Synthesis of the Dideoxynucleosides ddC and CNT from Glutamic Acid, Ribonolactone, and Pyrimidine Bases

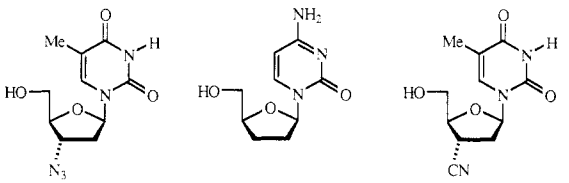
Masami Okabe,* Ruen-Chu Sun, Steve Y.-K. Tam, Louis J. Todaro, and David L. Coffen

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

Received April 21, 1988

2,3-Dideoxyribose in suitably protected form was prepared from glutamic acid and coupled with silylated cytosine to give a mixture of the α- and β-anomers of 2′,3′-dideoxycytidine. The anomer ratio depended on the Lewis acid used in the coupling, with $EtAlCl_2$ favoring the β-anomer ddC, a potent anti-HIV drug. Conjugate addition of cyanide to a 4-[(silyloxy)methyl]butenolide prepared from D-ribonolactone gave a mixture of (racemic) α- and β-3-cyanobutyrolactones. Both isomers were reduced to lactols and coupled with thymine to give α/β-anomer pairs. The α-cyano lactone, the structure of which was established by X-ray crystallography, afforded an authentic sample of the putative (but in fact inactive) anti-HIV substance known in AIDS research as CNT.

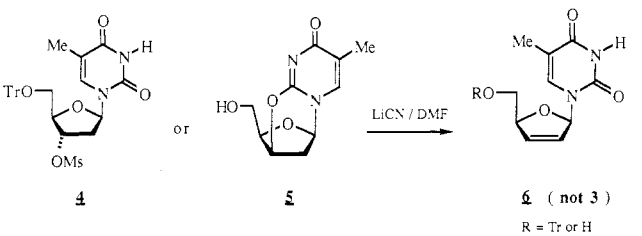
Reverse transcriptase inhibitors[1] have thus far proven to be the most potent medications for containing the effects of the human immunodeficiency virus (HIV) in virulent stages of infection. The most promising agents of this class of drugs are 3′-deoxy DNA nucleosides, or analogues thereof, capable of undergoing 5′-phosphorylation by host kinases but teleologically incapable of DNA chain continuation. 3′-Deoxy-3′α-azidothymidine (AZT, **1**), the prototype of the class, was rapidly followed in clinical development by 2′,3′-dideoxycytidine (ddC, **2**). Several other candidates have emerged, including substances related to the purine group of nucleosides. In July of 1987, it was announced that 3′-deoxy-3′α-cyanothymidine (CNT, **3**) showed anti-HIV activity in vitro and was being considered for clinical study.[2]



1 AZT **2** ddC **3** CNT

Unexpectedly, our attempts to duplicate the preparation of CNT by the methods specified in the patent application[3] failed to give any trace of CNT. Contrary to the results reported, the reactions of the 3′-*O*-mesylate (**4**) or the 2′,3′-anhydro nucleoside (**5**) with lithium cyanide in DMF under the specified conditions gave only a low yield (20–40%) of elimination product **6**, a known compound,[4] along with a large amount of unreacted starting material. All of our attempts to obtain CNT from the reported methods have been unsuccessful. Authentic CNT was finally prepared by the unambiguous synthesis described herein and was shown to be inactive in the standard in vitro test using HIV infected $CD4^+$ ATH8 cells.

Since chemistry based on DNA nucleosides obtained from limited natural sources can be inimical to the broad application of these agents in AIDS therapy, schemes utilizing abundant raw materials were targeted for investigation. From this investigation emerged a synthesis of ddC from glutamic acid and cytosine and a closely related synthesis of CNT from ribonolactone and thymine.



4 **5** **6** (not 3)

R = Tr or H

Results and Discussion

Synthesis of ddC. (*S*)-(+)-γ-(Hydroxymethyl)-γ-butyrolactone (**9**), a logical precursor of 2,3-dideoxyribose, has been previously prepared from L-glutamic acid (**7**),[5] from D-mannitol,[6] and from D-ribonolactone.[7] Fewer steps and the low cost of L-glutamic acid made the route from this material the preferred one.

The nitrous acid deamination of glutamic acid, which proceeds with retention of configuration,[8] readily affords a 56% yield of crystalline **8** on a mole scale. Some difficulty in isolation arises from the water-soluble nature of **8**. Subsequent steps shown in Scheme I include protecting the 5-hydroxy group with *tert*-butyldimethylsilyl chloride (TBSCl). They proceed to protected dideoxyribose **12** in 63% overall yield based on **8**.

Initial coupling experiments with **12** and silylated cytosine were patterned after the method of Niedballa and Vorbruggen,[9] in which stannic chloride is used to drive the coupling reaction (Scheme II).

In relation to other Lewis acids tried, stannic chloride is flawed vis-à-vis this particular combination of sugar and base by both poor yield and unfavorable α/β-anomer ratio. Although the 2:1 α/β-anomer ratio improved on aging the reaction mixture, decomposition of both anomers pro-

(1) Dagani, R. *Chem. Eng. News* **1987**, *20*, 41. Kim, C.-H.; Marquez, V. E.; Broder, S.; Mitsuya, H.; Driscoll, J. S. *J. Med. Chem.* **1987**, *30*, 862 and references cited therein.

(2) July 10, 1987 Federal Register advertisement. Reports of other syntheses of CNT appeared during the preparation of this manuscript: Fleet, G. W. J.; Son, J. C.; Derome, A. E. *Tetrahedron* **1988**, *44*, 625. Calvo-Mateo, A.; Camarasa, M.-J.; Diaz-Ortiz, A.; De las Heras, F. G. *Tetrahedron Lett.* **1988**, *29*, 941. Parkes, K. E. B.; Taylor, K. *Tetrahedron Lett.*, in press.

(3) U.S. Patent Application, Serial Number 07/043,827, filed on April 29, 1987.

(4) Horwitz, J. P.; Chua, J.; DaRooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205.

(5) (a) Taniguchi, M., Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547. (b) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Ibid.* **1978**, *34*, 1449. (c) A synthesis of ddC from L-glutamic acid appeared during the preparation of this manuscript: Farina, V.; Benigni, D. A. *Tetrahedron Lett.* **1988**, *29*, 1239.

(6) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 951.

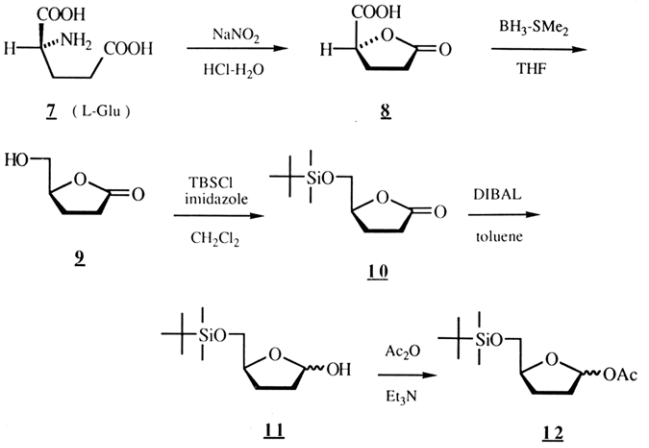
(7) (a) Camps, P.; Cardellach, J.; Font, J.; Ortuno, R. M.; Ponsati, O. *Tetrahedron* **1982**, *38*, 2395. (b) Lundt, I.; Pedersen, C. *Synthesis* **1986**, 1052.

(8) Cervinka, O.; Hub, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2927.

(9) Niedballa, U.; Vorbruggen, H. *J. Org. Chem.* **1974**, *39*, 25.

