, CH_3Si), 0.94 (9H, s, *t*-BuSi), 1.85 (1 H, m), 1.95 (1 H, m), 2.15 (1 H, m), 2.25 (3 H, s, CH_3CO), 2.50 (1 H, m), 3.75 (1 H, dd, J = 11 and 2 Hz, H_A-5′), 4.15 (1 H, dd, J = 11 and 2 Hz, H_B-5′), 4.22 (1 H, m, H-4′), 6.07 (1 H, dd, J = 6 and 2 Hz, H-1′), 7.3 (1 H, d, J = 8 Hz, H-5), 8.56 (1 H, d, J = 8 Hz, H-6); MS (HR, FAB) calcd for $C_{17}H_{29}N_3O_4Si$ 368.2006 (M^+ + H), found 368.2012.

(*S*)-(−)-2-Acetoxypropanoyl Bromide. Thionyl chloride (51 mL) was added, with stirring, to 8.45 g (0.64 mol) of (*S*)-(−)-2-acetoxypropanoic acid (from (*S*)-lactic acid and acetic anhydride in the presence of *p*-toluenesulfonic acid). The mixture was stirred at 25 °C over the weekend and then at 90 °C for 30 min. It was cooled to room temperature, diluted with 20 mL of CH_2Cl_2, and treated with 82.0 g (0.94 mol) of anhyd LiBr. Stirring was continued at room temperature for 6 h, 100 mL of CH_2Cl_2 was added, and the solids were removed by filtration. The filtrate was evaporated (water aspirator, 30 °C), and the residue was distilled to give 73.4 g of a pale yellow oil: bp 76–78 °C/(12 Torr): $[\alpha]^{25}_D$ −2.70° ($CHCl_3$, c = 1.295); ^1H NMR ($CDCl_3$) δ 1.58 (3 H, d, J = 6 Hz, CH_3CH), 2.17 (1 H, q, J = 6 Hz, CH_3CH); MS m/z 165/167 (1, M − HCO), 107 (10), 87 (7, M − COBr), 43 (100, CH_3CO). Anal. Calcd for $C_5H_7BrO_3$: C, 30.80; H, 3.62; Br, 40.97. Found: C, 30.94; H, 3.78; Br, 41.21.

2-Acetoxybenzoyl Bromide. This was prepared by treating 2-acetoxybenzoyl chloride with LiBr as described for the preparation of (*S*)-(−)-2-acetoxypropanoyl bromide: bp 116–118 °C; IR ($CHCl_3$) 1772, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s, CH_3CO), 7.12 (1 H, d, J = 6 Hz, Ar H), 7.43 (1 H, t, J = 6 Hz, Ar H), 8.25 (1 H, d, J = 6 Hz, Ar H); MS m/z 163 (30, M^+ − Br). The ^1H NMR and mass spectra indicated the presence of starting chloride, which was not separable by distillation. The mixture was used in the bromoacetylation reaction.

Bromoacetylation of *N*-Acetylcytidine (4). (A) Using HBr in Acetic Acid: Preparation of 10. A mixture of 5.0 g (0.0175 mol) of **4**, 5.0 mL of acetic anhydride, and 50 mL of 30% hydrogen bromide in acetic acid was stirred under argon at 50 °C for 18.0 h and then cooled to room temperature. The mixture was extracted with 250 mL of CH_2Cl_2, and the extract was washed with 2 × 250 mL of 0.05 M potassium phosphate buffer (pH 7) and 250 mL of saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated to give 6.1 g (81%) of bromo acetates **10** as a foam,[3b] which was used without purification.

