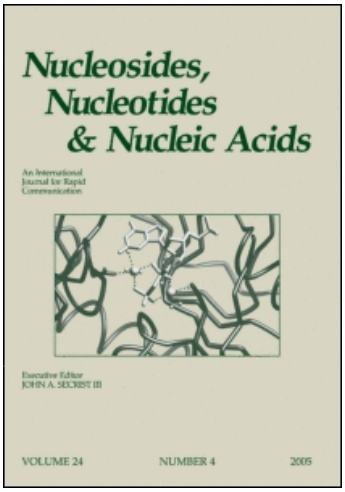


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of the 2'-,3'-Didehydro-2'-,3'-dideoxy and 2'-,3'-Dideoxy Derivatives of 6-Azauridine and a New Route to 2'-,3'-Didehydro-2'-,3'-dideoxy-5-chlorouridine

Andre Rosowsky[a]; Niranjan N. Pai[a]
[a] Dana-Farber Cancer Institute and the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts

To cite this Article Rosowsky, Andre and Pai, Niranjan N.(1991) 'Synthesis of the 2'-,3'-Didehydro-2'-,3'-dideoxy and 2'-,3'-Dideoxy Derivatives of 6-Azauridine and a New Route to 2'-,3'-Didehydro-2'-,3'-dideoxy-5-chlorouridine', Nucleosides, Nucleotides and Nucleic Acids, 10: 4, 837 — 851
To link to this Article: DOI: 10.1080/07328319108046665
URL: http://dx.doi.org/10.1080/07328319108046665

NUCLEOSIDES & NUCLEOTIDES, 10(4), 837-851 (1991)

Synthesis of the 2',3'-Didehydro-2',3'-dideoxy and 2',3'-Dideoxy Derivatives of 6-Azauridine and a New Route to 2',3'-Didehydro-2',3'-dideoxy-5-chlorouridine

Andre Rosowsky* and Niranjan N. Pai

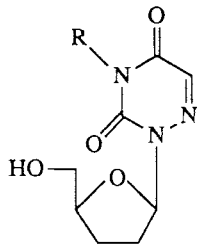
Dana-Farber Cancer Institute and the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115.

SUMMARY

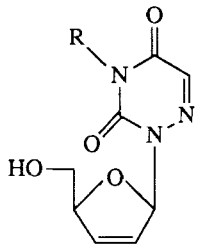
The 5'-O-(4,4'-dimethoxytrityl) and 5'-O-(*tert*-butyldimethylsilyl) derivatives of 2',3'-O-thiocarbonyl-6-azauridine and 2',3'-O-thiocarbonyl-5-chlorouridine were synthesized from the parent nucleosides by reaction with 4,4'-dimethoxytrityl chloride and *tert*-butyldimethylsilyl chloride, respectively, followed by treatment with 1,1'-thiocarbonyldiimidazole. Introduction of a 2',3'-double bond into the sugar ring by reaction of the 5'-protected 2',3'-O-thionocarbonates with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine was unsuccessful, but could be accomplished satisfactorily with trimethyl phosphite. Reactions were generally more successful with the 5'-silylated than with the 5'-tritylated nucleosides. Formation of 2',3'-O-thiocarbonyl derivatives proceeded in higher yield with 5'-protected 6-azauridines than with the corresponding 5-chlorouridines because of the propensity of the latter to form 2,2'-anhydro derivatives. In the reaction of 5'-O-(*tert*-butyldimethylsilyl)-2',3'-O-thiocarbonyl-6-azauridine with trimethyl phosphite, introduction of the double bond was accompanied by N^3-methylation. However this side reaction was not a problem with 5'-O-(*tert*-butyldimethylsilyl)-2',3'-O-thiocarbonyl-5-chlorouridine. Treatment of 5'-O-(*tert*-butyldimethylsilyl)-2',3'-didehydro-2',3'-dideoxy-6-azauridine with tetrabutylammonium fluoride followed by hydrogenation afforded 2',3'-dideoxy-6-azauridine. Deprotection of 5'-O-(*tert*-butyldimethylsilyl)-2',3'-didehydro-2',3'-dideoxy-5-chlorouridine yielded 2',3'-didehydro-2',3'-dideoxy-5-chlorouridine.

Several pyrimidine 2',3'-dideoxynucleoside and 2',3'-didehydro-2',3'-dideoxynucleoside analogues have been found to possess high potency and selectivity as inhibitors of human immunodeficiency virus type 1 (HIV-1), the causative agent of AIDS.[1] Enzymatic conversion of the nucleoside analogues to 5'-triphosphates in infected cells leads to competitive inhibition of viral reverse transcriptase activity.[2-4] This prevents copying of the viral genome and subsequent integration into host DNA, a critical step in the replicative lifecycle of retroviruses.[5]

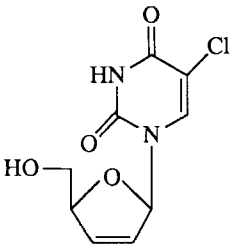
Notable examples of 2',3'-dideoxynucleoside analogues in the pyrimidine series include 2',3'-dideoxyuridine,[6,7] 2',3'-dideoxythymidine,[8,9] 2',3'-dideoxy-5-ethyluridine,[10] 2',3'-dideoxycytidine,[8,11-18] and 2',3'-dideoxy-5-methylcytidine.[19] Halogenation of C^5 in uridine has also been explored,[19-21] as well as replacement of C^5 by nitrogen to form 2',3'-didehydro-2',3'-dideoxy-5-azauridine and 2',3'-dideoxy-5-azacytidine.[19] Unsaturated analogues of several of these compounds are also known, prominent examples of which are 2',3'-didehydro-2',3'-dideoxyuridine,[7,22,23] 2',3'-didehydro-2',3'-dideoxythymidine,[22-27] and 2',3'-didehydro-2',3'-dideoxycytidine.[12,18,22,24,28,29] In the present paper we report the synthesis of 2',3'-dideoxy-6-azauridine (**1**) and 2',3'-didehydro-2',3'-dideoxy-6-azauridine (**2**) as potential antiretroviral agents. Also isolated as minor products in the synthesis of **1** and **2** were the corresponding N^3-methyl derivatives **3** and **4**. To our knowledge, **1**-**4** are the first reported 2',3'-dideoxyriboside derivatives of 6-azauracil. In addition to the preparation of these new 6-aza derivatives, we describe a synthesis of 2',3'-didehydro-2',3'-dideoxy-5-chlorouridine (**5**) from 5-chlorouridine. Our route to **5** differs from that recently developed by another group,[21] involving chlorination of 2',3'-didehydro-2',3'-dideoxyuridine.