0022-3263/88/1953-4780$01.50/0

Scheme I



ceeded faster than the $\alpha \rightarrow \beta$ isomerization. The products **15** and **16** (or their N-silylated precursors) proved stable to titanium tetrachloride, boron trifluoride etherate, trimethylsilyl triflate, and to ethylaluminum dichloride when these were used as coupling reagents. Of these, ethylaluminum dichloride was best, giving a 2:3 α/β-anomer mixture in 71% yield. Titanium tetrachloride afforded a 1:1.2 mixture in 61% yield.

The amino silyl group is labile and lost either during the coupling reaction or workup. Thus **15** and **16** are obtained directly from the coupling reactions. These are separated by chromatography on silica gel and deblocked at the 5′-position to give ddC (**2**) and its α-anomer (**17**). Characterization of the two stereoisomers by spectroscopy is abetted by comparison of the ddC with an authentic sample prepared from cytidine.

The overall yield of ddC produced by this method is 13.9% based on glutamic acid and 35.8% based on cytosine. Antipodal ddC synthesized in the same manner from D-glutamic acid showed no activity against HIV.

Synthesis of CNT. Unlike the case with ddC at the time this investigation was carried out, samples of material from various sources being designated as CNT lacked rigorous structural and stereochemical definition. Thus, in addition to the question of raw material availability, control of the 3′ stereochemistry was an issue in selecting the synthesis scheme.

Cyanide addition to a 4-(hydroxymethyl)butenolide (**21**) was chosen as a route to the required 3-cyanoribose derivative (**26**) in anticipation of a preference for formation of the desired 3α relative configuration (Scheme III).

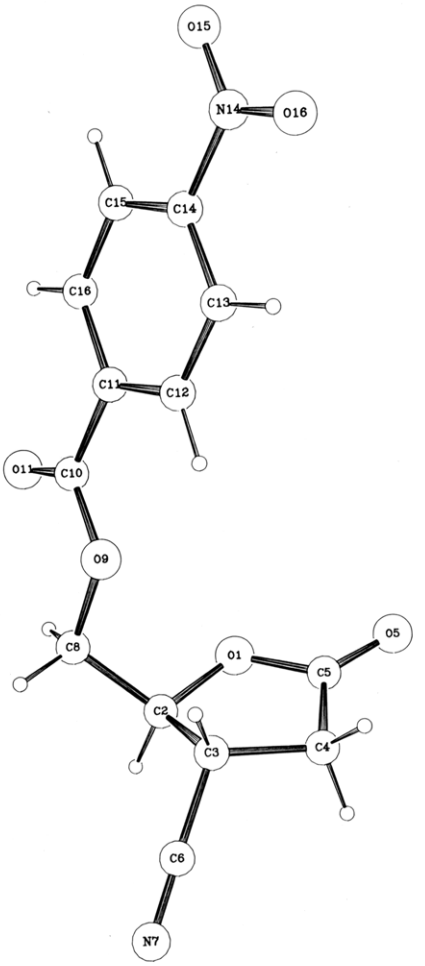
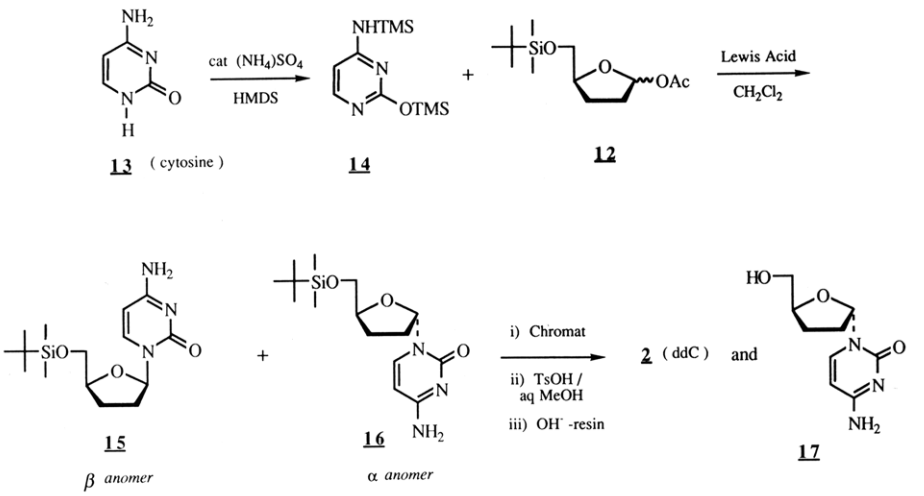


Figure 1. A persepctive drawing of a molecule of **28**.

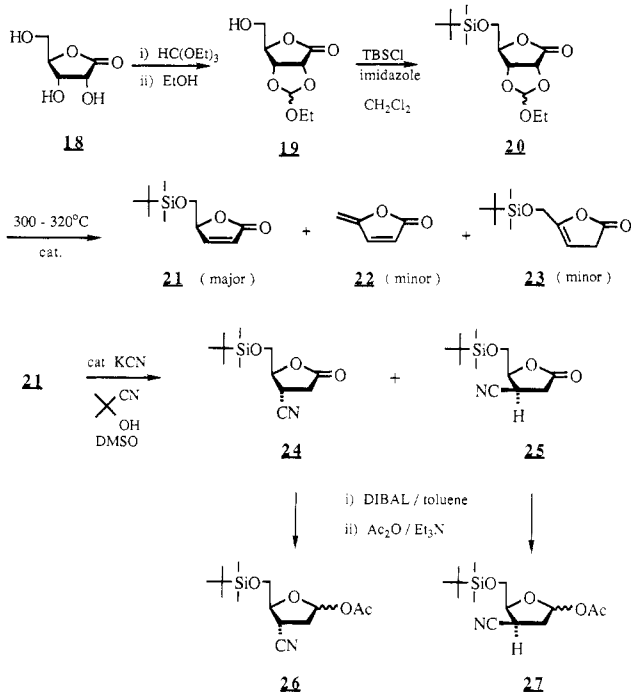
Three features emerged from this plan in its execution, one favorable and two unfavorable. The scheme affords all four stereoisomers at the 1′- and 3′-positions, a desirable feature in view of the structural uncertainties associated with CNT. On the negative side, compound **21** easily racemizes and the intermediates derived from it are racemic. In addition, the low yields in some steps preclude this scheme as the basis for a practical route to CNT. Both points are rendered moot by the absence of anti-HIV activity in CNT.

Four methods of preparing butenolides similar to **21** are reported. One starts with glutamic acid and entails in-

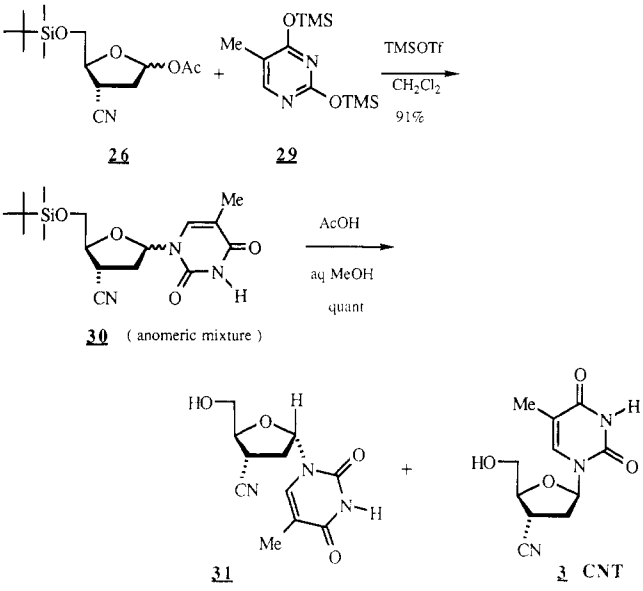
Scheme II



Scheme III



Scheme IV



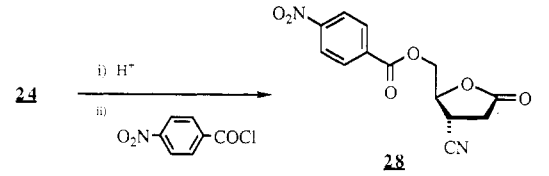
troduction of a double bond into the derived butyrolactone.[7a,10] The other three methods start with D-ribonolactone[11] and give products with differing optical purity.