(B) Using 2-Acetoxy-2-methylpropanoyl Bromide: Preparation of 11. A stirred, cooled (5 °C) suspension of 142.6 g (0.50 mol) of **4** in 1.25 L of CH_3CN was treated dropwise with 225 mL of 2-acetoxy-2-methylpropanoyl bromide during 30 min. At the completion of the addition a homogeneous solution resulted. Although the reaction was complete within 2 h, for convenience the mixture was stirred at room temperature overnight. It was cooled to 5 °C, diluted with 1.25 L of ethyl acetate and 2.0 L of saturated $NaHCO_3$, and stirred for 15 min. The organic phase was collected, and the aqueous phase was reextracted with 500 mL of ethyl acetate. The combined extracts were washed with 1.0 L of saturated brine, dried ($MgSO_4$), and evaporated to give 264.7 g (102%) of crude bromo acetates as a white solid. HPLC analysis gave the following results: bromo acetates **10** (8.91%, RRT = 15.03 min and 1.88%, RRT = 18.53 min), bromo acetates **11** (55.19%, RRT = 48.17 min and 30.09%, RRT = 60.2 min). Repeated crystallizations of a 10-g sample of the mixture of bromo acetates from 2-propanol gave 3.0 g of one of the isomers of **11**: mp 194–196 °C; $[\alpha]^{25}_D$ +41.19° ($CHCl_3$, c = 0.995); UV (EtOH) 212 (ε 15120), 246 (ε 14180), 296 (ε 6950) nm; IR ($CHCl_3$) 3395, 1750, 1738, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (6 H, d, J = 1 Hz), 2.06 (3 H, s), 2.18 (3 H, s), 2.24 (3 H, s), 4.32 (1 H, d, J = 1 Hz, H-3′), 4.50 (3 H, m, H-5′ + H-4′), 5.47 (1 H, s, H-2′), 5.96 (1 H, s, H-1′), 7.46 (1 H, d, J = 8 Hz, H-5), 8.11 (1 H, d, J = 8 Hz, H-6), 8.38 (1 H, s, N*H*); ^{13}C NMR ($CDCl_3$) δ 50.57 (q, CH_3), 20.95 (q, CH_3), 24.26 (q, CH_3), 24.39 (q, CH_3), 24.71 (q, CH_3), 49.02 (d, C-3′), 64.98 (t, C-5′), 77.72 (d, C-2′), 78.90 (s, Me_2C(OAc)CO), 82.41 (d, C-4′), 90.57 (d, C-1′), 96.69 (d, C-5), 144.00 (d, C-6), 154.77 (s, C-2), 163.44 (s, C-4), 168.92 (s, CO), 170.16 (s, CO), 171.38 (s, CO), 172.15 (s, CO); MS m/z 502 (2, $M^+ - CH_3$). Anal. Calcd for $C_{19}H_{24}BrN_3O_9$: C, 44.03; H, 4.67; Br, 15.42; N, 8.11. Found: C, 43.97; H, 4.67; Br, 15.39; N, 8.03.

(C) Using (*S*)-(−)-2-Acetoxypropanoyl Bromide: Preparation of 12. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and argon inlet was charged with 28.52 g (0.1 mol) of **4** in 250 mL of CH_3CN. The mixture was cooled to 10 °C, treated with 48.75 g (0.25 mol) of (*S*)-(−)-2-acetoxypropanoyl bromide during 15 min, and stirred at room temperature overnight. It was cooled to 10 °C, diluted with 400 mL of cold (0 °C) saturated $NaHCO_3$, and extracted with 250 mL of ethyl acetate. The extract was washed with 200 mL of saturated brine, dried ($MgSO_4$), and evaporated to give 45.45 g of a white foam. HPLC analysis gave the following results: regioisomer A, 40%