1,3 : R = H,Me



2,4 : R = H,Me

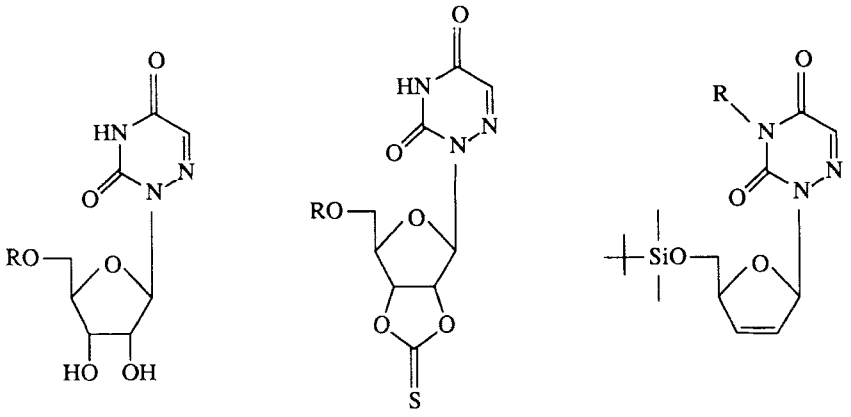


5

Condensation of 6-azauridine with 4,4'-dimethoxytrityl chloride afforded **6** (65%), and further reaction with 1,1'-thiocarbonyldiimidazole (TCDI)[30] converted **6** into **7** (80%). In contrast with our previous experience in the purine series,[31] repeated attempts to obtain an olefin from **7** and 1,2-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DPD)[32] under various conditions gave complex product mixtures whose ^1H NMR spectra showed no evidence of vinyl protons in the δ 5.5-6.5 region. This was surprising in view of a pilot experiment in which 5'-O-(4,4'-dimethoxytrityl)-2',3'-O-(thiocarbonyl)uridine was converted, albeit in modest yield (39%), to 2',3'-didehydro-2',3'-dideoxy-5'-O-(4,4'-dimethoxytrityl)uridine. Deoxygenation of **7** was also attempted with trimethyl phosphite,[33] but was similarly unsuccesful. We therefore turned our attention to a different 5'-blocking group, and prepared 5'-O-(*tert*-butyldimethylsilyl)-6-azauridine

(**8**, 55% yield from 6-azauridine and *tert*-butyldimethylsilyl chloride) and 5'-(*tert*-butyldimethylsilyl)-2',3'-O-thiocarbonyl-6-azauridine (**9**, 82% yield from **8** with TCDI). Attempted deoxygenation of **9** with DPD under various conditions was again unsuccessful, suggesting that the presence of nitrogen at position **6** of the base, rather than the nature of the 5'-protecting group, was responsible for our inability to successfully use DPD in the olefin-forming reaction. Although the nature of the products formed from **7** or **9** on heating with DPD was not elucidated, one possibility is the formation of 2,2'-anhydro derivatives, which are known to form in the azauridine series.[34] In contrast to **7**, deoxygenation of **9** was successfully achieved with trimethyl phosphite, which gave **10** in 76% yield. A minor product (17%) was also isolated, however, whose spectral and microanalytic-al data were consistent with the N^3-methyl derivative **11**.[18,35] It has been reported that N^3-methylation in the presence of trimethyl phosphite can be prevented by carrying out the reaction in an inert atmosphere and not using base during the workup (see ref. 7). Alternatively, N^3-methylation can be avoided by replacing trimethyl phosphite with triethyl phosphite (see. ref. 23). Whether or not this reaction occurs in the presence of trimethyl phosphite apparently also depends on the structure of the nucleoside, as we found N^3-methylation to be negligible with **16** even though it was a significant side product with **9** under the same conditions.

Compounds **10** and **11** were identified as olefins by their 300 MHz ^{1}H NMR spectra, which contained vinyl proton signals at δ 5.9 (1H, doublet of triplets, $C_{2'}$-H) and 6.4 (1H, doublet of triplets, $C_{3'}$-H). The allylic character of the $C_{4'}$ and $C_{1'}$ hydrogens was also demonstrated by the presence of signals at δ 4.8 (1H, multiplet) and 7.0 (1H, quartet), respectively. Long-range coupling between the anomeric and olefinic hydrogens was evident. The N^3-methyl group in **11** was clearly visible as a singlet at δ 3.2 for which there was no counterpart in the spectrum of **10**, and was also detectable in the ^{13}C NMR spectrum as an extra signal at δ 26.8. Removal of the 5'-protecting group from **10** and **11** was accomplished with tetrabutylammonium fluoride (TBAF), yielding **2** and **4**, respectively. Catalytic hydrogenation of **2** and **4** over 10% Pd-C afforded the saturated analogues **1** and **3**. Disappearance of the double bond in the reduction of **2** was confirmed by the absence of vinyl protons in the ^{1}H NMR spectrum of the product, and by a change in the chemical shift of the $C_{1'}$ hydrogen from δ 7.0 to δ 6.3, and of the $C_{4'}$ hydrogen from δ 4.8 to δ 4.2. Similar changes were observed in the reduction of **4**. In the ^{13}C NMR spectrum, the signal due to $C_{1'}$ was at δ 92.1 in **2** and at δ 86.0 in **1**, whereas the signal due to $C_{4'}$ was at δ 88.7 in **2** and δ 82.3 in **1**.



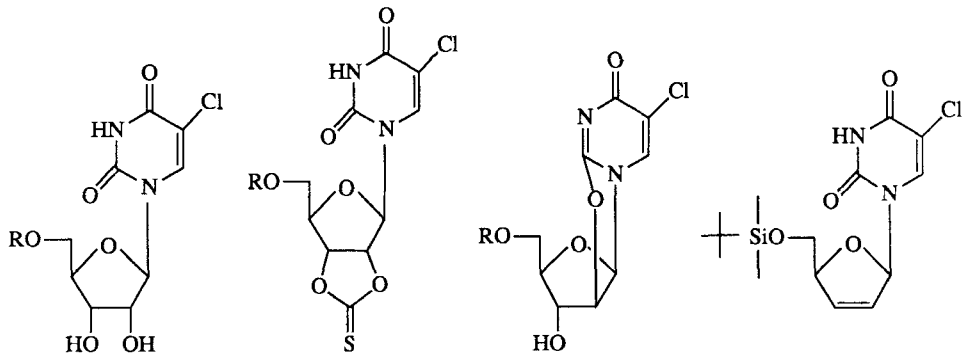
6 : R = DMTr
8 : R = *t*-BuMe$_2$Si

7 : R = DMTr
9 : R = *t*-BuMe$_2$Si

10 : R = H
11 : R = Me

Initial attempts to obtain the 5-chloro compound **5** were made via 5'-O-DMTr intermediates as had been done previously in the synthesis of 2-chloro-2',3'-didehydro-2',3'-dideoxyadenosine.[31] Condensation of 5-chlorouridine with 4,4'-dimethoxytrityl chloride in pyridine was uneventful, giving **12** (55%). However, attempted conversion of **12** into the 2',3'-O-thiocarbonyl derivative **13** was complicated by formation of side products, one of which we believe to be the 2,2'-anhydronucleoside **14** (ca. 8% yield after purification). Pure **13** was obtained in <5% yield after extensive column chromatography and recrystalliztion. Isolation of **14** in pure form was likewise very difficult, as it appeared from its ^{1}H NMR spectrum to tenaciously retain imidazole. After considerable experimentation, the only satisfactory way to remove the imidazole from impure **14** was found to be by preparative TLC. Imidazole was undectable on the plate under UV light, but became visible by iodination. It is possible that the electronegative chlorine atom at C^5 makes N^3 sufficiently acidic to form an imidazolium salt. Several other side products apparently containing an imidazole moiety were present in addition to **14**, but were not identified. The low yield and difficulty of purification of **13**, along with concerns about our eventual ability to remove the DMTr group without cleavage of the glycoside bond, led us at this point to discard tritylation in favor of silylation for 5'-protection. Reaction of 5-chlorouridine with *tert*-butyldimethylsilyl chloride in DMF containing excess imidazole afforded **15** (53%), but further condensation with TCDI led to the 2',3'-O-thiocarbonyl derivative **16** in only 36% yield, along with a side product (estimate yield 40%) whose elemental analysis and spectral properties were consistent with the 2,2'-anhydro derivative **17**. Once again, other uncharacterized side products were observed. It appeared that the problems associated with the formation of a thionocarbonate mainly reflected a propensity of 5-chlorouridine to form 2,2'-anhydro derivatives, though to some extent the nature of the 5'-