Pyrolysis of the bicyclic ortho ester **20** was deemed most suitable for multigram-scale quantities. Compound **20** can be distilled unchanged at 260 °C (60 mm) and requires an acid catalyst to induce the fragmentation reaction leading to **21**. 1,2,4-Benzenetricarboxylic anhydride served as an effective catalyst because of its high boiling point. The pyrolysis was conducted at 300–320 °C (bath) at 60–80 mm of pressure, giving a distillate, which, on redistillation, afforded a 46% overall yield of butenolide **21** with 93% and 70% chemical purity and ee, respectively. Byproducts of the pyrolysis include compounds **22** and **23**.

Stereochemical events downstream of **21** were simplified by deliberately and fully racemizing it with triethylamine.[12]

Conjugate hydrocyanation of **21** lacked literature precedents, despite the fact that smooth, high-yield additions of HCN to acrylates, crotonates, etc., are well known.[13] After several trials with other reagents and combinations, it was found that KCN/acetone cyanohydrin/DMSO at 65 °C gave usable yields of the epimeric hydrocyanation products **24** (22.5% yield) and **25** (16.1% yield). Elimination to form **22**, which polymerizes, consumed much of the starting material **21**.

The epimers were separated by chromatography on silica gel and the α- and β-isomer assignments made on the basis of the $J_{3,4}$ coupling constants in their proton NMR spectra: 5.1 Hz for **24** and 8.1 Hz for **25**. To confirm these assignments, the TBS group of **24** was replaced by a *p*-nitrobenzoyl group, this derivative being nicely crystalline



and amenable to X-ray crystallographic structure analysis. A computer-drawn structure of **28** is shown in Figure 1.

Selective reduction of the separated epimers **24** and **25** afforded lactols, which were acetylated to give compounds **26** and **27**, suitably functionalized for coupling with silylated thymine (Schemes IV and V).

For these couplings, trimethylsilyl triflate proved to be the reagent of choice.[14] In the case of the α-cyano epimer **26**, the coupling yield was high, 91%, with a 5:4 α/β-anomer mixture **30** being formed. Chromatographic separation was more readily effected after hydrolytic removal of the *tert*-butyldimethylsilyl protecting group. Assignment of structure to the α- and β-anomeric isomers was made on the basis of characteristic NMR features (Table I).

Since protons that are syn to the base are more deshielded than those which are anti to it, the H-4′ proton of an α-anomer appears at a lower field than that of a β-anomer and the H-5′ protons of an α-anomer appear at

Table I. ^{1}H NMR Chemical Shifts δ (ppm)

compd	(abbr)	H-4′	H-5′
15	(TBS-β-ddC)[a]	4.13 (anti)[c]	3.87 (syn)[c]
16	(TBS-α-ddC)[a]	4.38 (syn)	3.64 (anti)
2	(β-ddC)[b]	4.00 (anti)	3.60 (syn)
17	(α-ddC)[b]	4.36 (syn)	3.39 (anti)
30$^\beta$	(TBS-α-CN-β-T)[a]	4.26 (anti)	3.96 (syn)
30$^\alpha$	(TBS-α-CN-α-T)[a]	4.61 (syn)	3.79 (anti)
32	(TBS-β-CN-β-T)[a]	4.26 (anti)	4.02 (syn)
33	(TBS-β-CN-α-T)[a]	4.59 (syn)	3.92 (anti)
3	(α-CN-β-T)[b]	4.13 (anti)	3.66 (syn)
31	(α-CN-α-T)[b]	4.54 (syn)	3.52 (anti)
34	(β-CN-β-T)[b]	4.16 (anti)	3.73 (syn)
35	(β-CN-α-T)[b]	4.54 (syn)	3.62 (anti)

[a] Spectra were recorded in $CDCl_3$. [b] In DMSO-d_6. [c] Relative stereochemistry to the base.

(10) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303.

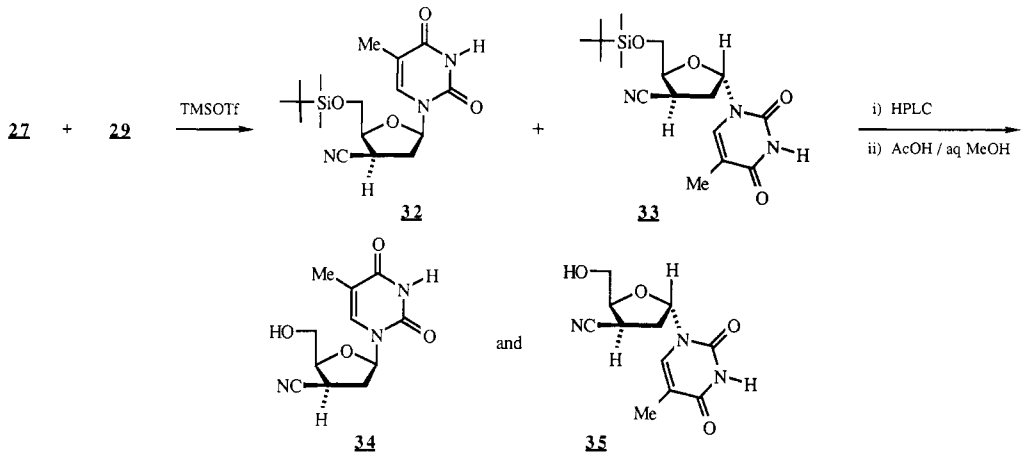
(11) (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (b) Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737. (c) Vekemans, J. A. J. M.; Franken, G. A. M.; Chittenden, G. J. F.; Godefroi, E. F. *Tetrahedron Lett.* **1987**, *28*, 2299.

(12) Vekemans, J. A. J. M.; Boerekamp, J.; Godefroi, E. F.; Chittenden, G. J. F. *Recl. Trav. Chim. pays-Bas* **1985**, *104*, 266.

(13) Nagata, W.; Yoshioka, M. *Org. React. (N.Y.)* **1977**, *25*, 255.

(14) Vorbruggen, H.; Krolikeiwicz, K.; Bennua, B. *Chem. Ber.* **1981**, *144*, 1234.

Scheme V



a higher field than those of a β-anomer. For example, the difference in chemical shifts of the H-4′ protons of **3** and **31** is more than 0.4 ppm, so that the assignment was made without any difficulty.

Coupling of the β-cyano epimer **27** with silylated thymine (Scheme V) proceeded poorly but gave sufficient amounts of each anomer for complete characterization. The separation of anomeric isomers, in this case, was conveniently effected prior to deblocking, by use of preparative HPLC. The stereochemistry of nucleosides **34** and **35** obtained on hydrolysis were again assigned on the basis of their NMR spectra.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on Varian XL-200 and XL-400 instruments and are reported in parts per million from tetramethylsilane. Electron-impact mass spectra were determined on a VG ZAB-1F instrument at 70 eV. Elemental analyses were carried out in our Microanalytical Laboratory under the direction of Dr. F. Scheidl.