(RRT = 28.53 min) and regioisomer B, 24% (RRT = 37.60 min). Reversed-phase chromatography (C_{18} column) with 40% methanol in water gave a pure sample of one of the regioisomers, which was crystallized from 2-propanol: mp 186–187 °C; UV (EtOH) 211 (ε 17600), 248 (ε 15030), 298 (ε 7310) nm; IR ($CHCl_3$) 3395, 1750, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (3 H, d, J = 7 Hz), 2.15 (3 H, s), 2.18 (3 H, s), 2.25 (3 H, s), 4.30 (1 H, br s, H-3'), 4.45 (1 H, dd, J = 11 and 3 Hz, H_A-5'), 4.58 (1 H, s, H-4'), 4.59 (1 H, dd, J = 11 and 3 Hz, H_B-5'), 5.08 (1 H, q, J = 7 Hz, CH_3CH OAc), 5.49 (1 H, s, H-2'), 5.98 (1 H, s, H-1'), 7.50 (1 H, d, J = 8 Hz, H-5), 8.12 (1 H, d, J = 8 Hz, H-6), 9.02 (1 H, br s, NH); MS m/z 504 (55, M^+). Anal. Calcd for $C_{18}H_{22}BrN_3O_9$: C, 42.87; H, 4.40; Br, 15.84; N, 8.33. Found: C, 42.77; H, 4.46; Br, 15.77; N, 8.19.

(D) Using 2-Acetoxybenzoyl Bromide: Preparation of 13. To a stirred, cooled (5 °C) solution of 4.50 g (0.0158 mol) of **4** in 45 mL of CH_2Cl_2 was added 11.5 g (0.047 mol) of 2-acetoxybenzoyl bromide. The mixture was stirred at room temperature for 4.0 h, diluted with 70 mL of saturated $NaHCO_3$, and the organic phase collected. The aqueous phase was reextracted with 50 mL of CH_2Cl_2, and the combined organic extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated to give 10.4 g of a white foam. Reversed-phase chromatography (C_{18} column) of a 3.5-g portion with 40% methanol in water gave 1.22 g of a mixture of bromo acetates **13**: UV (EtOH) 298 (ε = 9600), 243 (ε 20000), 217 (ε 17500), 203 (ε 47000) nm; IR ($CHCl_3$) 3390, 1752, 1722, 1660 cm^{-1}; MS m/z 471 (0.5, M^+ – HBr).

Reductive Elimination of the Bromo Acetates 10–13 To Give Alkenes 14–17. (A) Using Zn–Cu Couple. Preparation of Zn–Cu Couple. Zinc dust (4.5 kg) was washed with 3 × 3.75 L of 3% aqueous hydrochloric acid for 3–5 min and the hydrochloric acid decanted from the solid after each wash. The zinc dust was then washed with 4 × 3.0 L of water and treated with a solution of 240.0 g of copper(II) sulfate in 7.5 L of deionized water. The suspension was stirred rapidly as the solution of cupric sulfate was added. The aqueous layer was decanted, and the solid was washed with 4 × 3.0 L of deionized water, 4 × 3.0 L of ethanol, and 3 × 3.0 L of ether. The solid was dried (140 Torr) at 25 °C for 18 h and then at 130 °C (0.5 Torr) for 3 h to give 3.84 kg of zinc–copper couple, which was stored under argon.

