



## Synthesis of 2',3'-Dideoxy-3'-hydroxymethylcytidine; A Unique Antiviral Nucleoside

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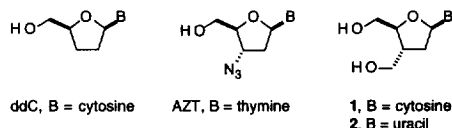
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**Abstract:** The synthesis of 2',3'-dideoxy-3'-hydroxymethylcytidine **1** was accomplished using two different approaches. First, uridine and cytidine were used to prepare the key intermediate epoxides **15** and **31** which were opened with cyanide, deoxygenated by elimination to vinyl nitriles **17** and **36**, and reduced by 1,4 hydride addition to the saturated nitriles **18** and **37**. Secondly, a novel Rh-catalyzed hydroformylation reaction of 2',3'-didehydro-2',3'-dideoxycytidine **46** was used to prepare **1** in four steps. The attempted use of 2'-deoxyuridine and 2'-deoxycytidine to prepare **1** is also discussed.  
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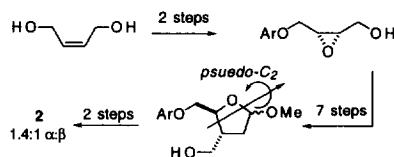
### INTRODUCTION

Nucleoside analogs are used extensively as chemotherapeutic agents targeting Human Immunodeficiency Virus (HIV), the virus responsible for Acquired Immunodeficiency Syndrome (AIDS).<sup>1</sup> While representatives of this class of molecules such as 3'-azido-3'-deoxythymidine (AZT) and 2',3'-dideoxycytidine (ddC) are currently employed for the treatment of patients with AIDS, the rapid emergence of viruses which are resistant to these drugs has limited their clinical utility.<sup>2</sup> Recently, 2',3'-dideoxy-3'-hydroxymethylcytidine **1** was identified as a promising antiviral agent with potent anti-HIV activity.<sup>3</sup> A unique property of **1** is its ability to *prevent infection* when administered to Macaque monkeys *after they are inoculated* with Simian Immunodeficiency Virus (SIV), a virus similar to HIV. In addition, viral passage experiments in HIV-infected cells indicate that it is substantially more difficult to develop mutants resistant to **1** than to AZT.<sup>4</sup>



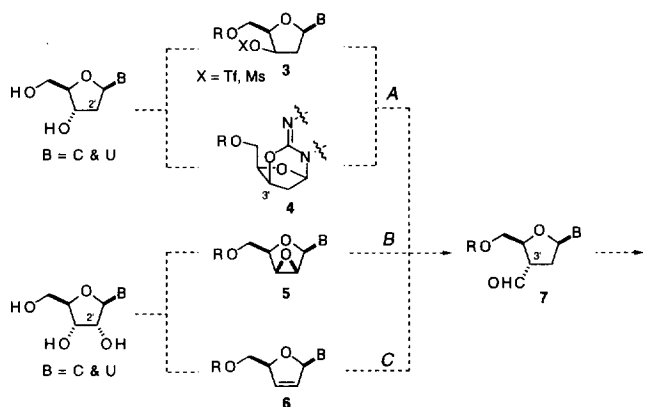
Based on these encouraging results, access to multigram quantities of **1** became necessary to complete preclinical studies on this drug candidate. The uridine analog **2** was previously prepared by methods which are limited by formation of epimeric mixtures at the 3'-center and by lack of stereoselectivity in the glycosylation reaction.<sup>5</sup> Since the putative anomeric oxonium ion intermediate exhibits pseudo-C<sub>2</sub> symmetry, it is not surprising that glycosylation is non-selective. Recently, Samuelsson reported an 11 step synthesis of **1** in 8% overall yield starting from 1,4-butanediol (Scheme 1).<sup>6</sup> Although this route was initially explored for the

synthesis of **1**, it was apparent that the poor stereoselectivity observed in the late-stage glycosylation step (1.4:1  $\alpha$ : $\beta$ ) would prevent the efficient preparation of **1**.



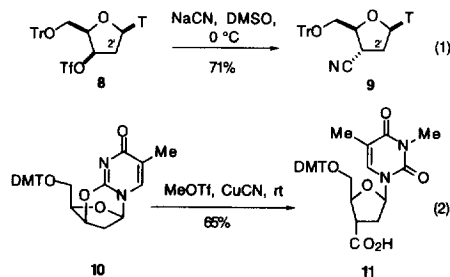
Scheme 1. Samuelsson Approach to **1**.

In order to circumvent the problems associated with non-selective glycosylation, we decided to take advantage of the naturally occurring anomeric stereochemistry present in uridine, cytidine and their 2'-deoxy analogs (Scheme 2). Three separate approaches to **1** will be discussed in this paper: (A) attempted addition of cyanide to the 3'-mesylate or triflate **3**, or the 3'-anhydronucleoside **4**, prepared from 2'-deoxyuridine and 2'-deoxycytidine respectively, (B) addition of cyanide to protected uridine and cytidine 2',3'-epoxide **5** and, (C) metal-catalyzed hydroformylation of protected 2',3'-didehydro-2',3'-dideoxycytidine **6**. It was anticipated that all three strategies would converge to a common intermediate **7** which could be easily converted to **1**.