protecting group might also be important. As in the 6-azauridine series (see above), attempted formation of an olefin by heating **16** with DPD met with failure. However, heating in trimethyl phosphite at 115 °C for 5 h afforded the olefin **18** (71%), with no significant amounts of N^3-methyl side product. Desilylation of **18** was performed with TBAF in tetrahydrofuran at room temperature, and was monitored by TLC. The reaction appeared to be complete in 1 h, with only a single visible spot on the plate. The identity of the product **5** was evident from its ^{1}H NMR spectrum, which contained signals at δ 4.87 ($C_{4'}$-H, allylic), 5.93 ($C_{2'}$-H, vinylic), 6.42 ($C_{3'}$-H, vinylic), and 6.89 ($C_{1'}$-H, allylic). The yield of **5** after chromatography through silica gel proved to be <20%, and some 5-chlorouracil was recovered. We therefore concluded that the glycoside bond in **5**, like that in the previously studied unsaturated 2-chloroadenine derivative,[31] was acid-labile.



12 : R = DMTr
15 : R = *t*-BuMe$_2$Si

13 : R = DMTr
16 : R = *t*-BuMe$_2$Si

14 : R = DMTr
17 : R = *t*-BuMe$_2$Si

18

Although the apparent instability of the glycoside bond in **5** suggested to us that it would be better to synthesize this compound by chlorination of 2',3'-didehydro-2',3'-dideoxyuridine, rather than by deoxygenation of 5-chlorouridine, implementation of this strategy was forestalled by the appearance of a paper independently describing the synthesis of **5** from 2',3'-didehydro-2',3'-dideoxyuridine in 44% overall yield by 5'-acetylation, chlorination (NCS/pyridine), deprotection (NH_3/MeOH), and recrystallization of the final product without silica gel chromatography.[21]

Experimental Section

^{1}H NMR spectra were obtained at 60 MHz on a Varian Model EM360 spectrometer, and ^{1}H and ^{13}C NMR spectra at 300 MHz on a Varian Model VXR300 instrument. Proton chemical shifts are reported in δ units relative to Me_4Si. Where microanalyses indicate the presence of an organic

solvent such as EtOAc or hexane in the analytical sample, appropriate ^1H NMR signals at 300 MHz were observed. Mass spectra were obtained on a Finnigan MAT-312 instrument. TLC was performed on Whatman MK6F and Baker 250F silica gel plates containing a fluorescent indicator. Spots were visualized in a viewing chamber under 254-nm UV light. Column chromatography was performed on Baker 3405 (60-200 mesh) or Baker "Flash" (40 mm) silica gel. Where specified, silica gel column dimensions are given as the internal diameter. Melting points were determined on a Fisher-Johns hot-stage apparatus and are not corrected. Solvents were routinely stored over 4A molecular sieves. Chemicals were purchased from Aldrich (Milwaukee, WI) and Sigma (St. Louis, MO). 5-chlorouridine was synthesized from uridine according to Ryu and MacCoss.[36]

5'-O-(4,4'-Dimethoxytrityl)-6-azauridine (6). 4',4'-Dimethoxytrityl chloride (10.2 g, 30 mmol) was added in five equal portions every hour to a solution of 6-azauridine (6.13 g, 25 mmol) in pyridine (100 mL) and DMF (30 mL). After 6 h, the reaction mixture was poured into H_2O (500 mL). The resulting yellow gum was taken up in CH_2Cl_2 (600 mL), and the solution was washed with H_2O (2 x 100 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column (250 g, 5 cm) which was eluted successively with the following $CHCl_3$-MeOH mixtures: 100:0 and 99.75:0.25 (500 mL each), 99.5:0.5 (1000 mL), and 98:2, 97:3, and 96:4 (500 mL each). Fractions eluted with 97:3 and 96:4 $CHCl_3$-MeOH contained a single product by TLC and were pooled and evaporated to obtain a white powder (8.83 g, 65% yield); mp 106-108 °C (EtOAc-hexane); TLC: R_f 0.25 (silica gel, 1:12.5 MeOH-$CHCl_3$); IR (KBr): ν 3440, 1700, 1520, 1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10-3.30 (m, 2H, $C_{5'}$-H), 3.68 (s, 6H, OCH_3), 4.08 (m, 1H, $C_{4'}$-H), 4.23 (t, 1H, $C_{3'}$-H), 4.52 (t, 1H, $C_{2'}$-H), 6.20 (d, 1H, $C_{1'}$-H), 6.68-6.78 (d, 4H, aromatic protons), 7.04-7.40 (m, 9H, aromatic protons, NH, and C_5-H). Anal. ($C_{29}H_{29}N_3O_8 \cdot 0.5H_2O$) Calcd: C, 62.58; H, 5.43; N, 7.55. Found: C, 62.39; H, 5.38; N, 7.52.

5'-O-(4,4'-Dimethoxytrityl)-2',3'-O-(thiocarbonyl)-6-azauridine (7). TCDI (0.214 g, 1.2 mmol) was added to a solution of **6** (0.547 g, 1 mmol) in MeCN (8 mL). After 5 h of stirring, the solvent was evaporated under reduced pressure, leaving a yellow oil which was chromatographed on a silica gel column (40 g, 2 cm) using the following $CHCl_3$-MeOH mixtures as eluents (250 mL each, collected in 60 mL fractions): 100:0, 99:1, 98:2, 96:4, 95:5. Fractions 6-16 were pooled and evaporated, and the residue was recrystallized from a mixture of EtOAc and hexanes to obtain a white solid (0.45 g, 80%); mp 129-131 °C ; TLC: R_f 0.55 (silica gel, 10:1

$CHCl_3$-MeOH); IR (KBr): ν 3450, 1760, 1520, 1340, 1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.08-3.23 and 3.30-3.40 (m, 2H, $C_{5'}$-H), 3.80 (s, 6H, OCH_3), 4.60 (m, 1H, $C_{4'}$-H), 5.40 (dd, 1H, $C_{2'}$-H or $C_{3'}$-H), 5.58 (dd, 1H, $C_{2'}$-H or $C_{3'}$-H), 6.45 (s, 1H, $C_{1'}$-H), 6.76-6.86 (d, 4H, aromatic protons), 7.08 (s, 1H, C_5-H), 7.18-7.42 (m, 9H, aromatic protons, NH). Anal. ($C_{30}H_{27}N_3O_8S \cdot 0.3H_2O$) Calcd: C, 60.55; H, 4.68; N, 7.06; S, 5.39. Found: C, 60.58; H, 4.74; N, 7.07; S, 5.63.