Alkenes 14 and 15. A stirred deoxygenated mixture of a solution of 259.0 g of bromo acetate mixture (**10** and **11**) in 2.5 L of CH_3CN was treated with 100 g of zinc–copper couple, and the mixture was stirred under argon overnight. It was filtered through Celite, the flask was rinsed with 200 mL of CH_3CN, and the rinse was used to wash the Celite. The combined filtrate and washing were evaporated at 40 °C, and the residue was dissolved in 1.25 L of CH_2Cl_2. The solution was added to a previously prepared solution of 200 g of EDTA disodium salt dihydrate in 2.0 L of water containing 200 g of $NaHCO_3$. The mixture was stirred vigorously for 1.5 h and filtered over Celite, which was washed with 300 mL of CH_2Cl_2. The combined filtrate and washing were dried ($MgSO_4$), filtered, and concentrated to ca. 800 mL. To this was added 30 mL of acetic anhydride and 40 g of poly-4-vinylpyridine, and the mixture was stirred under argon at room temperature for 3 h. After filtration and evaporation, followed by coevaporation with 250 mL of toluene, the residue was stirred with 500 mL of ether. The product was collected by filtration, washed with 200 mL of ether, and dried to give 143.3 g of a mixture of alkenes **14** and **15**. HPLC analysis indicated 6.02% of **14** (RRT = 5.83 min) and 90.8% of **15** (RRT = 13.50 min). Reversed-phase TLC (C_{12}, 250 μm) with 40% methanol in water showed **14** at R_f 0.30 and **15** at R_f 0.40; the starting material showed a major spot at R_f 0.13 and a minor spot at R_f 0.20. Crystallization of a 3.0-g portion of the mixture from hot tetrahydrofuran gave 1.8 g of **15**: mp 173–175 °C; $[\alpha]^{25}_D$ +123.5° ($CHCl_3$, c = 1.0); UV (EtOH) 212 (ε 18900), 247 (ε 15660), 298 (ε 7600) nm; IR ($CHCl_3$) 3400, 1735, 1662, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (6 H, s), 2.0 (3 H, s), 2.25 (3 H, s), 4.24 (1 H, dd, J = 11 and 3 Hz, CH_A-5'), 4.54 (1 H, dd, J = 11 and 3 Hz, CH_B-5'), 5.14 (1 H, s, H-4'), 6.04 (1 H, d, J = 6 Hz, H-3'), 6.18 (1 H, d, J = 6 Hz, H-2'), 6.85 (1 H, s, H-1'), 7.42 (1 H, d, J = 8 Hz, H-5), 7.92 (1 H, d, J = 8 Hz, H-6), 9.20 (1 H, s, NH); ^{13}C NMR ($CDCl_3$) δ 20.93 (q, CH_3), 24.01 (q, CH_3), 24.65 (q, 2 × CH_3), 64.14 (t, C-5'), 77.81 (s, $(CH_3)_2C(OAc)_2CO$), 84.76 (d, C-4'), 91.72 (d, C-1'), 97.08 (d, C-5), 127.67 (d, C-3'), 132.10 (d, C-2'), 144.33 (d, C-6), 155.24 (s, C-2), 163.19 (s, C-4), 169.79 (s, CO), 171.52 (s, CO), 172.08 (s, CO); MS m/z 379 (8, M^+). Anal. Calcd for $C_{17}H_{21}N_3O_7$: C, 53.82; H, 5.58; N, 11.08. Found: C, 53.75; H, 5.63; N, 11.01.

Alkene 14. Reduction of 6.1 g (0.014 mol) of the bromo acetate mixture **10** under the conditions given above gave a 57% yield of the alkene **14**, which was crystallized from 1:2 THF–petroleum ether: mp >300 °C (lit.[11] mp >280 °C); ^1H NMR. (DMSO-d_6) δ 1.91 (3 H, s, CH_3CO), 2.09 (3 H, s CH_3CO), 4.10 (1 H, dd, J = 12 and 3 Hz, CH_A-5'), 4.40 (1 H, dd, J = 12 and 3 Hz, CH_B-5'), 5.03 (1 H, s, H-4'), 6.05 (1 H, d, J = 6 Hz, H-3'), 6.18 (1 H, d, J = 6 Hz, H-2'), 6.81 (1 H, s, H-1'), 7.33 (1 H, d, J = 8 Hz, H-5), 7.90 (1 H, d, J = 8 Hz, H-6), 10.9 (1 H, br s, NH).