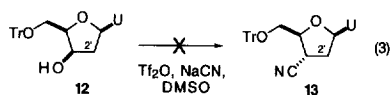


Scheme 2. Strategy for the Preparation of **1**

**Strategy A.** The use of 2'-deoxynucleosides potentially provided the most straightforward route to **1**, since no 2'-deoxygenation protocol would be required. An efficient route to AZT using this strategy has been employed.<sup>7</sup> Two examples relevant to the incorporation of a hydroxymethyl equivalent, such as cyanide, were relevant. First, Schreiber reported the reaction of 2'-deoxy-3'-*epi*-triflate **8**, derived from 2'-deoxythymidine, with NaCN to provide protected 3'-cyano thymidine **9** along with the corresponding 2',3'-olefin (eq 1).<sup>8</sup> Also, Saha reported the reaction of anhydronucleoside **10** with CuCN in the presence of MeOTf to provide **11**, the nitrile addition product being hydrolyzed to the carboxylic acid in the presence of cuprous ion (eq 2).<sup>9</sup>



3'-Epi-5'-trityl uridine **12** was prepared according to literature methods<sup>10</sup> and treated with  $\text{Ti}_2\text{O}$  and NaCN under the same conditions described by Schreiber, but the reaction afforded no desired product, yielding mostly decomposition and 2',3' elimination products (eq 3). All attempts to isolate the intermediate triflate, or even observe its formation by  $^1\text{H}$  NMR spectroscopy, were unsuccessful.<sup>11</sup> Therefore although substitution of the 3'-mesylate of deoxyuridine with azide, amine, and some carbon nucleophiles has been successful, cyanide appears to be unreactive toward the corresponding protected uridine and cytidine derivatives.<sup>12</sup>



**Strategy B.** The second strategy explored for the preparation of **1** depended on the regioselective opening of epoxide **5** with a hydroxymethylene equivalent, followed by deoxygenation of the 2'-position (Scheme 2). Initially, we focused on the use of uridine as starting material to avoid potential problems associated with the reactive  $\text{N}^4$  of cytidine. Ample precedent existed for the regioselective opening of variously protected nucleoside epoxides such as **5** with nucleophiles, including lithium acetylide, thiols, amines, and cuprates.<sup>13</sup> Of particular interest was the work of Jones who reported addition of LiCN to **15** in 22% yield. Additionally, Matsuda reported the addition of LiCN to the thymidine analog of **15** in 60% and Häbich and Barth reported the reaction of  $\text{Et}_2\text{AlCN}$  with a uridine epoxide in 52%.<sup>14</sup>

Epoxide **15**, prepared in high yield by methods similar to those previously reported,<sup>15</sup> was treated with LiCN in THF<sup>16</sup> to afford the desired 3'-nitrile **16** in 53% yield (Scheme 3). Attempts to improve the yield of the epoxide opening by variation of solvent, stoichiometry and reaction time were unsuccessful. Significantly, the time of reaction between epoxide and LiCN was important since the desired product **16** was unstable to the reaction conditions (Figure 1, Table 1). In the original Jones report, the reaction was allowed to proceed in DMSO at 47 °C for 8 h and may account for the reported low yield. Addition of catalytic Lewis acids failed to improve the yield of **16**.<sup>17</sup> Alternatively, use of  $\text{Et}_2\text{AlCN}$  provided a 3:1 mixture of 2':3'-cyano regioisomers in 70% yield. This result contrasts with the results of Häbich and Barth who reported observing less than 0.5% of the 2'-regioisomer.

Several procedures were considered for 2'-deoxygenation of hydroxy nitrile **16** using conditions described for similar nucleosides, including radical deoxygenation of the corresponding thionocarbonate and elimination through the thiocarbonylimidazole ester.<sup>18</sup> Neither of these methods were found to be as straightforward as

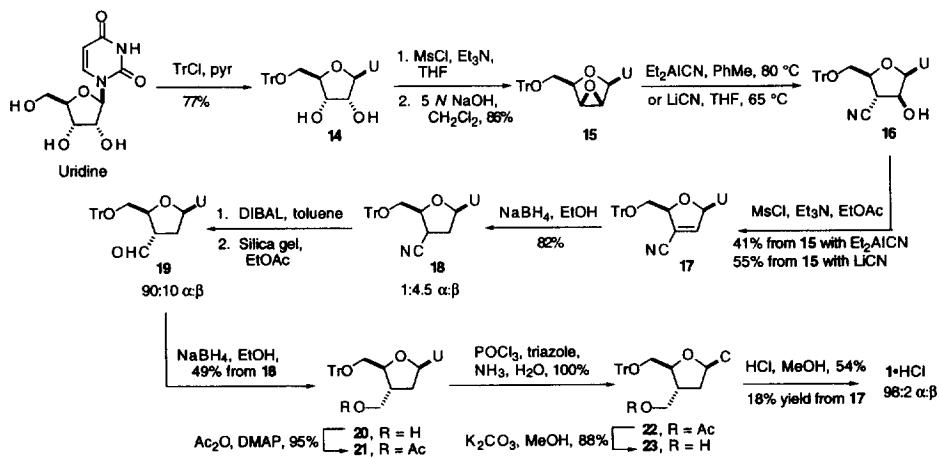
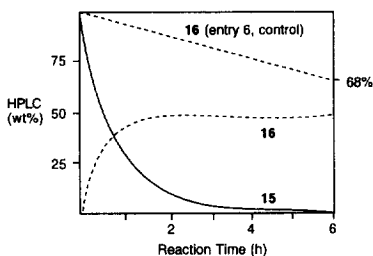
treatment of **16** with MsCl to afford the intermediate 2'-mesylate which readily eliminated to the desired unsaturated nitrile **17** upon warming in EtOAc.