5'-O-(*tert*-Butyldimethylsilyl)-6-azauridine (8). *tert*-Butyldimethylsilyl chloride (1.81 g, 12 mmol) was added over 20 min with exclusion of moisture to a stirred solution of 6-azauridine (2.45 g, 10 mmol) and imidazole (1.63 g, 24 mol) in dry DMF (20 mL) at 0 °C. Stirring was continued at room temperature for 72 h, and the solvent was evaporated under reduced pressure. The oily residue was dissolved in EtOAc (80 mL), and the solution was extracted with H_2O (3 x 25 mL). The organic layer was dried (Na_2SO_4), and evaporated to a white foam (2.72 g) which was chromatographed on a silica gel column (80 g, 3 cm). The column was eluted successively with $CHCl_3$ (500 mL), 1:1 $CHCl_3$-EtOAc (500 mL), and EtOAc (1000 mL), (150 mL fractions collected). Fractions 3-8 were pooled and evaporated, yielding a white solid (1.97 g, 55%); mp 138-139 °C; TLC: R_f 0.45 (silica gel, EtOAc); IR (KBr): ν 3400, 1730, 1690, 1420 cm^{-1}; ^1H NMR (d_6-acetone) δ 0.05 (s, 6H, MeSi), 0.90 (s, 9H, t-BuSi), 3.80 (dq, 2H, $C_{5'}$-H), 3.95 (q, 1H, $C_{4'}$-H), 4.30 (t, 1H, $C_{3'}$-H), 4.45 (m, 1H, $C_{2'}$-H), 6.07 (d, 1H, $C_{1'}$-H), 7.43 (s, 1H, C_5-H); ^{13}C NMR (d_6-acetone) δ -5.2 (MeSi), 26.2 (t-Bu), 64.4 ($C_{5'}$), 71.5 ($C_{4'}$), 73.8 ($C_{3'}$), 85.4 ($C_{2'}$), 90.8 ($C_{1'}$), 136.7 (C_5). Anal. ($C_{14}H_{23}N_3O_6Si$) Calcd: C, 46.77; H, 7.02; N, 11.69; Si, 7.81. Found: C, 46.99; H, 6.99; N, 11.73; Si,7.52.

5'-O-(*tert*-Butyldimethylsilyl)-2',3'-O-(thiocarbonyl)-6-azauridine (9). TCDI (536 mg, 3 mmol) was added to a stirred solution of **8** (721 mg, 2 mmol) in anhydrous MeCN (5 mL) at 0 °C under N_2, and stirring was continued 15 min at 0 °C and 45 min at room temperature. The solvent was evaporated under reduced pressure (bath temp 35 °C), and the residue was purified by flash chromatography on a silica gel column (40 g, 2 cm) using the following eluents (30-50 mL fractions collected): 1:3 EtOAc-hexanes (130 mL), 1:1 EtOAc-hexanes (420 mL), 1:1 EtOAc (250 mL), EtOAc (200 mL), 98:2 EtOAc-MeOH (250 mL), 96:4 EtOAc-MeOH (250 mL), 95:5 EtOAc-MeOH. Fractions 6-18 were pooled and evaporated to obtain a white solid (0.443 g); mp 190-191 °C. Fractions 19-29 were rechromatographed on a smaller silica gel column (10 g, 1.5 cm diameter) using 1:2 EtOAc-hexanes (310 mL) followed by EtOAc as the eluents (30-50 mL fractions collected). Fractions 1-8 from the second column were concentrated to a small volume

and added to cold hexanes to obtain a white solid; mp 188-189 °C. The combined product from the two columns weighed 656 mg (82%); TLC: R_f 0.48 (silica gel, 9:1 $CHCl_3$-MeOH); IR (KBr): ν 3420, 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.03 (s, 3H, MeSi), 0.04 (s, 3H, MeSi), 0.87 (s, 9H, t-BuSi), 3.63 (dd, 1H, $C_{5'}$-H), 3.78 (dd, 1H, $C_{5'}$-H), 4.40 (m, 1H, $C_{4'}$-H), 5.48 (dd, 1H, $C_{3'}$-H), 5.66 (dd, 1H, $C_{2'}$-H), 6.40 (d, 1H, $C_{1'}$-H), 7.44 (s, 1H, C_5-H). Anal. ($C_{15}H_{23}N_3O_6SiS$) Calcd: C, 44.88; H, 5.79; N, 10.47; S, 7.97. Found: C, 45.29; H, 5.85; N, 10.20; S, 7.83.

5'-O-(tert-Butyldimethylsilyl)-2',3'-didehydro-2',3'-dideoxy-6-azauridine (10) and 5'-O-(tert-Butyldimethylsilyl)-2',3'-didehydro-2',3'-dideoxy-N^3-methyl-6-azauridine (11). A stirred suspension of compound **9** (1.56 g, 3.89 mmol) in $P(OMe)_3$ (25 mL) was heated to reflux (118-120 °C) for 5 h. Solvent evaporation under reduced pressure gave an oil which was purified by flash chromatography on a silica gel column (80 g, 2 cm) using the following EtOAc-hexanes mixtures (15 mL fractions collected): 1:5 (200 mL), 1:4 (750 mL), 1:3 (700 mL). Evaporation of fractions 46-80 gave the major product (**10**) as an oil (0.97 g, 76% yield); TLC: R_f 0.17 (silica gel, 3:7 EtOAc-hexanes); ^1H NMR (d_6-acetone) δ 0.04 (s, 6H, MeSi), 0.88 (s, 9H, t-BuSi), 3.70 (d, 2H, $C_{5'}$-H), 4.80 (m, 1H, $C_{4'}$-H), 5.88 (dt, 1H, $C_{2'}$-H), 6.37 (dt, 1H, $C_{3'}$-H), 7.0 (q, 1H, $C_{1'}$-H), 7.40 (s, 1H, C_5-H). Anal. ($C_{14}H_{23}N_3O_4SSi \cdot 0.2$ EtOAc) Calcd: C, 51.80; H, 7.26; N, 12.24; Si, 8.19. Found: C, 51.34; H, 7.29; N, 11.87; Si, 8.63.

Evaporation of fractions 24-32 gave the minor product (**11**) as an oil (229 mg, 17% yield); TLC: R_f 0.43 (silica gel, 3:7 EtOAc-hexanes); ^1H NMR (d_6-acetone) δ 0.04 (s, 6H, MeSi), 0.88 (s 9H, t-BuSi), 3.21 (s, 3H, N^3-Me), 3.90 (d, 2H, $C_{5'}$-H), 4.80 (m, 1H, $C^{4'}$-H), 5.88 (dt, 1H, $C^{2'}$-H), 6.36 (dt, 1H, $C^{3'}$-H), 7.03 (q, 1H, $C^{1'}$-H), 7.45 (s, 1H, C^5-H). Anal. ($C_{15}H_{25}N_3O_4Si$) Calcd: C, 53.06; H, 7.44; N, 12.38; Si, 8.27. Found: C, 53.06; H, 7.24; N, 12.07; Si, 8.51.