Alkene 16. Reduction of 1.47 g of the bromo acetate mixture **12** with zinc–copper couple as described previously gave 570 mg of **16**: mp 125 °C (from hot THF); $[\alpha]^{25}_D$ +119.04° (c = 1.025, $CHCl_3$); UV (EtOH) 214 (ε 17420), 247 (ε 15420), 298 (ε 7520) nm; IR ($CHCl_3$) 3400, 1745, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (3 H, d, J = 7 Hz, CH_3CH), 2.09 (3 H, s, CH_3CO), 2.27 (3 H, s, CH_3CO), 4.36 (1 H, dd, J = 11 and 3 Hz, H_A-5'), 4.46 (1 H, dd, J = 11 and 3 Hz, H_B-5'), 4.97 (1 H, q, J = 7 Hz, CH_3CHO), 5.17 (1 H, br s, H-4'), 6.14 (1 H, d, J = 6 Hz, H-3'), 6.18 (1 H, d, J = 6 Hz, H-2'), 6.95 (1 H, br s, H-1'), 7.45 (1 H, d, J = 8 Hz, H-5), 8.00 (1 H, d, J = 8 Hz, H-6), 9.30 (1 H, br s, NH); MS m/z 365 (0.5, M^+). Anal. Calcd for $C_{16}H_{19}N_3O_7$: C, 52.60; H, 5.24; N, 11.50. Found: C, 52.45, H, 5.26; N, 11.46.

Alkene 17. Reduction of 30.5 g of the bromo acetate mixture **13** with 10 g of zinc–copper couple gave 6.3 g of alkene **17**: mp 265 °C; $[\alpha]^{25}_D$ –20.29° (DMSO, c = 1.034); UV (EtOH) 203 (ε 48400), 243 (ε 21550), 299 (ε 9800) nm; IR ($CHCl_3$) 1725, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (3 H, s, CH_3CO), 2.12 (3 H, s, CH_3CO), 3.75 (1 H, dd, J = 11 and 3 Hz, H_A-5'), 3.95 (1 H, dd, J = 11 and 3 Hz, H_B-5'), 4.89 (1 H, br s, H-4'), 5.85 (1 H, d, J = 6 Hz, H-3'), 5.95 (1 H, d, J = 6 Hz, H-2'), 6.80 (1 H, s, H-1'), 7.15 (1 H, d, J = 6 Hz, ArH), 7.20 (1 H, d, J = 6 Hz, ArH), 7.27 (1 H, t, J = 6 Hz, Ar H), 7.65 (1 H, d, J = 8 Hz, H-5), 7.72 (1 H, t, J = 6 Hz, ArH), 7.88 (1 H, d, J = 8 Hz, H-6). Anal. Calcd for $C_{20}H_{19}N_3O_7$: C, 58.13; H, 4.59; N, 10.16. Found: C, 57.83; H, 4.82; N, 9.95.

(B) Electrochemical Reduction. Preparation of Alkene 15. To the catholyte reservoir was added 10.0 g (0.019 mol) of **11** and 500 mL of 0.25 M tetraethylammonium tosylate in acetonitrile. To the anolyte reservoir was added 500 mL of 0.25 M tetraethylammonium tosylate in acetonitrile. Both the catholyte and anolyte were circulated through the electrolytic cell at a flow rate of 250 mL/min/cell. The cell was divided by an anion-exchange membrane (Ionac MA-3475, Sybron Chemical Division, Birmingham, NJ), and the initial current density was 0.8 mA/cm^2 at –4.0V. The reaction was monitored by TLC and HPLC. During the first 30 min, analysis of an aliquot indicated 60% conversion. About 90 min later, TLC analysis showed total disappearance of the starting material. The catholyte solution was collected and evaporated to dryness at room temperature in vacuo, and the dried residue was then dissolved in 200 mL of deionized water and extracted with 3 × 200 mL of methylene chloride. The extract was dried (Na_2SO_4) and was then evaporated to yield 3.07 g of a tan-colored solid (42% yield). Crystallization of a 0.5-g sample from 8 mL of hot tetrahydrofuran gave 0.22 g of **15**, mp 170–172 °C, identical with the sample prepared previously.