Table 1. Effect of Time on LiCN Opening of **15**.

Entry	Time (h)	<b>16</b> <sup>a</sup> (%)	<b>15</b> (%)	Total (%)
1	0.75	39.5	33.1	72.6
2	1.5	49.8	11.5	61.3
3	3.0	53.1	1.5	54.4
4	4.0	49.3	1.1	50.4
5	6.5	47.4	0	47.4
6 <sup>b</sup>	6.0	67.9	---	67.9

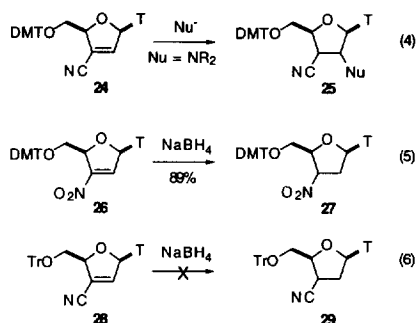
<sup>a</sup> HPLC weight% based on external calibration. <sup>b</sup> On subjecting **16** to the reaction conditions (Figure 1).

Figure 1. Reaction Time-vs-Amounts of **15** and **16**



Scheme 3. Synthesis of **1** from Uridine

While reports by Chattopadhyaya<sup>19</sup> on the Michael addition reaction to the unsaturated nitrile **24** (eq 4) and unsaturated nitro compound **26** (eq 5) suggested that reaction of **17** with NaBH<sub>4</sub> was a reasonable approach for reduction of the 2',3'-dideoxynitrile, a conflicting report by Matsuda suggested that NaBH<sub>4</sub> reduction of **17** would not be successful (eq 6).<sup>20</sup> However we found that NaBH<sub>4</sub> did effect the desired reduction to afford **18** as a 1:4.5 mixture of 3'-nitrile epimers in 82% yield.<sup>21</sup> An impurity resulting from uracil extrusion was also formed in about 10% yield.<sup>22</sup>



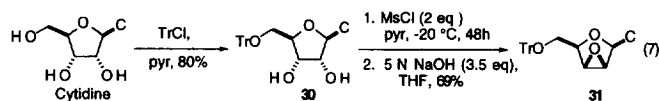
Although treatment of the epimeric mixture of nitriles **18** with NaOMe provided a 3.6:1 mixture of  $\alpha$ : $\beta$  epimers in about 30% yield, uracil was a major by-product observed in the reaction. It seemed more likely that equilibration of aldehydes **19** under acidic conditions might be more successful.<sup>23</sup> Reduction of nitriles **18** with DIBAL afforded **19** as a 1:4 mixture of 3'- $\alpha$ : $\beta$  stereoisomers in about 50% yield.<sup>24</sup> Treatment of the resulting aldehyde with silica gel in EtOAc successfully effected equilibration of **19** to a 90:10 mixture of the 3'- $\alpha$  and 3'- $\beta$  isomers. Other solvents, such as MeOH and MeCN, were also investigated but provided poor interconversion. Reduction of **19** with NaBH<sub>4</sub> was carried out in THF to provide hydroxymethyl alcohol **20** in 49% overall yield from **18**.

After protection of alcohol **20** as the acetate, the synthesis of **1** was completed by quantitative conversion of uracil to cytosine using the triazole method.<sup>25</sup> The acetate conveniently hydrolyzed during the workup using K<sub>2</sub>CO<sub>3</sub>/MeOH. Finally, deprotection of the trityl group was achieved in MeOH with HCl(g). The HCl salt of **1** precipitated directly from the reaction mixture upon addition of EtOAc in 54% yield. The absolute configuration of **2** as well as the 3'- $\beta$  isomer of **1** was confirmed by X-ray crystallography. This completed a 12 step synthesis of **1**, as a 98:2 mixture of  $\alpha$ : $\beta$  epimers, in 7% overall yield from uridine (Scheme 3).

**Cytidine.** Confident that the overall strategy to prepare **1** through epoxide **5** was a practical approach, we decided to explore the use of cytidine as the starting material which would eliminate the 3-step conversion of uracil to cytosine. Although the epoxide of dimethoxytrityl cytidine was previously been prepared, albeit in only 30% yield,<sup>26</sup> none of the subsequent steps described for the uridine route were reported with cytidine-derived intermediates. Potentially competing reactions with the N<sup>4</sup>-cytosyl amine and the potential for conversion of cytosine to uracil under nucleophilic conditions made this approach more challenging.<sup>27</sup>