2',3'-Didehydro-2',3'-dideoxy-6-azauridine (2). Compound **10** (777 mg, 2.38 mmol) was dissolved in dry THF (5 mL), TBAF in THF (6.25 mL of 1 M solution) was added, and the reaction mixture was stirred for 90 min. Evaporation of the solvent under reduced pressure gave an oil which was purified by chromatography on a silica gel column (40 g, 2 cm) using the following eluents (15 mL fractions collected): 3:7 hexanes-acetone (480 mL), 3:2 hexanes-acetone (90 mL), acetone (360 mL). Evaporation of fractions 25-40 gave an oil (0.42 g) which was applied onto a second column (18 g, 1.5 cm diameter). The column was eluted with 99:1 $CHCl_3$-MeOH (250 mL, collected in 15 mL fractions) and 98:2 $CHCl_3$-MeOH (450 mL, collected in 10-15 mL fractions). Evaporation of fractions 26-50 gave an oil (0.31 g) which was purified further by preparative HPLC (C_{18} silica gel, 5% MeCN in 0.01 M NH_4OAc, pH 7.0, flow rate 6 mL/min).

The peak eluting at 13 min was freeze-dried to constant weight to obtain an oil (0.23 g). The analytical sample was prepared by chromatographing this material once more through a silica gel column (20 g) eluted with 1:1 (200 mL) and 2:1 (100 mL) EtOAc-hexanes (10-15 mL fractions collected). Evaporation of TLC-homogeneous fractions 22-30 again yielded an oil; TLC: R_f 0.24 (silica gel, EtOAc); IR (KBr) ν 3420, 1660, 1640, 1540, 1460 cm^{-1}; ^1H NMR (d_6-acetone) δ 3.60 (dd, 2H, $C_{5'}$-H), 4.81 (m, 1H, $C_{4'}$-H), 5.84 (dt, 1H, $C_{2'}$-H), 6.32 (dt, 1H, $C_{3'}$-H), 6.98 (m, 1H, $C_{1'}$-H), 7.38 (s, 1H, C_5-H); ^{13}C NMR (d_6-acetone) d 64.9 ($C_{5'}$), 88.7 ($C_{4'}$), 92.1 ($C_{1'}$), 126.2 ($C_{3'}$), 134.2 ($C_{2'}$), 136.6 (C_5), 148.8 (C_2), 157.0 (C_4). Anal. ($C_8H_9N_3O_4$) Calcd: C, 45.49; H, 4.30; N, 19.90. Found: C, 45.64; H, 4.25; N, 19.62.

2',3'-Didehydro-2,3,-dideoxy-N^3-methyl-6-azauridine (4). Compound **11** (150 mg, 0.44 mmol) was dissolved in THF (2 mL), TBAF in THF (0.45 mL of 1 M solution) was added, and the reaction mixture was stirred for 40 min. Evaporation of the solvent under reduced pressure gave an oil which was purified by chromatography on a silica gel column (10 g, 1 cm) with 1:1 EtOAc-hexanes as the eluent (15 mL fractions collected). Evaporation of fractions 7-18 gave an oil (95 mg, 96% yield); TLC: R_f 0.34 (silica gel, 3:7 EtOAc-hexanes); IR (KBr): ν 3420, 1680, 1640 cm^{-1}; ^1H NMR (d_6-acetone): δ 3.22 (s, 3H, N^3-Me), 3.62 (m, 2H, $C_{5'}$-H), 4.85 (m, 1H, $C_{4'}$-H), 5.86 (dt, 1H, $C_{2'}$-H), 6.35 (dt, 1H, $C_{3'}$-H), 7.03 (m, 1H, $C_{1'}$-H), 7.45 (s, 1H, C_5-H); ^{13}H NMR (d_6-acetone) δ 26.8 (N^3-Me), 64.9 ($C_{5'}$), 88.8 ($C_{4'}$), 93.0 ($C_{1'}$), 126.1 ($C_{3'}$), 134.2 ($C_{2'}$), 135.4 (C_5), 149.7 (C_2), 256.5 (C_4). Anal. ($C_9H_{11}N_3O_4$) Calcd: C, 47.99; H, 4.93; N, 18.66. Found: C, 47.58; H, 4.82; N, 18.19.

2',3'-Dideoxy-6-azauridine (1). A solution of **2** (70 mg, 0.12 mmol) in MeOH (12 mL) was hydrogenated for 2 h in the presence of 10% Pd-C (16 mg) in a Parr shaker apparatus at an initial H_2 pressure of 2.5 atm. After filtration of the catalyst, the solution was evaporated under reduced pressure to obtain an oil which was chromatographed on a silica gel column (10 g, 1.5 cm) using 1:1 EtOAc-hexanes (100 mL) and EtOAc (150 mL) as the eluents (10 mL fractions collected). Fractions 13-19 were pooled and evaporated to an oil (36 mg, 50% yield); TLC: R_f 0.18 (silica gel, EtOAc); ^1H NMR ($CDCl_3$) δ 2.00 (m, 2H, $C_{3'}$-H), 2.28 (m, 2H, $C_{2'}$-H), 3.24 (dd, 1H, $C_{5'}$-H), 3.76 (dd, 1H, $C_{5'}$-H), 4.20 (m, 1H, $C_{4'}$-H), 6.32 (t, 1H, $C_{1'}$-H), 7.40 (s, 1H, C_5-H); ^{13}H NMR ($CDCl_3$) δ 25.9 ($C_{2'}$ or $C_{3'}$), 30.5 ($C_{2'}$ or $C_{3'}$), 64.5 ($C_{5'}$), 82.3 ($C_{4'}$), 86.0 ($C_{1'}$), 135.8 ($C_{5'}$), 148.2 (C_2), 156.2 (C_4). Anal. ($C_8H_{11}N_3O_4$) Calcd: C, 45.06; H, 5.21; N, 19.71. Found: C, 44.99; H, 4.91; N, 19.49.

2',3'-Dideoxy-N^3-methyl-6-azauridine (3). A solution of **4** (44 mg, 0.19 mmol) in MeOH (5 mL) was hydrogenated for 2 h in the presence of 10% Pd-C (10 mg) in a Parr shaking

apparatus at an initial H_2 pressure of 1.5 atm. Filtration and evaporation afforded an oil (45 mg). The product was redissolved in MeOH and passed through a C_{18} silica gel mini-column (Waters Sep-Pak), and the eluate was evaporated to an oil (38 mg, 86% yield); ^{1}H NMR ($CDCl_3$) δ 1.90-2.18 (m, 2H, $C_{2'}$-H or $C_{3'}$-H), 2.22-2.32 (m, 2H, $C_{2'}$-H or $C_{3'}$-H), 2.48 (broad s, 1H, 5'-OH), 3.27 (s, 3H, N^3-Me), 3.54 (dd, 1H, $C_{5'}$-H), 3.76 (dd, 1H, $C_{5'}$-H), 4.19 (m, 1H, $C_{4'}$-H), 6.36 (t, 1H, $C_{1'}$-H), 7.40 (s, 1H, C_5-H); ^{13}C NMR ($CDCl_3$) δ 25.9 ($C_{2'}$ or $C_{3'}$), 26.9 (N^3-Me), 30.8 ($C_{2'}$ or $C_{3'}$), 64.6 ($C_{5'}$), 82.1 ($C_{4'}$), 87.7 ($C_{1'}$), 134.5 (C_5), 148.6 (C_2), 155.6 (C_4). Anal. ($C_9H_{13}N_3O_4 \cdot 0.4H_2O$) Calcd: C, 46.10; H, 5.94; N, 17.93. Found: C, 46.33; H, 6.04; N, 17.62.