(*S*)-γ-Butyrolactone-γ-carboxylic Acid (8). Sodium nitrite (104 g, 1.5 mol) in 144 mL of water and 5.6 N HCl (250 mL, 1.4 mol) were added simultaneously to a suspension of L-glutamic acid (147 g, 1.0 mol) in 500 mL of water with vigorous stirring over 5 h. During the addition, the temperature was maintained at 15–20 °C. After the addition was completed, the mixture was stirred at room temperature overnight. The water was removed by coevaporation with toluene at 40 °C. Ethyl acetate (1 L) and powdered Na_2SO_4 (100 g) were added to the residue, and the mixture was mechanically stirred overnight. The precipitates were removed by filtration and washed with ethyl acetate. The combined solutions were stirred with 20 g of AG50W-X4 (200–400 mesh, H^+ form) for 30 min to remove the residual amino acid. After filtration of the mixture, the solution was concentrated and the residual water was removed by coevaporation with toluene. The product **8** crystallized from CH_2Cl_2 while stored in a refrigerator. A yield of 73.7 g (56%) was obtained, mp 61–67 °C (lit.[5b] mp 71–73 °C). This material was used for the next step without further purification.

(*S*)-γ-(Hydroxymethyl)-γ-butyrolactone (9).[5b] To a solution of **8** (65 g, 0.5 mol) in 300 mL of anhydrous THF was added borane–dimethyl sulfide complex (53 mL, 0.53 mol) over 40 min. During the addition, the temperature was kept below 40 °C by ice–water cooling. After the mixture was stirred at room temperature for an additional 2 h, the reaction was quenched carefully with methanol (100 mL). Most of the solvent was removed by rotary evaporation. Methanol (50 mL) was added to the residue and removed by evaporation. This procedure was repeated three times in order to remove any trimethyl borate formed. The residue was dried by coevaporation with toluene to afford 59 g (102%) of crude **9**, which was used for the next reaction without purification.

(*S*)-γ-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-γ-butyrolactone (10). A mixture of crude **9** (59 g, 0.5 mol) and imidazole (44 g, 0.66 mol) in 250 mL of CH_2Cl_2 was cooled with an ice–water bath followed by the addition of *tert*-butyldimethylsilyl chloride (90.5 g, 0.60 mol). The mixture was stirred at 0 °C for 15 min and at room temperature for 2 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was distilled under reduced pressure to give 102.7 g of **10** (91% from **8**): bp 88–92 °C (0.05 mmHg); $[\alpha]_D$ +11.11° (*c* 0.92, $CHCl_3$); MS, *m/e* 215 ($M^+ - CH_3$), 173 ($M^+ - C_4H_9$); IR (neat) 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 2.17 (m, 1 H), 2.25 (m, 1 H), 2.46 (m, 1 H), 2.59 (m, 1 H), 3.67 (dd, 1 H, *J* = 10.5 and 2.5 Hz), 3.86 (dd, 1 H, *J* = 10.5 and 2.5 Hz), 4.58 (m, 1 H). Anal. Calcd. for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63; Si, 12.19. Found: C, 57.39; H, 9.97; Si, 12.50.

Lactol 11. To a solution of **10** (46 g, 0.2 mol) in 400 mL of toluene at −78 °C was added a 1.5 M solution of Dibal in toluene (147 mL, 0.22 mol) over 1 h. During the addition, the temperature was kept below −68 °C. After being stirred for an additional 5 min, the reaction mixture was quenched with 40 mL of MeOH and allowed to warm to room temperature. EtOAc (300 mL) and saturated $NaHCO_3$ solution (40 mL) were added, and the mixture was stirred for 2 h. Powdered Na_2SO_4 (200 g) was then added, and the mixture was stirred overnight. The precipitate was removed by filtration and washed with EtOAc. The solvent was removed, and 46 g of crude lactol **11** (99% yield) was obtained. This material was used for the next step without purification. An analytical sample was obtained by column chromatography: $[\alpha]_D$ +16.1° (*c* 0.94, $CHCl_3$); IR (neat) 3425 cm^{-1}; MS, *m/e* 217 ($M^+ - CH_3$), 215 ($M^+ - OH$), 175 ($M^+ - C_4H_9$); NMR ($CDCl_3$) δ 0.08 and 0.13 (s, 6 H), 0.90 and 0.93 (s, 9 H), 1.70–2.16 (m, 4 H), 3.57 (m, 1 H), 3.74 and 3.79 (d, *J* = 8 Hz, and dd, *J* = 10.5 and 3 Hz, respectively, 1 H), 4.27 (m, 1 H), 5.40 and 5.56 (m, 1 H). Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41; Si, 12.09. Found: C, 56.99; H, 10.33; Si, 12.21.

Acetylation of 11. A mixture of crude **11** (46 g, 0.2 mol), acetic anhydride (22.5 mL, 0.24 mol), and triethylamine (33 mL, 0.24 mol) was stirred at 0 °C for 20 min and then at room temperature overnight. EtOAc and water were added to the mixture. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was distilled under reduced pressure to give 37.7 g (69% yield) of the acetate **12** (2:1 mixture of anomers): bp 77–83 °C (0.05 mmHg); $[\alpha]_D$ +18.82° (*c* 1.17, $CHCl_3$); IR (neat) 1748 cm^{-1}; MS, *m/e* 231 ($M^+ - CH_3CO$), 215 ($M^+ - CH_3CO_2$); NMR ($CDCl_3$) (major isomer) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.84–2.20 (m, 4 H), 2.03 (s, 3 H), 3.60 (m, 2 H), 4.29 (m, 1 H), 6.29 (d, *J* = 5 Hz, 1 H), (minor isomer) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.74–2.15 (m, 4 H), 2.01 (s, 3 H), 3.64 (dd, *J* = 10 and 5 Hz, 1 H), 3.75 (dd, *J* = 10 and 5 Hz, 1 H), 4.26 (m, 1 H), 6.25 (m, 1 H). Anal. Calcd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55; Si, 10.23. Found: C, 57.00; H, 9.68; Si, 10.02.

2,4-Bis(trimethylsilyl)cytosine (14).[15] A mixture of cytosine

(15) Schroeder, A. C.; Hughes, R. G.; Bloch, A. *J. Med. Chem.* **1981**, *24*, 1078.

(3.7 g, 33 mmol), hexamethyldisilazane (25 mL), and NH_4SO_4 (8 mg) was refluxed for 1 h and then cooled to room temperature. The mixture was concentrated in vacuo, and the residue was coevaporated twice with toluene to afford **14** as a white solid, which was used for the next step without purification.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxycytidines (15 and 16). To **14** prepared above was added a solution of the acetate **12** (8.22 g, 30 mmol) in anhydrous CH_2Cl_2 (80 mL). Then a 1.8 M solution of $EtAlCl_2$ in toluene (16.7 mL, 30 mmol) was slowly added to the mixture over 2.5 h. During the addition, the temperature was maintained below 27 °C. After the completion of the addition, the mixture was stirred at room temperature for an additional 40 min and then slowly poured into an ice-cold mixture of CH_2Cl_2 and saturated $NaHCO_3$ solution. The mixture was stirred for 10 min and filtered through a Celite pad. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give 9.8 g of crude products; α:β (16:15) = 2:3. The crude products were purified by column chromatography (400 g of silica gel; eluted with 8–20% 2-propanol in $CHCl_3$) to give 4.05 g (41.5%) of pure β-anomer **15**, 1.16 g (12%) of the mixture, and 1.71 g (17.5%) of α-anomer **16**.

15: mp 204–206 °C; $[\alpha]_D$ +45.81° (*c* 1.02, CH_3OH); IR (KBr) 3355, 1662, 1620 cm^{-1}; MS, *m/e* 325 (M^+), 310 ($M^+ - CH_3$), 268 ($M^+ - C_4H_9$); NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.82 (m, 1 H), 1.90 (m, 1 H), 2.07 (m, 1 H), 2.40 (m, 1 H), 3.70 (dd, *J* = 10.5 and 2 Hz, 1 H), 4.04 (dd, *J* = 10.5 and 2.5 Hz, 1 H), 4.13 (m, 1 H), 5.60 (d, *J* = 7 Hz, 1 H), 5.85 (b, 2 H), 6.07 (dd, *J* = 6.5 and 2.5 Hz, 1 H), 8.15 (d, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{15}H_{27}N_3O_3Si$: C, 55.35; H, 8.36; N, 12.91; Si, 8.63. Found: C, 55.23; H, 8.39; N, 12.59; Si, 8.45.