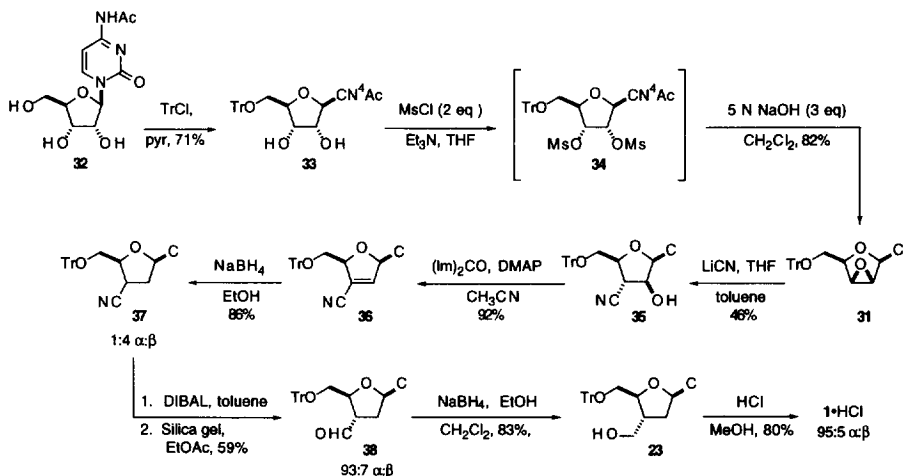
Epoxide **31** was first prepared in 69% overall yield by treatment of trityl cytidine **30**, with MsCl and NaOH similar to the conditions used to prepare the uridine epoxide **15** (eq 7). However the long reaction times and use

of pyridine as a solvent made the reaction extremely difficult to analyze. Thus, a more convenient method to prepare **31** was developed using *N*<sup>4</sup>-acetyl cytidine **32** as the starting material.<sup>28</sup> Preparation of 5'-trityl-*N*<sup>4</sup>-acetyl cytidine **33** was achieved in 71% yield. Unlike the mesylation of **30**, reaction of **33** with MsCl was complete in less than 30 min at -20 °C in THF to afford the bismesylate **34**. Treatment of the reaction mixture with NaOH afforded **31** in 82% yield which crystallized directly from the reaction mixture (Scheme 4).



As with the uridine series, LiCN or Et<sub>2</sub>AlCN was used to introduce cyanide to epoxide **31**. Et<sub>2</sub>AlCN afforded a 57% yield of a 5:1 mixture of 3' and 2' regioisomers, while LiCN afforded only the desired 3' regioisomer **35** in 46% yield. As observed with **16**, the hydroxy nitrile **35** was unstable to the LiCN reaction conditions decomposing by a ring opening elimination to produce cytosine.

Although the 3'-mesylate was efficiently utilized for 2'-deoxygenation in the uridine sequence, treatment of **35** under identical conditions afforded only a 65% yield of unsaturated nitrile **36** due to competitive mesylation of the cytosine *N*<sup>4</sup>-amine. Alternatively, when the elimination was performed under milder conditions using 1,1'-carbonyldiimidazole [(Im)<sub>2</sub>CO], **36** was obtained in 92% yield.<sup>29</sup> Reduction of **36** with NaBH<sub>4</sub> in EtOH



Scheme 4: Synthesis of **1** from *N*<sup>4</sup>-Acetyl Cytidine

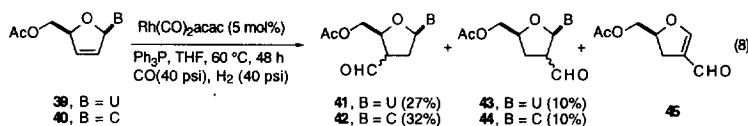
provided a 1:4 ratio of the  $\alpha,\beta$  saturated nitriles **37** in 86% isolated yield.<sup>30</sup> It was possible to isolate the  $\beta$ -nitrile in 70% yield and >99:1 selectively by crystallization of the crude reaction mixture from toluene. Based on the results obtained with the uridine route, no attempt was made to epimerize the 3'-nitrile.

Reduction of **37** using DIBAL, followed by silica gel equilibration of the resulting mixture of 3'-aldehydes, proceeded as in the uridine series to provide **38** in 59% yield and 93:7  $\alpha,\beta$  selectivity. Reduction of **38** with

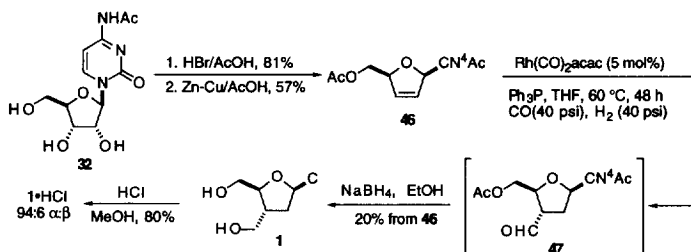
$\text{NaBH}_4$  was performed in  $\text{EtOH}/\text{CH}_2\text{Cl}_2$  to afford an 83% yield of **23**. In contrast to the uridine route, this reaction does not proceed efficiently in  $\text{EtOH}$  alone. Finally, detritylation of **23** with  $\text{HCl}$  in  $\text{MeOH}$  provided **1** as the  $\text{HCl}$  salt in 80% yield. This completed an 8 step synthesis of **1**, as a 95:5 mixture of  $\alpha$ : $\beta$  epimers, in 9% overall yield from  $\text{N}^4$ -acetyl cytidine.