5'-O-(4,4'-Dimethoxytrityl)-5-chlorouridine (12). 4,4'-Dimethoxytrityl chloride (6.1 g, 18 mmol) was added in three equal portions at intervals of 2 h to a solution of 5-chlorouridine[36] (4.2 g, 15 mmol) in dry pyridine (50 mL) cooled to 0 °C. After 6 h, MeOH (75 mL) was added, and the reaction mixture was evaporated under reduced pressure. The residue was partitioned between 5% $NaHCO_3$ (80 mL) and CH_2Cl_2 (200 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 80 mL), and the CH_2Cl_2 layers were combined, dried ($MgSO_4$), and evaporated to an orange gum which was purified by column chromatography on silica gel (75 g, 3 cm) using the following $CHCl_3$-MeOH mixtures as eluents: 100:0 (1000 mL, 200 mL fractions), 99:1 (1000 mL, 200 mL fractions), 95:5 (1500 mL, 150 mL fractions). Fractions 12-17 were pooled and evaporated to obtain a white solid (4.8 g, 55%); mp 122-123 °C; IR (KBr): ν 3400, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.42 (m, 2H, $C_{5'}$-H), 3.76 (s, 6H, OMe), 4.23 (m, 1H, $C_{4'}$-H), 4.38-4.50 (m, 2H, $C_{2'}$-H and $C_{3'}$-H), 5.88 (m, 1H, $C_{1'}$-H), 6.80-6.88 and 7.22-7.44 (m, 14H, aromatic protons and NH), 8.80 (C_6-H). Anal. ($C_{30}H_{29}N_2O_8Cl$) Calcd: C, 62.01; H, 5.03; N, 4.82; Cl, 6.10. Found: C, 62.27; H, 5.20; N, 4.76; Cl, 5.89.

5'-O-(4,4'-Dimethoxytrityl)-2',3'-O-(thiocarbonyl)-5-chlorouridine (13) and 2,2'-Anhydro-5'-O-(4,4'-dimethoxytrityl)-5-chlorouridine (14). TCDI (0.990 g, 5.16 mmol) was added in a single portion to a stirred solution of **12** (1.16 g, 1.42 mmol) in dry MeCN (30 mL), and stirring under N_2 was continued for 24 h. The solvent was evaporated, and the residual yellow gum was chromatographed on a silica gel column (80 g, 3 cm) using the following $CHCl_3$-MeOH mixtures as eluents (150 mL each, collected in 50 mL fractions): 100:0, 99.5:0.5; 99:1; 95:5; 90:10. Evaporation of fraction 5 and recrystallization from $CHCl_3$-hexanes gave a pale-yellow solid (0.107 g) which was rechromatographed on a silica gel column (25 g, 2 cm) using 1:1 EtOAc-hexanes as the eluent (500 mL, collected in 40 mL fractions). The residue on

evaporation of fractions 1-3 was recrystallized from EtOAc-hexanes to obtain **13** as a white solid (37 mg, 4% yield); mp 135-138 °C (EtOAc-hexane); IR (KBr): ν 3400, 1700, 1540, 1300, 1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.38 (m, 2H, $C_{5'}$-H), 3.70 (s, 6H, OMe), 4.44 (m, 1H, $C_{4'}$-H), 5.38 (dd, 1H, $C_{3'}$-H), 5.62 (dd, 1H, $C_{2'}$-H), 5.68 (d, 1H, $C_{1'}$-H), 6.70-6.85 and 7.15-7.40 (m, 14H, aromatic protons and NH), 7.55 (s, 1H, C_6-H). Anal. ($C_{31}H_{27}N_2O_8ClS \cdot 0.25EtOAc$) Calcd: C, 59.58; H, 4.53; N, 4.34; Cl, 5.50; S, 4.97. Found: C, 59.81; H, 4.73; N, 4.27; Cl, 5.14; S, 4.90.

Evaporation of fractions 12-14 from the first silica gel column gave a white solid (0.923 g) whose ^1H NMR spectrum showed it to contain peaks attributable to imidazole protons. Attempted purification of this material by repeated chromatography on silica gel were unsuccessful, but a sample (80 mg) from a different run was purified by preparative TLC (1000 μm layer, 85:15 $CHCl_3$-MeOH). The UV-absorbing area was scraped off the plate and extracted with 95:5 $CHCl_3$-MeOH, and the extract was evaporated to obtain **14** as a white solid (62 mg, 7.8% yield); mp 128-130 °C; IR (KBr): ν 3450, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76-3.02 (m, 2H, $C_{5'}$-H), 3.68 (s, 6H, OMe), 4.36 (m, 2H, $C_{3'}$-H and $C_{4'}$-H), 4.98 (broad s, 1H, 3'-OH), 5.24 (d, 1H, $C_{2'}$-H), 6.12 (d, 1H, $C_{1'}$-H), 6.64-6.71 (d, 4H, aromatic protons), 7.06-7.28 (m, 9H, aromatic protons and NH), 7.48 (s, 1H, C_6-H). Anal. ($C_{30}H_{27}N_2ClO_7 \cdot 0.4CHCl_3$) Calcd: C, 59.77; H, 4.54;N, 4.58. Found: C, 59.59; H, 4.75; N, 4.36.

5'-O-(*tert*-Butyldimethylsilyl)-5-chlorouridine (15). A stirred solution of 5-chlorouridine (3.0 g, 10.8 mmol) and imidazole (1.76 g, 25.9 mmol) in dry DMF (100 mL) was stirred during dropwise addition of *tert*-butyldimethylsilyl chloride (1.95 g, 12.9 mmol), and the reaction mixture was stirred with exclusion of moisture for 20 h. The solvent was evaporated under reduced pressure and the product applied onto a silica gel column (100 g, 3 cm) which was eluted with the following $CHCl_3$-MeOH mixtures: 97:3 (1 x 200 mL and 3 x 100 mL, 9:1 (5 x 200 mL), 4:1 (2 x 200 mL), 75:25 (3 x 200 mL). Fractions 5-9 were evaporated to a solid (2.33 g) which was further purified by recrystallization from EtOAc to obain a white powder (1.42 g, 53% yield); mp 238-239 °C; TLC: R_f 0.59 (silica gel, 4:1 $CHCl_3$-MeOH); IR (KBr): ν 3400, 3020, 2970, 2950, 1700, 1760, 1650 cm^{-1}; ^1H NMR (d_6-acetone): δ 0.15 (s, 3H, MeSi), 0.17 (s, 3H, MeSi), 0.88 (s, 9H, t-BuSi), 3.94 (dq, 2H, $C_{5'}$-H), 4.07 (m, 1H, $C_{4'}$-H), 4.23 (m, 2H, $C_{2'}$-H and $C_{3'}$-H), 5.92 (d, 1H, $C_{1'}$-H), 8.05 (s, 1H, C_6-H). Anal. ($C_{15}H_{28}N_2O_6ClSi$) Calcd: C, 45.84; H, 6.43; N, 7.13; Cl, 9.02; Si, 7.52. Found: C, 46.08; H, 6.37; N, 7.17; Cl, 8.89; Si, 7.83.