N^4-Acetyl-5'-*O*-acetyl-2',3'-dideoxycytidine (18). Hydrogenation of a 2.0-g (6.8 mmol) sample of alkene **14**[11] in 100 mL of methanol over 200 mg of 10% palladium on charcoal at room temperature and atmospheric pressure gave, after removal of the catalyst and solvent, 2.05 g of a solid, which was crystallized from 2-propanol to give 1.81 g (91%) of **18**: mp 196 °C; $[\alpha]^{25}_D$ +145.69° ($CHCl_3$, c = 0.9980); UV (EtOH) 214 (ε 20720), 246 (ε 14750), 299 (ε 7420) nm; IR ($CHCl_3$) 3450, 1742, 1722, 1662, 1557 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (1 H, m), 2.03 (1 H, m), 2.08 (3 H, s), 2.18 (1 H, m), 2.25 (3 H, s), 2.58 (1 H, m), 4.32 (3 H, br s, H-4' + H-5'), 6.05 (1 H, d, J = 4 Hz, H-1'), 7.41 (1 H, d, J = 7 Hz, H-5), 8.12 (1 H, d, J = 7 Hz, H-6), 9.28 (1 H, s, NH); ^{13}C NMR ($CDCl_3$) δ 20.78 (CH_3), 24.71 (CH_3), 24.91 (C-3'), 33.11 (C-2'), 64.38 (C-5'), 79.81 (C-4'), 88.11 (C-1'), 96.11 (C-5), 143.89 (C-6), 155.01 (C-2), 163.05 (C-4), 170.42 (CH_3CO), 171.3 (CH_3CO); MS m/z 295 (M^+, 10). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.61; H, 5.89; N, 14.18.

N^4-Acetyl-5'-*O*-(acetoxyisobutyryl)-2',3'-dideoxycytidine (19). A 5-L, three-necked, round-bottomed flask (creased)

equipped with a mechanical stirrer was charged with a mixture of 142.3 g of the alkenes **14** and **15** in 800 mL of methanol. The mixture was warmed until a solution was obtained, diluted with 800 mL of tetrahydrofuran, and then cooled to room temperature. A total of 8.9 g of 10% palladium on charcoal was added under argon, and the mixture was hydrogenated with stirring at room temperature and atmospheric pressure until hydrogen uptake ceased (11.0, ca. 3 h). The mixture was filtered over Celite, and the Celite was washed with 300 mL of methanol. The combined filtrate and washing were evaporated to give 132.7 g of a mixture of **18** and **19** as a somewhat hygroscopic foam. HPLC analysis of the mixture indicated **19** (90.4%, RRT = 17.93 min), **18** (5.6%, RRT = 7.4 min), and *N*-acetylcytosine (0.92%, RRT = 3.67 min). Flash column chromatography of a 1.0-g portion of the mixture over silica (10 g, 70–230 mesh) with 1% methanol in CH_2Cl_2 gave 300 mg of **19** as a colorless foam: $[\alpha]^{25}_D$ + 136.08° ($CHCl_3$, c = 1.02); UV (EtOH) 213 (ϵ 17 800) 245, (ϵ 13 950), 297 (ϵ 7300) nm; IR ($CHCl_3$) 3400, 1738, 1662, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (6 H, s), 1.70 (1 H, m), 2.02 (3 H, s, CH_3), 2.10 (2 H, m), 2.24 (3 H, s, CH_3CO), 2.55 (1 H, m), 4.38 (2 H, br dd, J = 11 and 3 Hz, H-5′), 6.05 (1 H, t, J = 2 Hz, H-1′), 7.44 (1 H, d, J = 8 Hz, H-5), 8.17 (1 H, d, J = 8 Hz, H-6), 9.20 (1 H, s, NH); ^{13}C NMR ($CDCl_3$) δ 20.96 (q, CH_3), 24.33 (q, CH_3), 24.49 (q, CH_3), 24.66 (q, CH_3), 24.82 (t, C-3′), 39.10 (t, C-2′), 65.14 (t, C-5′), 77.86 (s, C-7′), 79.37 (d, C-4′), 87.89 (d, C-1′), 96.35 (d, C-5), 143.95 (d, C-6), 154.95 (s, C-2), 163.06 (s, C-4), 169.98 (s, CO), 171.41 (s, CO), 172.25 (s, CO); MS m/z 381 (1, M^+). Anal. Calcd for $C_{17}H_{23}N_3O_7$: C, 53.57; H, 6.08; N, 11.02. Found: C, 53.32; H, 6.23; N, 11.04.