**Strategy C.** Although an efficient synthesis of **1** was achieved from both uridine and cytidine by cyanide opening of epoxide **5**, a more direct approach would involve functionalization of 2',3'-dideoxy-2',3'-dideoxynucleoside **6** by hydrometalation-carbonylation (Scheme 2). Of interest was the hydroformylation reaction of **39** or **40** since it would provide the corresponding 3'-carboxyaldehydes in a single step. The major problem to be addressed was regioselectivity. Facial selectivity was not an issue since it was already determined that aldehydes **19** and **38** were easily equilibrated to the desired  $\alpha$ -epimer. While hydroformylation of functionalized olefins<sup>31</sup> and olefinic pyranosides<sup>32</sup> was known, no precedent existed for the hydroformylation of a nucleoside olefin.

Initial screening of catalysts was performed using **39**.<sup>33</sup> Wilkinson's catalyst,  $\text{RhCl}(\text{PPh}_3)_3$ , afforded predominantly the eliminated product **45**, while  $\text{Rh}_2\text{O}_3$  gave a 22% yield of **41:43** as a 1:1 mixture of regioisomers (eq 8). The most successful catalyst examined was  $\text{Rh}(\text{CO})_2\text{acac}\cdot\text{PPh}_3$ , which afforded a 37% yield of a 2.7:1 mixture of **41:43**. Application of these conditions to **40**,<sup>34</sup> provided a 3.2:1 ratio of **42:44** in 42% combined yield. Attempts to improve the yield and regioselectivity of the reaction by varying the reaction time, solvents, catalyst load, pressure and ligands have so far been unsuccessful. The stereochemistry of the hydroformylation was determined by application of this methodology to the synthesis of **1**.



Cytidine 2',3'-olefin **46** was prepared according to literature procedures and hydroformylated using the optimized conditions described above.<sup>35</sup> Since the product aldehyde **47** was difficult to characterize, it was treated directly with  $\text{NaBH}_4$  which in addition to reducing the aldehyde, deacylated the 5'-O and  $\text{N}^4$ -acetyl protecting groups to afford **1** in 20% overall yield from **46** as a 94:6 ratio of  $\alpha$ : $\beta$  stereoisomers. The high stereoselectivity observed for **1** could imply that equilibration to the thermodynamic ratio of aldehydes occurred under the hydroformylation conditions. Treatment of **1** with  $\text{HCl}$  in  $\text{MeOH}$ , completed a 5 step synthesis of the  $\text{HCl}$  salt of **1**, as a 94:6 mixture of  $\alpha$ : $\beta$  epimers, from  $\text{N}^4$ -acetyl cytidine in 7% overall yield (Scheme 5).

Scheme 5: Synthesis of **1** from *N*<sup>4</sup>-Acetyl Cytidine by Hydroformylation

## SUMMARY

While attempts to prepare **1** by addition of cyanide to 3'-*epi* cytidine and 3'-*epi* uridine were not successful, **1** was prepared in good overall yield using epoxide **5** derived from uridine and cytidine. The intermediate cyanoalcohols were found to be unstable to the reaction conditions using LiCN. Finally, we reported an expedient preparation of **1** using a previously unexplored hydroformylation reaction of **46**. The hydroformylation reaction was not regioselective, but did provide the desired alcohol epimer of **1**. The α:β epimeric ratio of **1** from each route, as determined by HPLC, was comparable.

## EXPERIMENTAL SECTION

**General.** All reactions were run under a nitrogen atmosphere. Reagents were used as received unless otherwise noted. Tetrahydrofuran (THF) was analyzed by Karl-Fischer titration and dried if the water content was greater than 0.03% (either stored over 4Å molecular sieves or distilled from a sodium benzophenone ketyl solution). Proton NMR spectra were obtained at either 500 or 300 MHz and carbon NMR spectra were obtained at 75.5 MHz. NMR chemical shifts are reported in δ units referenced to either TMS or to residual proton signals in the deuterated solvents. All yields are corrected for chemical purity of both the limiting reagent and the product (Yield = (weight of product x purity/MW of product)/(weight of limiting reagent x purity/MW of limiting reagent) x 100). If the purity of a product is not specified it is greater than 99%.

**5'-*O*-(Triphenylmethyl)uridine (**14**).** A mixture of triphenylmethyl chloride (2.98 kg, 10.7 mol), uridine (2.75 kg, 11.2 mol), and pyridine (5.45 L) was heated at 70–85 °C for 1.25 h and then cooled to 20 °C. One-half of the reaction mixture was charged to a mixture of CH<sub>2</sub>Cl<sub>2</sub> (13.4 L) and water (15.0 L). The mixture was stirred while 6 N HCl (5.5 L, 33 mol) was added over 20 min. The organic phase containing **14** was concentrated by rotary evaporation, while the remaining reaction mixture was treated as above. The resultant oil was charged to EtOAc (10.0 L) and the solution stirred at 10 °C for 16 h, after which time the precipitated product was isolated by vacuum filtration, rinsed with EtOAc (3.0 L) and dried *in vacuo* to yield 4.03 kg of **14** (77% yield). mp 188.9–191.0 (lit.<sup>36</sup> 200 °C). Spectral data: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 3.74 (m, 2H), 4.43 (br s, 1H), 4.45 (br s, 2H), 5.58 (br d, 1H), 5.58 (d, *J* = 7.80 Hz, 1H), 5.91 (br d, 1H), 6.15 (br d, 1H), 7.68 (m, 15H), 8.04 (d, *J* = 7.80 Hz, 1H), 11.37 (br s, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 63.3, 69.6, 73.4, 82.3, 86.4, 89.0, 101.5, 127.2 (3C), 128.0 (6C), 128.3 (6C), 140.7, 143.5 (3C), 150.5, 163.0; IR (KBr) 3436, 1707,



1675, 1653  $\text{cm}^{-1}$ ; UV (EtOH)  $\lambda_{\text{max}}$  262 nm,  $\epsilon$  9799; MS (FD)  $m/z$  486 (100%),  $m/z$  243 (28%). Anal. Calcd for  $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_6$ : C, 69.12; H, 5.39; N, 5.76. Found C, 69.04; H, 5.51; N, 5.83.