16: mp 199–203 °C; $[\alpha]_D$ −53.96° (*c* 0.31, CH_3OH); IR (KBr) 3365, 1665, 1620 cm^{-1}; MS, *m/e* 325 (M^+), 268 ($M^+ - C_4H_9$); NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.91 (m, 2 H), 2.02 (m, 1 H), 2.57 (m, 1 H), 3.64 (d, *J* = 4.5 Hz, 2 H), 4.38 (m, 1 H), 5.68 (d, *J* = 7 Hz, 1 H), 5.95 (b, 2 H), 6.03 (dd, *J* = 7 and 3 Hz, 1 H), 7.45 (d, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{15}H_{27}N_3O_3Si$: C, 55.35; H, 8.36; N, 12.91; Si, 8.63. Found: C, 55.33; H, 8.40; N, 13.03; Si, 8.45.

2′,3′-Dideoxycytidine (2). To a solution of **15** (4 g, 12.3 mmol) in MeOH (37 mL) and H_2O (5.5 mL) was added *p*-toluenesulfonic acid monohydrate (2.47 g, 13 mmol). After the mixture was stirred at room temperature for 7 h, 37 mL of Bio-Rex 9 (20–50 mesh, OH^- form) was added to remove the acid. The resin was filtered off and washed with methanol. The filtrate and washings were concentrated to afford 2.46 g (95% yield) of **2**: mp 214–217 °C (from 2-propanol); $[\alpha]_D$ +105.9° (*c* 0.53, MeOH), +80.61° (*c* 0.49, H_2O); UV (water) λ_{max} 271 nm (ϵ 8720); IR (KBr) 3400, 1649 cm^{-1}; MS, *m/e* 211 (M^+), 181 ($M^+ - CH_2OH$); NMR (DMSO-d_6) δ 1.76 (m, 1 H), 1.84 (m, 2 H), 2.24 (m, 1 H), 3.54 (m, 1 H), 3.66 (m, 1 H), 4.00 (m, 1 H), 4.98 (t, *J* = 5.4 Hz, 1 H), 5.68 (d, *J* = 7.4 Hz, 1 H), 5.93 (dd, *J* = 6.6 and 3.2 Hz, 1 H), 7.01 (br s, 1 H), 7.06 (br s, 1 H), 7.90 (d, *J* = 7.4 Hz, 1 H). Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.29; H, 6.20; N, 20.05.

2′,3′-Dideoxy-α-cytidine (17). Deprotection of **16** was performed in a similar manner to afford **17** (95% yield): mp 169–172 °C (from 2-propanol); $[\alpha]_D$ −83.39° (*c* 0.56, MeOH), −59.55° (*c* 0.53, H_2O); UV (water) λ_{max} 271 nm (ϵ 9520); IR (KBr) 3370, 1652, 1638 cm^{-1}; MS, *m/e* 211 (M^+); NMR (DMSO-d_6) δ 1.79 (m, 1 H), 1.83 (m, 1 H), 1.91 (m, 1 H), 2.30 (m, 1 H), 3.39 (m, 2 H), 4.36 (m, 1 H), 4.78 (t, *J* = 5.7 Hz, 1 H), 5.70 (d, *J* = 7.4 Hz, 1 H), 5.97 (dd, *J* = 6.2 and 3.8 Hz, 1 H), 7.02 (br s, 1 H), 7.10 (br s, 1 H), 7.54 (d, *J* = 7.4 Hz, 1 H). Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 18.89. Found: C, 51.01; H, 6.22; N, 19.14.

Racemic 4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]butenolide (21). A mixture of ribonolactone (14.8 g, 100 mmol) and triethyl orthoformate (25 mL, 150 mmol) was heated at 110 °C (bath temperature) for 3 h. Ethanol (25 mL) was added, and refluxing was continued for another hour. After being cooled to room temperature, the mixture was concentrated at room temperature in vacuo. The residue was dissolved in 50 mL of CH_2Cl_2 followed by the addition of imidazole (10.2 g, 150 mmol). After cooling to 0 °C, *tert*-butyldimethylsilyl chloride (18.1 g, 120 mmol) was added. The mixture was stirred at 0 °C for 30 min and at room temperature overnight. The reaction mixture was poured into 300 mL of petroleum ether and washed with water (4 × 30 mL). The solution was dried over Na_2SO_4 and concentrated to afford crude silylated ortho ester **20**. The crude **20** was transferred into a 100-mL flask equipped with a distillation head having a 15-cm column. After removal of the solvent, 1,2,4-benzenetricarboxylic anhydride (384 mg, 2 mmol) was added, and the mixture was heated at 300–320 °C (bath temperature under 60–80 mmHg of pressure for 3 h to afford 23.56 g of a distillate, which contained the butenolide **21** as a major component and byproducts (**22** and **23**). Redistillation of the distillate to afford 11.24 g of **21** in a 93% purity (46% overall yield): bp 90 °C/(0.1 mmHg); $[\alpha]_D$ −93° (*c* 1, $CHCl_3$). The optically active **21** (7.5 g) was dissolved in 75 mL of 2-propanol and treated with Et_3N (3.4 mL) at room temperature for 4 h. After distillation, 7.0 g of the racemate **21** was obtained.

21: IR ($CHCl_3$) 1758 cm^{-1}; NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 9 H), 3.80 (dd, *J* = 10.8 and 5.5 Hz, 1 H), 3.93 (dd, *J* = 10.8 and 4.4 Hz, 1 H), 5.06 (m, 1 H), 6.17 (dd, *J* = 5.6 and 1.7 Hz, 1 H), 7.52 (dd, *J* = 5.6 and 1.0 Hz, 1 H). Anal. Calcd for $C_{11}H_{20}O_3Si$: C, 57.86; H, 8.83; Si, 12.29. Found: C, 57.57; H, 8.76; Si, 12.18.

22: NMR ($CDCl_3$) δ 4.92 (m, 1 H), 5.24 (m, 1 H), 6.26 (m, 1 H), 7.41 (d, *J* = 5 Hz, 1 H).

23: NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 3.19 (m, 2 H), 4.31 (m, 2 H), 5.37 (m, 1 H).

Hydrocyanation of 21. A mixture of the lactone **21** (8.34 g, 36.6 mmol), DMSO (13.4 mL), and acetone cyanohydrin (13.4 mL, 146 mmol) was heated to 65 °C. Then powdered KCN (1.19 g, 18.3 mmol) was added. The mixture was stirred at 65 °C for 2 h and then poured into a mixture of saturated NH_4Cl solution (40 mL) and water (80 mL). The aqueous mixture was extracted with petroleum ether 10 times. The combined extracts were washed with water three times, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel. Elution with 15% EtOAc in hexane gave 2.1 g (22.5%) of α-cyano lactone **24**, and elution with 25% EtOAc in hexane gave 1.5 g (16.1%) of β-cyano lactone **25**.

24: R_f 0.37 (20% EtOAc in hexane); IR (neat) 2245, 1798 cm^{-1}; MS, *m/e* 240 ($M^+ - CH_3$), 198 ($M^+ - C_4H_9$); NMR ($CDCl_3$) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 9 H), 2.85 (dd, *J* = 17.7 and 7.0 Hz, 1 H), 3.00 (dd, *J* = 17.7 and 10.0 Hz, 1 H), 3.57 (ddd, *J* = 10.0, 7.0, and 5.1 Hz, 1 H), 3.82 (dd, *J* = 11.9 and 1.9 Hz, 1 H), 3.96 (dd, *J* = 11.9 and 2.6 Hz, 1 H), 4.73 (m, 1 H). Anal. Calcd for $C_{12}H_{21}NO_3Si$: C, 56.44; H, 8.29; N, 5.48; Si, 11.00. Found: C, 56.58; H, 8.54; N, 5.58; Si, 11.26.