Compound 20. A solution of 720 mg (1.97 mmol) of alkene **16** in 10 mL of methanol and 10 mL of tetrahydrofuran was hydrogenated over 200 mg of 10% palladium on charcoal at room temperature and atmospheric pressure until hydrogen uptake ceased (40 mL). The mixture was filtered over Celite, and the filtrate was evaporated to give a gum. Chromatography on 10 g of silica (70–230 mesh) with 10% methanol in methylene chloride gave 290 mg of **20** as a foam: $[\alpha]^{25}_D$ +88.43° ($CHCl_3$, c = 0.99); UV (EtOH) 299 (ϵ 6420), 246 (ϵ 1241), and 214 (ϵ 16 500) nm; IR 3405, 1745, 1725, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (3 H, d, J = 7 Hz, CH_3CH), 1.75 (1 H, m), 2.05–2.15 (2 H, m), 2.15 (3 H, s, CH_3CO), 2.26 (3 H, s, CH_3CO), 2.55 (1 H, m), 4.35 (1 H, d, J = 11 Hz, H_A-5′), 4.40 (1 H, m, H-4′), 4.50 (1 H, d, J = 11 Hz, H_B-5′), 6.05 (1 H, m, H-1′), 7.47 (1 H, d, J = 8 Hz, H-5), 8.13 (1 H, d, J = 8 Hz, H-6), 9.71 (1 H, s, N*H*); MS m/z 367 (3, M^+). Anal. Calcd for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.01; H, 5.97; N, 12.19.

Compound 21. A solution of 1.66 g (3 mmol) of **17** in 30 mL of methanol and 30 mL of DMF was hydrogenated over 300 mg of 10% palladium on charcoal at room temperature and atmospheric pressure until hydrogen absorption ceased (113 mL). Workup in the usual manner gave 1.7 g of a gum, which was purified by chromatography over 15 g of silica gel with 2% methanol in methylene chloride as eluent to give 970 mg of **21** as a foam: UV (EtOH) 298 (ϵ 9450), 243 (ϵ 19 500), 203 (ϵ 42 350) nm: IR ($CHCl_3$) 3405, 1750, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (1 H, m), 1.89 (3 H, s), 2.05 (1 H, m), 2.25 (3 H, s), 2.45 (1 H, m), 3.90 (1 H, dd, J = 12 and 3 Hz, H_A-5′), 4.22 (1 H, dd, J = 12 and 3 Hz, H_B-5′), 4.30 (1 H, m, H-4′), 6.02 (1 H, d, J = 3 Hz, H-1′), 7.08 (1 H, d, J = 7 Hz, H-5), 7.20 (1 H, t, ArH), 7.30 (1 H, d, ArH), 7.67 (1 H, t, J = 6 Hz, ArH), 8.00 (1 H, d, J = 6 Hz, ArH), 8.10 (1 H, d, J = 8 Hz, H-6), 9.37 (1 H, s, N*H*). Anal. Calcd for $C_{20}H_{21}N_3O_7$: C, 57.83; H, 5.10; N, 10.12. Found: C, 57.55; H, 5.03; N, 9.95.