**1-[2,3-Anhydro-5-*O*-(triphenylmethyl)- $\beta$ -D-lyxofuranosyl]-2,4 (1H, 3H)-pyrimidinedione (15).** Methanesulfonyl chloride (1.66 kg, 14.5 mol) was added over 0.75 h at  $-5$ – $5$   $^{\circ}\text{C}$  to a solution **14** (3.00 kg, 6.17 mol) and triethylamine (2.00 kg, 19.7 mol) in THF (9.0 L). After stirring for an additional 0.5 h the solution was added to a mixture of water (6.0 L), 12 N HCl (0.54 L, 6.6 mol) and  $\text{CH}_2\text{Cl}_2$  (7.0 L). The mixture was gently stirred for 2 min and the phases separated. The organic layer, containing 2',3'-dimethanesulfonate-5'-*O*-(triphenylmethyl)uridine, was added to a mixture of water (6.0 L) and 50% sodium hydroxide (1.68 kg, 21 mol) and the mixture stirred at 40  $^{\circ}\text{C}$  for 1.5 h. The reaction mixture was added to acetonitrile (3.75 L) and 10% brine (4.0 L). The mixture was gently stirred while the pH of the aqueous phase was adjusted to 0.8 with 3.0 N HCl. The phases were separated and the organic phase was gently stirred with a saturated aqueous solution of NaCl (3.0 L). The phases were separated and the organic fraction was concentrated by rotary evaporation to an oil and was diluted with EtOH (8.0 L). The resulting suspension was stirred at 50  $^{\circ}\text{C}$  for 20 min before the precipitated product was isolated by vacuum filtration, rinsed with EtOH (2.0 L), and dried *in vacuo* to yield 2.53 kg of **15** (98% purity,<sup>37</sup> 86% yield). mp 182.4–184.9  $^{\circ}\text{C}$ . Spectral data:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  3.75 (m, 2H), 4.56 (d,  $J$  = 3.19 Hz, 1H), 4.59 (d,  $J$  = 3.19 Hz, 1H), 4.73 (t,  $J$  = 5.72 Hz, 1H), 6.04 (d,  $J$  = 7.8 Hz, 1H), 6.52 (s, 1H), 7.69 (m, 15H), 7.87 (d,  $J$  = 7.87 Hz, 1H), 11.49 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  55.9, 56.1, 62.2, 76.7, 81.7, 87.1, 102.4, 127.2 (3C), 127.9 (6C), 128.5 (6C), 141.3, 143.4 (3C), 150.5, 163.3; IR ( $\text{CHCl}_3$ ) 3400, 3080, 3010, 1693, 1640, 1450, 1264  $\text{cm}^{-1}$ ; UV (EtOH):  $\lambda_{\text{max}}$  260 nm,  $\epsilon$  10000; MS (FD)  $m/z$  469 (100%). Anal. Calcd. for  $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_5$ : C, 71.78; H, 5.16; N, 5.98. Found: C, 71.96; H, 5.16; N, 5.86.

**3'-Cyano-2',3'-didehydro-2',3'-dideoxy-5'-*O*-(triphenylmethyl)-uridine (17). Procedure using  $\text{Et}_2\text{AlCN}$ :** Diethylaluminum cyanide (1.0 M in toluene, 1.00 L, 1.00 mol) was added dropwise over 10 min to a thin slurry of **15** (300.2 g, 0.641 mol) in THF (1.5 L) while maintaining the temperature below 40  $^{\circ}\text{C}$ . After heating at reflux (75  $^{\circ}\text{C}$ ) for 1–2 h, the solution was cooled to room temperature and poured slowly into a cold mixture of 2 N HCl (2.2 L, 2.2 mol) and EtOAc (800 mL) while maintaining the temperature below 15  $^{\circ}\text{C}$ . The mixture was warmed to 25  $^{\circ}\text{C}$  and stirred for 30 min. The aqueous layer was separated and the organic phase was washed with 1 N HCl (2 x 1 L) and a saturated aqueous solution of NaCl (1 L). The combined aqueous fractions were back extracted with EtOAc (500 mL) and the combined organic fractions were dried over  $\text{MgSO}_4$ . Removal of the solvent by rotary evaporation afforded 360.5 g of a foam containing<sup>38</sup> a mixture of **16** (192.2 g, 60% yield), the 2'-cyano isomer (52.7 g, 17% yield), toluene (54 g, 15% by weight), and several small impurities (62 g). The crude product was used without purification.