5'-O-(*tert*-Butyldimethylsilyl)-2',3'-O-(thiocarbonyl)-5-chlorouridine (16). A suspension of **15** (786 mg, 2 mmol) was stirred in MeCN (5 mL) and DMF (2 mL) until a clear

solution was obtained. The solution was cooled to 0 °C and TCDI (535 mg, 3 mmol) was added, and stirring under N_2 was continued at 0 °C for 45 min and room temperature for 15 min. The solvent was evaporated, first at aspirator pressure and then under high vacuum to remove DMF, and the oily residue was chromatographed on a silica gel column (40 g, 2 cm), using the following eluents (40-50 mL fractions were collected): 4:1 hexanes-EtOAc (250 mL), 3:1 (615 mL), 1:1 (250 mL), EtOAc (250 mL), 95:5 $CHCl_3$-MeOH (250 mL). Evaporation of fractions 9-14 gave **16** as a white powder (0.311 g, 36% yield); mp 102-104 °C; TLC: R_f 0.51 (silica gel, 2:3 hexanes-EtOAc); IR (KBr): ν 3470, 2970, 2950, 2840, 1710, 1340, 1290, 1160 cm^{-1}; 1H NMR ($CDCl_3$) δ 0.07 (s, 3H, MeSi), 0.09 (s, 3H, MeSi), 0.88 (s, 9H, t-BuSi), 3.88 (dq, 2H, $C_{5'}$-H), 4.58 (q, 1H, $C_{4'}$-H), 5.44 (dd, 1H, $C_{3'}$-H), 5.57 (dd, 1H, $C_{2'}$-H), 5.88 (d, 1H, $C_{1'}$-H), 7.64 (s, 1H, C_6-H), 8.01 (broad s, 1H, NH). Anal. ($C_{16}H_{23}N_2O_6ClSiS$) Calcd: C, 44.17; H, 5.34; N, 6.44; Cl, 8.15; Si, 6.45. Found: C, 44.30; H, 5.40; N, 8.32; Cl, 8.32; Si, 6.18.

Evaporation of fractions 29-31 from the silica gel column gave a pale-yellow solid (555 mg) whose ^1H NMR spectrum contained protons attributable to imidazole. A portion of the solid (70 mg) was purified by preparative TLC (silica gel, 1000 μm layer, 85:15 $CHCl_3$-MeOH). The UV-absorbing band (R_f 0.27) was scaped off and extracted with 95:5 $CHCl_3$-MeOH (3 x 45 mL). A second band (R_f 0.18), which was only faintly UV-absorbing, was extracted with 95:5 $CHCl_3$-MeOH (3 x 45 mL) and 95:5 EtOAc-MeOH (45 mL), was found to consist of imidazole. Evaporation of the extracts from the first band gave the 2,2'-anhydro compound **17** as a white solid (41 mg). From the product recovery in this small portion of purified material, the total yield of **17** in the TCDI reaction was estimated to be 40%. The analytical sample was reprecipitated from EtOAc-hexanes; IR (KBr): ν 3400, 2980, 2960, 2940, 1650, 1550, 1500 cm^{-1}; ^1H NMR (d_6-acetone): δ 0.00 (s, 3H, MeSi), 0.02 (s, 3H, MeSi), 0.84 (s, 9H, t-BuSi), 2.92 (broad s, 1H, 5'-OH), 3.60 (dd, 2H, $C_{5'}$-H), 4.24 (m, 1H, $C_{4'}$-H), 4.60 (m, 1H, $C_{3'}$-H), 5.40 (d, 1H, $C_{2'}$-H), 6.45 (d, 1H, $C_{1'}$-H), 8.15 (s, 1H, C_6-H); MS (FAB): m/e 375. Anal. ($C_{15}H_{23}N_2O_5ClSi \cdot 0.15$ C_6H_{14}) Calcd: C, 49.23; H, 6.54; N, 7.22, Si, 7.24. Found: C, 49.16; H, 6.63; N, 7.05; Si, 7.31.

5'-O-(*tert*-Butyldimethylsilyl)-2',3'-didehydro-2',3'-dideoxy-5-chlorouridine (18). A mixture of **16** (214 mg, 0.49 mmol) and $P(OMe)_3$ (3 mL) was heated at 115 °C for 5 h. After evaporation under reduced pressure a white solid and yellow oil were obtained. Recrystallization of the mixture from EtOAc afforded a solid which was chromatographed on silica gel column (20 g, 2 cm) with $CHCl_3$ (100 mL) and 99:1 $CHCl_3$-MeOH (200 mL) as the eluents (10

mL fractions collected). Fractions 8-22 were pooled and evaporated to a white solid which was rechromatographed on silica gel (20 g) using 4:1 EtOAc-hexanes (200 mL; 15 mL fractions collected). Evaporation of fractions 4 and 5 afforded a white solid (121 mg, 71% yield); TLC: R_f 0.33 (1:1 EtOAc-hexane); ^1H NMR ($CDCl_3$) δ 0.5 (s, 6H, MeSi), 0.90 (s, 9H, t-BuSi), 3.88 (dq, 2H, $C_{5'}$-H), 4.90 (m, 1H, $C_{4'}$-H), 5.86 (dt, 1H, $C_{2'}$-H), 6.26 (dt 1H, $C_{3'}$-H), 6.93 (m, 1H, $C_{1'}$-H), 7.92 (s, 1H, C_6-H), 8.75 (broad s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ -5.2 (MeSi), 26.0 (t-BuSi), 64.2 ($C_{5'}$), 87.7 ($C_{4'}$), 90.4 ($C_{1'}$), 109.1 (C_5), 126.2 ($C_{3'}$), 134;7 ($C_{2'}$), 137.5 (C_6), 149.2 (C_2). Anal. ($C_{15}H_{23}N_2O_4ClSi \cdot 0.25C_6H_{14}$) Calcd: C, 52.08; H, 7.04; N, 7.36; Cl, 9.32. Found: C, 52.25; H, 6.74; N, 7.12; Cl, 8.98.

2',3'-Didehydro-2',3'-dideoxy-5-chlorouridine (5). TBAF (1 mL of 1 M solution in THF) was added to a solution of **18** (120 mg, 0.33 mmol) in 1 mL of dry THF, and the solution was stirred at room temperature for 1 h (all starting material was consumed according to TLC). Evaporation under reduced pressure left an oil which was chromatographed on a silica gel column (10 g, 1 cm) using the following EtOAc-hexanes mixtures as eluents (150 mL each; 15 mL fractions collected): 50:50, 67:33, 100:0. Fractions 24-27 were pooled, reduced in volume, transferred to a vial, and evaporated with the aid of a stream of N_2 to obtain **5** as a white semi-solid (13.3 mg, 16.7%); TLC: R_f 0.30 (silica gel, EtOAc); ^1H NMR (d_6-acetone) δ, 3.80 (m, 2H, $C_{5'}$-H), 4.87 (m, 1H, $C_{4'}$-H), 5.93 (m, 1H, $C_{2'}$-H), 6.42 (dt, 1H, $C_{3'}$-H), 6.89 (m, 1H, $C_{1'}$-H), 8.45 (s, 1H, C_6-H). Anal. ($C_9H_9N_2ClO_4 \cdot 0.25EtOAc \cdot 0.3H_2O$) Calcd: C, 44.16; H, 4.31; N, 10.14; Cl, 13.03. Found: C, 43.85; H, 4.14; N, 10.14; Cl, 13.39.