2′,3′-Dideoxycytidine (3). (A) From 19. A 250-mL three-necked, round-bottomed flask equipped with a stirrer and an argon inlet tube was charged with 27.2 g (0.071 mol) of **19** in 71.0 mL of methanol. The mixture was stirred at room temperature until a solution was obtained and then treated with 7.14 mL of Triton B (40% benzyltrimethylammonium hydroxide in methanol). Stirring was continued at room temperature overnight, and the product was collected by filtration. It was washed with some cold methanol to give 9.33 g of crude ddC, with a purity of 99.17% (HPLC). Evaporation of the filtrate and washing gave a semisolid to which 20.0 mL of ethanol was added. The product was collected by filtration and washed with some cold ethanol to give an additional 1.05 g of crude **3** (96.67% pure by HPLC), a total of 10.38 g of crude **3**. Crystallization from 100 mL of 90% ethanol gave 9.28 g (62%) of **3** as colorless crystals, mp 219–221 °C, $[\alpha]^{25}_D$ +95.86° (CH_3OH, c = 1.46) [lit.[3a] mp 215–217 °C, $[\alpha]^{25}_D$ +81° (H_2O, c = 0.635)], with a purity of 99.7% as estimated by HPLC: UV (EtOH) 274 (ϵ 8300) nm; IR (KBr) 3385–3190, 1647 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75–1.90 (3 H, m), 2.2–2.3 (1 H, m), 3.52 (1 H, br d, J = 11 Hz, H_A-5′), 3.65 (1 H, br d, J = 11 Hz, H_B-5′), 3.98 (1 H, br s, H-4′), 4.87 (1 H, t, J = 3 Hz, O*H*), 5.68 (1 H, d, J = 8 Hz, H-5), 5.93 (1 H, br s, H-4), 7.00 (1 H, br s, N*H*), 7.05 (1 H, br s, N*H*), 7.90 (1 H, d, J = 8 Hz, H-6); ^{13}C NMR (DMSO-d_6) δ 23.86 (t, CH_2), 31.60 (t, CH_2), 61.27 (t, C-5′), 80.65 (d, C-4′), 84.90 (d, C-1′), 92.52 (d, C-5), 140.18 (d, C-6), 154.44 (s, C-2), 164.84 (s, C-4); MS m/z 211 (20, M^+). Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.22; H, 6.31; N, 19.94.

(B) From Compound 9. A solution of 0.301 g (0.819 mmol) of **9** and 0.270 g (0.856 mmol) of tetrabutylammonium fluoride trihydrate in THF was stirred at room temperature for 3.5 h. Evaporation gave an oily residue of N^4-acetyl-2′,3′-dideoxycytidine, which was dissolved in 5 mL of methanol and 0.03 mL of triethylamine (0.03 mL). The solution was kept at 47 °C for 5 h and evaporated to give a mixture of a partially crystalline material. To this was added a small amount of ethanol and then 8 mL THF. The colorless crystals were collected by filtration and washed with THF to give 0.0776 g (99.4% purity by reversed-phase HPLC analysis), mp 210–212 °C. The mother liquor was evaporated, redissolved in water, and passed through a column of Amberlite IR 116 in the pyridinium form. The column was washed with methanol and eluted with 1 M NH_4OH solution. Evaporation of the effluent gave an additional 94.4 mg of **3**. The total yield of **3** was 172 mg (95%).

X-ray Crystallographic Analysis of 15 (with Mr. L. J. Todaro). Crystals of **15** are orthorhombic, space group $P2_12_12_1$, with a = 8.113 (2) Å, b = 13.811 (2) Å, c = 16.690 (2) Å, Z = 4, d_{calcd} = 1.347 cm^{-3}, μ(CuKα) = 9.1 cm^{-1}. The intensity data, uncorrected for absorption, were measured on a Hilger–Watts diffractometer (Ni-filtered CuKα radiation, θ–2θ scans, pulse height discrimination) using a crystal of approximately 0.15 × 0.25 × 0.6 mm that was grown from tetrahydrofuran. Of the 1993 accessible reflections for θ < 70°, 1883 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[18] and was refined by full-matrix least-squares methods. Five reflections, which were strongly affected by extinction, were excluded from the final difference map. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and isotropic temperature factors were used for hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indicies are R = 0.050 and R_w = 0.064 for the remaining 1878 observed reflections. The final difference map had no peaks greater than ±0.3 eA^{-3}. Listings of final atomic parameters, final anisotropic thermal parameters, structure factors, bond lengths, and bond angles are given in Tables I–IV as supplementary material.

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Supplementary Material Available: Listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for **15** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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