Methanesulfonyl chloride (81.5 g, 0.712 mol) was added to a cooled mixture of the crude foam produced above (360.5 g), triethylamine (271 mL, 1.94 mol) and EtOAc (2.5 L) over 10 min while maintaining the temperature below 10  $^{\circ}\text{C}$ . The slurry was warmed to room temperature, stirred for 30 min, and then heated to 40  $^{\circ}\text{C}$  for 1–2 h. The reaction mixture was cooled to 25  $^{\circ}\text{C}$ , water (2 L) was added, and the mixture stirred for 1 h. The organic phase was washed with 2.0 M  $\text{NaHSO}_4$  (1.8 L) followed by a saturated aqueous solution of NaCl (2 x 2 L) and was dried with  $\text{MgSO}_4$ . The mixture was filtered, concentrated to an oil by rotary evaporation, redissolved in 3:1 EtOAc:toluene (3.9 L), and was stirred overnight. The resultant slurry was cooled at 0–10  $^{\circ}\text{C}$

for 2 h, filtered, and dried *in vacuo* to afford 140.5 g of **17** (91% purity, <sup>38,39</sup> 69% yield from **16**). Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.48 (dd, *J* = 1.6, 11.4 Hz, 1H), 3.74 (dd, *J* = 2.3, 11.5 Hz, 1H), 4.86 (dd, *J* = 2.0, 8.1, 1H), 5.00–5.02 (m, 1H), 6.72 (t, *J* = 1.6 Hz, 1H), 7.14 (dd, *J* = 1.3, 4.2 Hz, 1H), 7.25–7.39 (m, 15H), 7.82 (d, *J* = 8.1 Hz, 1H), 8.99 (br s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 62.4, 85.5, 88.0, 88.8, 103.0, 111.8, 119.4, 127.6 (3C), 128.1 (6C), 128.6 (6C), 140.3, 140.5, 142.4 (3C), 150.3, 163.2; IR (CHCl<sub>3</sub>) 3400, 3090, 3060, 3026, 2239, 1692, 1640, 1264 cm<sup>-1</sup>; MS (FD) *m/z* 477. Anal. Calcd for C<sub>29</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>: C, 72.94; H, 4.85; N, 8.80. Found: C, 72.77; H, 4.93; N, 8.51.

**Procedure using LiCN:** Acetone cyanohydrin (101.4 mL, 1.11 mol) was added dropwise over 30 min to a cooled (0 °C) mixture of lithium hydride (8.48 g, 1.07 mol) and THF (1.1 L) while maintaining the temperature below 2 °C. The mixture was then stirred at room temperature for 1 h and **15** (100 g, 0.213 mol) was added portionwise over 10 min. The solution was warmed to 65 °C and stirred at that temperature for 4 h. On cooling to 5 °C, triethylamine (297 mL, 2.13 mol) was added in one portion, followed by a slow addition of methanesulfonyl chloride (66.1 mL, 0.854 mol) while maintaining the temperature below 10 °C. The mixture was stirred overnight at room temperature, then partitioned between EtOAc (1.5 L) and a 50% saturated aqueous solution of NaCl (1.5 L). The phases were separated, silica gel (300 g) and anhydrous sodium sulfate (60 g) were added to the organic phase, and the mixture stirred for 30 min. The solid was removed by filtration and the process repeated. The filtrate was concentrated by rotary evaporation to an oil and crystallized from toluene/EtOAc (3/1 ratio, 300 mL). After drying *in vacuo* 63.97 g of **17** (88% pure, <sup>38,40</sup> 55% yield from **15**) was isolated as a crystalline solid.

**3'-Cyano-2',3'-dideoxy-5'-O-(triphenylmethyl)uridine (18α), and 1-[3-cyano-2,3-dideoxy-5-O-[trimethylphenyl]-β-D-threo-pento-furanosyl]-2,4(1H,3H)-pyrimidinedione (18β).** Sodium borohydride (11.1 g, 0.292 mol) was added in one portion at 0–5 °C to a mixture of **17** (139.5 g, 91% purity, 0.266 mol), CH<sub>2</sub>Cl<sub>2</sub> (700 mL), and EtOH (1.4 L). The mixture was warmed to 25 °C and stirred for 1 h. The yellow solution was concentrated to near dryness and EtOAc (1.4 L) followed by 1 M NaHSO<sub>4</sub> (700 mL) were added to the solid residue. After stirring for 10 min, the phases were separated, the organic phase washed with a saturated aqueous solution of NaCl, and dried over MgSO<sub>4</sub>. To crystallize a mixture of **18α/18β**, EtOAc/toluene (3/1 ratio, ca. 420 mL) was added and the mixture stirred for 24 h. The solid was isolated by filtration and dried *in vacuo* at 50 °C to afford 104.7 g (82% yield) of an 18:82 mixture<sup>41</sup> of **18α** and **18β** respectively. This mixture was used without purification in the DIBAL-H reduction step.