Evaporation of fractions 20-22 gave an unidentified oil (13.5 mg). Fraction 23 (9 mg) was a mixture of **5** and the unknown side product.

Acknowledgment. This work was supported by grant RO1-AI25715 from the National Institutes of Health, DHHS. We thank Dr. Jonathan Lee, of the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, for his help in obtaining the 300 MHz spectra, and Dr. Catherine Costello, Department of Chemistry, Massachusetts Institute of Technology, for providing mass spectral data.

References

1. Yarchoan, R; Broder, S. *Pharmac. Ther.* **1989**, *40*, 329.
2. Furman, P.A.; Fyfe, J.S.; St. Clair, M.H.; Weinhold, K.; Rideout, J.L.; Freeman, G.A.; Nusinoff-Lehrman, S.; Bolognesi, D.P.; Broder, S.; Mitsuya, H.; Barry, D.W. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 8333.

3. Mitsuya, H.; Jarrett, R.F.; Matsumura, M.; Di Marzo Veronese, F.; DeVico, A.L.; Sarngaharan, M.J.; Johns, D.G.; Reitz, M.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 2033.

4. Hao, Z.; Cooney, D.A.; Hartman, N.R.; Perno, C.F.; Fridland, A.; DeVico, A.L.; Sarngadharan, M.G.; Border, S.; Johns, D.J. *Mol. Pharmacol.* **1988**, *34*, 431.

5. Varmus, H. *Science* **1988**, *240*, 1427.

6. Eriksson, B.F.H.; Chu, C.K.; Schinazi, R.F. *Antimicrob. Agents Chemother.* **1989**, *33*, 1729.

7. Dudycz, L.W. *Nucleosides & Nucleotides* **1989**, *8*, 35.

8. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1911.

9. Baba, M.; Pauwels, R.; Herdewijn, P.; De Clercq, E.; Desmyter, T.; Vandeputte, M. *Biochem. Biophys. Res. Commun.* **1987**, *142*, 128.

10. Chu, C.K.; Schinazi, R.F.; Ahn, M.K.; Ullas, G.V.; Gu, S.P. *J. Med. Chem.* **1989**, *32*, 612.

11. Dahlberg, J.E.; Mitsuya, H.; Blam, S.B.; Broder, S.; Aaronson, S.A. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 2469.

12. Lin, T.S.; Chen, M.S.; McLaren, C.; Gao, Y.S.; Ghazzouli, I.; Prusoff, W.H. *J. Med. Chem.* **1987**, *30*, 440.

13. Balzarini, J.; Pauwels, R.; Baba, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D.G. *Biochem. Pharmacol.* **1988**, *37*, 897.

14. Perno, C.P.; Yarchoan, R.; Cooney, D.A.; Hartman, N.R.; Gartner, S.; Popovic, M.; Hao, Z.; Gerrard, T.L.; Wilson, Y.A.; Johns, D.G.; Broder, S. *J. Exptl. Med.* **1988**, *168*, 1111.

15. Hao, Z; Cooney, D.A.; Hartman, N.; Perno, C.F.; Fridland, A.; DeVico, A.L.; Sarngadharan, M.G.; Broder, S.; Johns, D.G. *Mol. Pharmacol.* **1988**, 34, 431.

16. Ullman, B.; Coons, T.; Rockwell, S.; McCartan, K. *J. Biol. Chem.* **1988**, *263*, 12391.

17. Carson, D.A.; Wasson, D.B. *Biochem. Biophys. Res. Commun.* **1988**, *155*, 829.

18. Chu, C.K.; Bhadti, V.S.; Doboszewski, B.; Gu, Z.P.; Kosugi, Y.; Pullaiak, K.C.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217.

19. Kim, C.H.; Marquez, V.E.; Broder, S.; Mitsuya, H.; Driscoll, J.S. *J. Med. Chem.* **1987**, *30*, 862.

20. Balzarini, J.; Van Aerschot, A.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1989**, *38*, 869.

21. Van Aerschot, A.; Everaert, D.; Balzarini, J.; Augustus, K.; Jie, L.; Janssen, G.; Peeters, O.; Blaton, N.; De Ranter, C.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1990**, *33*, 1833.

22. Balzarini, J.; Kang, G.J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D.G. *Mol. Pharmacol.* **1987**, *32*, 162.

23. Mansuri, M.M.; Starrett, J.E., Jr.; Wos, J.A.; Tortolani, D.R.; Brodfuehrer, P.R.; Howell, H.G.; Martin, J.C. *J. Org. Chem.* **1989**, *54*, 4780.

24. Balzarini, J.; Pauwels, R.; De Clercq, E.; Cooney, D.A.; Kang, K.J.; Dalal, M.; Johns, D.G.; Broder, S. *Biochem. Biophys. Res. Commun.* **1986**, *140*, 735.

25. Mansuri, M.M.; Starrett, J.E., Jr.; Hitchcock, M.J.M.; Sterzycki, R.Z.; Brankovan, V.; Lin, T.S. August, E.M.; Prusoff, W.H.; Sommadossi, J.P.; Martin, J.C. *J. Med. Chem.* **1989**, *32*, 461.

26. Martin, J.C.; Mansuri, M.M.; Starrett, J.E., Jr.; Sommadossi, J.P.; Brankovan, V.; Ghazzouli, I.; Ho, H.T.; Hitchcock, M.J.M. *Nucleosides & Nucleotides* **1989**, *8*, 841.

27. Ho, H.T.; Hitchcock, M.J.M. *Antimicrob. Agents Chemother.* **1989**, *33*, 844.

28. Lin, T.S.; Schinazi, R.F.; Chen, M.S.; Kinney-Thomas, A.; Ueda, T. *Biochem. Pharmacol.* **1987**, *36*, 311.

29. Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T. *Antimicrob. Agents Chemother.* **1987**, *31*, 907.

30. Tong, G.L.; Lee, W.W.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2854.

31. Rosowsky, A.; Solan, V.C.; Sodroski, J.G.; Ruprecht, R.M. *J. Med. Chem.* **1989**, *32*, 1135.

32. Corey, E.J.; Hopkins, P.B. *Tetrahedron Lett.* **1982**, 1979.

33. Corey, E.J.; Carey, F.; Winter, R.A.E. *J. Am. Chem. Soc.* **1965**, 87, 934.

34. Ruyle, W.V.; Shen, T.Y.; Patchett, A.A. *J. Org. Chem.* **1965**, *30*, 4353.

35. Holy, A; Cech, D. *Coll. Czech. Chem. Commun.* **1974**, *39*, 3157; see also earlier references cited in this paper.

36. Ryu, E.K.; MacCoss, M. *J. Org. Chem.* **1981**, *46*, 2819.

Received October 1, 1990.