25: R_f 0.15 (20% EtOAc in hexane); IR (neat) 2245, 1790 cm^{-1}; MS, *m/e* 240 ($M^+ - CH_3$), 198 ($M^+ - C_4H_9$); NMR ($CDCl_3$) δ 0.11 (s, 3 H), 0.14 (s, 3 H), 0.92 (s, 9 H), 2.81 (dd, *J* = 17.3 and 10.0 Hz, 1 H), 3.04 (dd, *J* = 17.3 and 10.0 Hz, 1 H), 3.63 (dt, *J* = 8.1 and 10.0 Hz, 1 H), 4.02 (dd, *J* = 11.7 and 2.3 Hz, 1 H), 4.07 (dd, *J* = 11.7 and 1.0 Hz, 1 H), 4.74 (br d, *J* = 8.1 Hz, 1 H). Anal. Calcd for $C_{12}H_{21}NO_3Si$: C, 56.44; H, 8.29; N, 5.48; Si, 11.00. Found: C, 56.22; H, 8.27; N, 5.37; Si, 11.19.

***p*-Nitrobenzoate 28.** Compound **24** was treated with AG50W-X4 (H^+ form) in 2-propanol and water to give the corresponding free alcohol, which was acylated with *p*-nitrobenzoyl chloride in CH_2Cl_2 to afford **28**: mp 141–143 °C; IR (KBr) 2240, 1802, 1730, 1520, 1348 cm^{-1}; MS, *m/e* 290 (M^+), 274 ($M^+ - O$); NMR ($CDCl_3$ + DMSO-d_6) δ 3.02 (dd, *J* = 17.6 and 9.4 Hz, 1 H), 3.10 (dd, *J* = 17.6 and 9.4 Hz, 1 H), 3.62 (dt, *J* = 7.4 and 9.4 Hz, 1 H), 4.69 (m, 2 H), 5.02 (m, 1 H), 8.24 (d, *J* = 9.0 Hz, 2 H), 8.32 (d, *J* = 9.0 Hz, 2 H). Anal. Calcd for $C_{13}H_{10}N_2O_6$: C, 55.80; H, 3.47; N, 9.65. Found: C, 55.94; H, 3.49; N, 9.76.

Dibal Reduction of 24. A solution of **24** (4.75 g, 18.6 mmol) in toluene (370 mL) and THF (30 mL) was cooled to −78 °C. Then a 1.5 M solution of Dibal in toluene (14.3 mL, 21.4 mmol) was added over 30 min. After the mixture was stirred for an additional 5 min, methanol (1 mL) was carefully added and the mixture was warmed to room temperature. Saturated Na_2SO_4 solution (9 mL) was added, and the mixture was stirred overnight. Powdered Na_2SO_4 (27 g) was then added, and the mixture was stirred for 1 h. The solid was filtered off and washed with EtOAc. The filtrate was concentrated, and the residue was chromatographed on silica gel. Elution with 15% EtOAc in hexane gave 1.87 g of **24** (39% recovery) and elution with 25% EtOAc in hexane gave 1.87 g of the corresponding lactol (39% yield): IR (neat) 3440, 2245 cm^{-1}; MS, *m/e* 256 ($M^+ - H$), 240 ($M^+ - OH$); NMR ($CDCl_3$) δ 5.51 and 5.64 (m, anomeric protons).

Acetate 26. The lactol (1.87 g, 7.28 mmol) prepared above was dissolved in 20 mL of CH_2Cl_2 and treated with Ac_2O (1.4 mL, 15 mmol) and Et_3N (2.1 mL, 15 mmol) overnight. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. The residue was passed through a short column (SiO_2, eluted with 10% EtOAc in $CHCl_3$) and then distilled under a reduced pressure to afford 1.86 g of **26** (85% yield): bp 100 °C (bath temperature) (0.03 mmHg); IR (neat) 2240, 1750 cm^{-1}; MS, *m/e* 298 (M^+ - H), 240 (M^+ - OAc); NMR ($CDCl_3$) δ 0.06, 0.07, 0.08, and 0.09 (s, 6 H), 0.89 and 0.92 (s, 9 H), 2.04 and 2.11 (s, 3 H), 2.34–2.56 (m, 2 H), 3.23–3.35 (m, 1 H), 3.71–3.88 (m, 2 H), 4.30 and 4.51 (m, 1 H), 6.32 and 6.37 (d, J = 4.3 Hz, and d, J = 4.0 Hz, respectively, 1 H). Anal. Calcd for $C_{14}H_{25}NO_4Si$: C, 56.16; H, 8.42; N, 4.68; Si, 9.38. Found: C, 56.01; H, 8.44; N, 4.48; Si, 9.29.

Dibal Reduction of 25. To a solution of **25** (1.36 g, 5.22 mmol) in toluene (100 mL) at −78 °C was added a 1.5 M solution of Dibal in toluene (4 mL, 6 mmol) over 40 min. After an additional 10 min, the reaction mixture was quenched with MeOH (0.5 mL) and warmed to room temperature. Saturated Na_2SO_4 solution (3 mL) was added, and the mixture was stirred for 2 h. Then powdered Na_2SO_4 (15 g) was added, and the mixture was stirred overnight. The solid was filtered off and washed with EtOAc. The filtrate was concentrated, and the residue was chromatographed on silica gel. Elution with 25% EtOAc in hexane gave 1.05 g of crude lactol: NMR ($CDCl_3$) δ 5.51 and 5.68 (m, anomeric protons). This material was used for the next reaction without further purification.

Acetate 27. The lactol (1.05 g, 4 mmol) prepared from **25** was acetylated in a similar manner. The product was purified by chromatography (SiO_2, eluted with 20% EtOAc in hexane) followed by distillation to afford 0.82 g of **27** (51% yield): bp 125 °C (bath temperature)(0.1 mmHg); IR (neat) 2240, 1749 cm^{-1}; MS, *m/e* 242 ($M^+ - C_4H_9$), 240 (M^+ - OAc); NMR ($CDCl_3$) δ 0.09, 0.10, 0.11, and 0.12 (s, 6 H), 0.91 (s, 9 H), 2.05 and 2.10 (s, 3 H), 2.32–2.67 (m, 2 H), 3.36 and 3.44 (m, 1 H), 3.83–4.02 (m, 2 H), 4.27 and 4.43 (m, 1 H), 6.30 and 6.40 (dd, J = 4.8 and 1.3 Hz, and d, J = 4.7 Hz, respectively, 1 H). Anal. Calcd for $C_{14}H_{25}NO_4Si$: C, 56.16; H, 8.42; N, 4.68; Si, 9.38. Found: C, 55.99; H, 8.65; N, 4.70; Si, 9.45.

2,4-Bis(trimethylsilyl)thymine (29). A mixture of thymine (454 mg, 3.6 mmol) and hexamethyldisilazane (10 mL) was refluxed overnight in the presence of NH_4SO_4 (5 mg). The mixture was concentrated and then coevaporated with toluene to afford **29**, which was used for the next step without purification.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′α-cyano-3′-deoxy-α/β-thymidine (30). To a mixture of **29** (prepared from 3.6 mmol of thymine) and acetate **26** (897 mg, 3 mmol) in CH_2Cl_2 (8 mL) was added TMSOTf (193 μL, 1 mmol). After the mixture was stirred at room temperature for 1 h, additional TMSOTf (386 μL, 2 mmol) was added. The mixture was stirred for an additional hour and poured into an ice-cold mixture of CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ solution (50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel. Elution with 30% EtOAc in $CHCl_3$ gave 1.0 g of an anomeric mixture of **30** (α/β = 5:4) in a 91% yield: mp 125–135 °C; IR (KBr) 2245, 1702, 1692 cm^{-1}; MS, *m/e* 350 ($M^+ - CH_3$), 308 ($M^+ - C_4H_9$); NMR ($CDCl_3$) (α-anomer) δ 0.10 (s, 6 H), 0.92 (s, 9 H), 1.97 (s, 3 H), 2.36 (m, 1 H), 2.93 (m, 1 H), 3.37 (m, 1 H), 3.75 (dd, J = 11 and 2.8 Hz, 1 H), 3.83 (dd, J = 11 and 3.4 Hz, 1 ,h), 4.61 (m, 1 H), 6.15 (t, J = 5.7 Hz, 1 H), 7.21 (br s, 1 H), 8.53 (br s, 1 H), (β-anomer) δ 0.14 (s, 6 H), 0.94 (s, 9 H), 1.92 (s, 3 H), 2.45 (m, 1 H), 2.74 (m, 1 H), 3.37 (m, 1 H), 3.86 (dd, J = 12 and 2.5 Hz, 1 H), 4.05 (dd, J = 12 and 2.0 Hz, 1 H), 4.26 (m, 1 H), 6.18 (m, 1 H), 7.34 (br s, 1 H), 8.53 (br s, 1 H). Anal. Calcd for $C_{17}H_{27}N_3O_4Si$: C, 55.86; H, 7.45; N, 11.50; Si, 7.68. Found: C, 55.97; H, 7.54; N, 11.59; Si, 7.53.

Racemic 3′α-Cyano-3′-deoxythymidines (3 and 31). Compound **30** (182 mg, 0.5 mmol) was dissolved in a mixture of AcOH–H_2O–MeOH (4:1:1, 6 mL). After being stirred at room temperature for 2 days, the mixture was concentrated to afford a mixture of **3** and **31** (115 mg, 92% yield) as a white solid. They were purified by chromatography on SiO_2.

3: R_f 0.52 (15% 2-propanol in $CHCl_3$); mp 164–166 °C; UV (water) λ_{max} 205 (ϵ 9170), 265 (ϵ 9530) nm; IR (KBr) 3425, 2245, 1690 cm^{-1}; MS, *m/e* 251 (M^+), 220 ($M^+ - CH_2OH$); NMR (DMSO-d_6) δ 1.77 (s, 3 H), 2.47 (m, 1 H), 2.66 (m, 1 H), 3.50 (q, J = 9.1 Hz, 1 H), 3.62 (br d, J = 12 Hz, 1 H), 3.71 (br d, J = 12 Hz, 1 H), 4.13 (m, 1 H), 5.32 (br s, 1 H), 6.12 (dd, J = 7.6 and 3.9 Hz, 1 H), 7.62 (br s, 1 H), 11.33 (br s, 1 H). Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.73. Found: C, 52.62; H, 5.05; N, 16.64.

31: R_f 0.42 (15% 2-propanol in $CHCl_3$); mp 189–193 °C; UV (water) λ_{max} 205 (ϵ 9080), 265 (ϵ 9770) nm; IR (KBr) 3450, 2245, 1725, 1685, 1672 cm^{-1}; MS, *m/e* 251 (M^+), 220 ($M^+ - CH_2OH$); NMR (DMSO-d_6) δ 1.80 (s, 3 H), 2.45 (m, 1 H), 2.73 (m, 1 H), 3.43 (dt, J = 9.9 and 8.2 Hz, 1 H), 3.52 (m, 2 H), 4.54 (dt, J = 8.2 and 4.1 Hz, 1 H), 5.14 (br s, 1 H), 6.06 (t, J = 6.7 Hz, 1 H), 7.71 (br s, 1 H), 11.35 (br s, 1 H). Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.73. Found: C, 52.26; H, 5.13; N, 16.45.

5′-*O*-(*tert*-Butyldimethylsilyl)-3β′-cyano-3′-deoxythymidines (32 and 33). These compounds were prepared from the acetate **27** (410 mg, 1.37 mmol) in a similar manner described for the preparation of **30**. After chromatography on silica gel (eluted with 60% EtOAc in hexane), 0.25 g (50% yield) of an anomeric mixture (**32**/**33** = 7:3) was obtained. These isomers were separated by HPLC (normal phase, eluted with 20% EtOAc in CH_2Cl_2).

32: R_f 0.31 (CH_2Cl_2–EtOAc, 2:1); mp 143–160 °C; IR (KBr) 3180, 2245, 1705–1670 cm^{-1}; MS, *m/e* 350 ($M^+ - CH_3$), 308 ($M^+ - C_4H_9$); NMR ($CDCl_3$) δ 0.17 (s, 6 H), 0.95 (s, 9 H), 1.96 (d, J = 1.2 Hz, 3 H), 2.35 (m, 1 H) 2.75 (m, 1 H), 3.41 (q, J = 7.2 Hz, 1 H), 4.02 (m, 2 H), 4.26 (m, 1 H), 6.15 (t, J = 6.6 Hz, 1 H), 7.47 (br s, 1 H), 8.19 (br s, 1 H). Anal. Calcd for $C_{17}H_{27}N_3O_4Si$: C, 55.86; H, 7.45; N, 11.50; Si, 7.68. Found: C, 55.87; H, 7.60; N, 11.38; Si, 7.89.

33: R_f 0.35 (CH_2Cl_2–EtOAc, 2:1) mp 64–72 °C; IR (KBr) 2245, 1688 cm^{-1}; MS, *m/e* 350 ($M^+ - CH_3$), 308 ($M^+ - C_4H_9$); NMR ($CDCl_3$) δ 0.13 (s, 3 H), 0.14 (s, 3 H), 0.94 (s, 9 H), 1.93 (s, 3 H), 2.59 (m, 1 H), 2.92 (m, 1 H), 3.61 (d, J = 8 Hz, 1 H), 3.88 (dd, J = 10.5 and 3.9 Hz, 1 H), 3.97 (dd, J = 10.5 and 2.9 Hz, 1 H), 4.59 (m, 1 H), 5.98 (dd, J = 7.6 and 3.8 Hz, 1 H), 7.02 (br s, 1 H), 8.25 (br s, 1 H). Anal. Calcd for $C_{17}H_{27}N_3O_4Si$: C, 55.86; H, 7.45; N, 11.50; Si, 7.68. Found: C, 55.71; H, 7.57; N, 11.25; Si, 7.89.

Racemic 3′β-Cyano-3′-deoxythymidine (34). Compound **32** was treated with AcOH–H_2O–MeOH (4:1:1) to afford the free nucleoside **34**: mp 199–201 °C; UV (H_2O) λ_{max} 204 (ϵ 9040), 266 (ϵ 9060) nm; IR (KBr) 3475, 2245, 1690 cm^{-1}; MS, *m/e* 251 (M^+), 220 ($M^+ - CH_2OH$); NMR (DMSO-d_6) δ 1.79 (s, 3 H), 2.30 (m, 1 H), 2.64 (m, 1 H), 3.73 (m, 3 H), 4.16 (m, 1 H), 5.30 (br t, 1 H), 6.07 (t, J = 7 Hz, 1 H), 7.66 (br s, 1 H), 11.38 (br s, 1 H). Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.29; H, 5.22; N, 16.73. Found: C, 51.94; H, 5.18; N, 16.33.

Racemic 3′β-Cyano-3′-deoxy-α-thymidine (35). Compound **35** was obtained from **33** in a similar manner: mp 86–92 °C; UV (H_2O) λ_{max} 205 (ϵ 8600), 267 (ϵ 9130) nm; IR (KBr) 3420, 2245, 1690 cm^{-1}; MS, *m/e* 251 (M^+), 220 ($M^+ - CH_2OH$); NMR (DMSO-d_6) δ 1.78 (s, 3 H), 2.54 (m, 1 H), 2.67 (m, 1 H), 3.62 (m, 2 H), 3.81 (m, 1 H), 4.54 (m, 1 H), 5.16 (t, J = 4.9 Hz, 1 H), 6.18 (dd, J = 6.8 and 5.6 Hz, 1 H), 7.50 (br s, 1 H), 11.32 (br s, 1 H). Anal. Calcd for $C_{11}H_{13}N_3O_4 \cdot {}^1/_4H_2O$: C, 51.66; H, 5.32; N, 16.43. Found: C, 51.31; H, 5.32; N, 16.26. Further attempts to dry **35** resulted in decomposition.

Crystallography. Crystals of compound **28** for structure analysis were grown from chloroform/hexane. The crystal data were as follows: space group $P2_1/n$; a = 12.124 Å; b = 5.493 Å; c = 19.205 Å; β = 92.63°; Z = 4; d_{calcd} = 1.509 g/cm^3; and μ (Cu Kα) = 10.0 cm^{-1}.

The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, $\omega - 2\theta$ scans). The size of the crystal used for data collection was approximately 0.04 × 0.12 × 0.63 mm; the data were not corrected for absorption. Of the 1887 independent reflections for $\theta < 60°$, 1332 were considered observed [$I > 3.0\sigma(I)$].

The structure was solved by a multiple-solution procedure[16] and was refined by full-matrix least squares. Four reflections, which were strongly affected by extinction, were excluded from

(16) Main, P.; Fiske, S.; Hull, S.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. MULTAN 11/82, University of York, England and University of Louvain, Belgium; 1982.

the final refinement and difference map. In the final refinement, the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure-factor calculations but their parameters were not refined. The final discrepancy indices are $R = 0.044$ and $R_w = 0.055$ for the remaining 1328 observed reflections. The final difference map has no peaks greater than ± 0.2 e A^{-3}.

Acknowledgment. The encouragement and advice provided by Dr. Manfred Weigele is greatly appreciated.

Stereospecific Synthesis of (−)-Anisomycin from D-Galactose

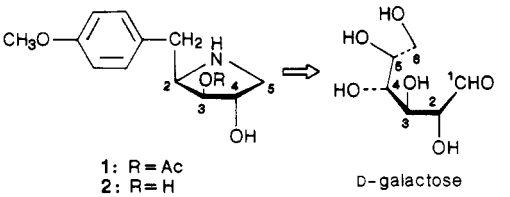
Hans H. Baer* and Mohebullah Zamkanei

Department of Chemistry, University of Ottawa, Ottawa, Ontario K1N 9B4, Canada

Received March 23, 1988

Synthesis starting from ethyl 2,3-di-*O*-benzyl-β-D-galactofuranoside (**3**), which is readily available from D-galactose, provided (2*R*,3*S*,4*S*)-2-(4-methoxybenzyl)pyrrolidine-3,4-diol (**2**, deacetylanisomycin) in eight steps with 18–20% overall yield. The sequence proceeded through the aldehyde **4** generated from **3** by periodate oxidation, conversion of **4** into ethyl 2,3-di-*O*-benzyl-5-deoxy-5-*C*-(4-methoxyphenyl)-α-L-arabinofuranoside (**6**) by Grignard reaction and subsequent ionic deoxygenation of the resulting alcohols **5**, and elaboration of the corresponding sugar oxime **8**. The latter was transformed by dehydrative mesylation into the L-arabinononitrile 4-mesylate **9**, which was reduced by diborane to the amine and cyclized by internal S_N2 reaction to give the dibenzyl ether **10** of **2**. Catalytic transfer hydrogenolysis then furnished **2**.

The streptomycetal antibiotic (−)-anisomycin (**1**) exhibits marked activity against some pathogenic protozoa and fungi.[1] The compound and its deacetyl derivative (**2**) have been used in the control of bean mildew and other fungal plant infections.[2] Early syntheses starting from L-tartaric acid,[3] diethyl L-tartrate,[4] or 2-(4-methoxybenzoyl)pyrrole[5] were nonstereoselective and gave low overall yields, but a highly selective synthesis from diethyl L-tartrate was recently accomplished by Iida et al.[6] who obtained **2** after 14, and **1** after 19 steps in yields of 5 and 2%, respectively. The racemic forms have been synthesized from D,L-tyrosine[7,8] and, most efficiently, from pyrrole-2-carboxaldehyde,[9] with the latter approach providing (±)-**2** and (±)-**1** in overall yields of 53 and 40% over 8 and 13 steps, respectively. Two chiral syntheses of **1** were based on the use of carbohydrates as starting materials. Thus, Verheyden et al.[10] described an 18-step sequence (8.5% yield) from 1,2;5,6-di-*O*-isopropylidene-D-glucose, and Buchanan et al.[11] reported a 13-step sequence (6% yield) from D-ribose. An alternative approach, comprising similar strategies but departing ultimately from (more economical) D-galactose, is disclosed in the present article. This sugar was considered particularly attractive from a viewpoint of stereochemical transformations required to reach the target: The C-2,3 moiety in D-galactose embodies the trans glycol grouping (C-4,3) of **2** with correct absolute configuration; conversion of OH-4 in the sugar into a leaving



group followed by its S_N2 displacement by amino nitrogen previously attached to C-1 was predicted to generate the pyrrolidine ring with its proper C-2 configuration; and the sugar C-5,6 terminal would serve to elaborate the benzylic substituent. Thus a single stereochemically significant and completely stereospecific transformation would be involved in the design that was realized as shown in Scheme I.

The known[12] ethyl 2,3-di-*O*-benzyl-β-D-galactofuranoside (**3**) served as the compound of departure. It is conveniently prepared from D-galactose via the diethyl dithioacetal[13] and ethyl β-D-galactofuranoside,[14] which is then protected as its 5,6-acetonide, benzylated, and deacetonated.[12] These five standard operations can be performed routinely on large scale, furnishing **3** in 30% yield.

Periodate oxidation of **3** gave the aldehyde **4** as an oil (ν_{max} 1730 cm^{-1}; ^1H NMR δ 9.63, d, J = 1.3 Hz), which, without further characterization, was allowed to react with (4-methoxyphenyl)magnesium bromide in ether. The resultant product was a mixture of epimeric alcohols (**5**), isolated in 87% yield after chromatography and fully characterized by ^1H NMR and analytical data. Epimer separation appeared possible but was difficult and was not pursued rigorously as the benzylic hydroxyl group was slated for removal in the next step. This was accomplished

(1) Jimenez, A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979; Vol. 5(2), pp 1–19.
(2) *The Merck Index*, 10th ed.; Rahway, NJ, 1983; p 691.
(3) Wong, C. M.; Buccini, J.; Te Raa, J. *Can. J. Chem.* **1968**, *46*, 3091.
(4) Felner, I.; Schenker, K. *Helv. Chim. Acta* **1970**, *53*, 754.
(5) Wong, C. M.; Buccini, J.; Chang, I.; Te Raa, J.; Schwenk, R. *Can. J. Chem.* **1969**, *47*, 2421.
(6) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069.
(7) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1969**, *17*, 1405.
(8) In a brief communication a synthesis of optically active **2** from D-tyrosine has also been announced: Shono, T.; Kise, N. *Chem. Lett.* **1987**, 697.
(9) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076.
(10) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363.
(11) Buchanan, J. G.; MacLean, K. A.; Wightman, R. H.; Paulsen, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1463.
(12) Thiem, J.; Wessel, H.-P. *Justus Liebigs Ann. Chem.* **1983**, 2173.
(13) Green, J. W.; Pacsu, E. *J. Am. Chem. Soc.* **1937**, *59*, 1205.
(14) Pascu, E. *Methods Carbohydr. Chem.* **1963**, *2*, 354.

0022-3263/88/1953-4786$01.50/0