**Purification of 18β.** The mixture of **18α/18β** prepared above was added to EtOAc (1.4 L) and heated at reflux. Enough additional EtOAc was added to get the product into solution. After cooling slowly and stirring overnight, white crystals were separated by vacuum filtration and dried to give 43.2 g of **18β** (92% purity, <sup>38,42</sup> 37.9% yield). mp 202–204 °C. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.40 (dt, *J* = 14.1, 4.5 Hz, 1H), 2.75–2.85 (m, 1H), 3.31–3.37 (m, 1H), 3.53 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.71 (dd, *J* = 10.5, 5.3 Hz, 1H), 4.18 (q, *J* = 5.3 Hz, 1H), 5.60 (d, *J* = 8.4 Hz, 1H), 6.13 (dd, *J* = 6.8, 4.6 Hz, 1H), 7.25–7.56 (m, 16H), 9.01 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 30.5, 36.7, 63.2, 78.8, 84.5, 87.9, 102.9, 118.1, 127.5 (3C), 128.0 (6C), 128.7 (6C), 139.1, 143.0 (3C), 150.4, 163.2; IR (CHCl<sub>3</sub>) 3400, 3064, 3030, 2250, 1694, 1632, 1450, 1270, 1091 cm<sup>-1</sup>;

UV (CH<sub>3</sub>CN):  $\lambda_{\max}$  260,  $\epsilon$  9659; MS (FD)  $m/z$  479. Anal. Calcd for C<sub>29</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.43; H, 5.43; N, 8.51.

**Analytical for 18 $\alpha$ :**<sup>43</sup> mp 212.6 - 215 °C. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.56-2.62 (m, 1H), 2.71-2.77 (m, 1H), 3.43 (q,  $J$  = 9.5 Hz, 1H), 3.54 (dd,  $J$  = 2.8, 11.5 Hz, 1H), 3.66 (dd,  $J$  = 2.7, 11.3 Hz, 1H), 4.26 (dt,  $J$  = 2.7, 9.1 Hz, 1H), 5.39 (dd,  $J$  = 2.0, 8.0 Hz, 1H), 6.13 (dd,  $J$  = 3.0, 6.9 Hz, 1H), 7.22-7.41 (m, 15H), 7.79 (d,  $J$  = 8.1 Hz, 1H), 8.42 (br s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  27.7, 37.3, 61.3, 82.5, 85.6, 88.0, 102.4, 117.5, 127-129.0 (15C), 139.7, 142.8 (3C), 150.0, 163.1; IR (CHCl<sub>3</sub>) 3400, 3090, 3063, 3025, 3014, 2250, 1691, 1450, 1273, 1114 cm<sup>-1</sup>; UV (EtOH):  $\lambda_{\max}$  330 nm,  $\epsilon$  1945; 260 nm,  $\epsilon$  9241; Anal. Calcd for C<sub>29</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>: C, 72.64; H, 5.26; N, 8.76. Found: C, 72.88; H, 5.37; N, 8.83.

**2',3'-Dideoxy-3'-formyl-5'-O-(triphenylmethyl)uridine (19).** A solution of diisobutylaluminum hydride (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.57 L, 1.57 moles) was added over 15 min to a -10 °C solution of 18 $\alpha$ /18 $\beta$  (302 g, 92% purity, 0.579 moles) and CH<sub>2</sub>Cl<sub>2</sub> (6 L) while maintaining the temperature below 0 °C. After stirring at this temperature for 1 h, the reaction was quenched by the slow addition (15 min) of cold 1 N HCl (2 L), while maintaining the temperature below 15 °C. The reaction mixture was then transferred to a mixture of EtOAc (6 L) and 1 N HCl (4 L).<sup>44</sup> The phases were separated and the organic phase was washed with 1 N HCl (4 L) and a saturated aqueous solution of NaCl (2 x 2.8 L). The organic phase was carried directly into the epimerization process below.

**Epimerization:** Silica Gel 60 (1.2 kg, 400 weight percent) was added to the solution of 19 $\alpha$ /19 $\beta$  isolated above and the mixture was stirred for 24 h at 25 °C. The progress of the epimerization was monitored by <sup>1</sup>H NMR (19 $\alpha$ , doublet at 7.87 ppm, 19 $\beta$ , doublet at 7.65 ppm) and the reaction was continued until the ratio of the aldehyde proton reached 90:10 in favor of the desired  $\alpha$ -isomer. The silica gel was removed by vacuum filtration and rinsed with EtOAc (4 x 1 L). The solvent was removed by rotary evaporation to afford 240 g of 19 as an impure foam. The crude product was reduced in the next step without purification. It was not possible to obtain an analytically pure sample or accurately determine the purity of the aldehyde. A sample was purified by flash chromatography for analysis. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.34-2.35 (m, 1H), 2.72-2.78 (m, 1H), 3.38 (q,  $J$  = 3.3 Hz, 1H), 3.47 (dd,  $J$  = 11, 3.2 Hz, 1H), 3.61 (dd,  $J$  = 10.9, 3.2 Hz, 1H), 4.5 (m, 1H), 5.38 (dd,  $J$  = 8.1, 2.4 Hz, 1H), 6.09 (m, 1H), 7.26-7.41 (m, 15H), 7.87 (d,  $J$  = 8.2 Hz, 1H), 8.19 (br s, 1H), 9.64 (d,  $J$  = 1.4 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  31.6, 47.8, 60.5, 77.3, 82.8, 99.5, 124.7-126.0, 135.0, 137.3, 140.5, 195.5; IR (CHCl<sub>3</sub>) 3400, 1691, 1449, 1272 cm<sup>-1</sup>; MS (FD)  $m/z$  482 (100%, M+); Anal. Calc'd for C<sub>29</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>: C, 72.18; H, 5.43; N, 5.80. Found: C, 72.13; H, 5.62; N, 5.78.

**2',3'-Dideoxy-3'-hydroxymethyl-5'-O-(triphenylmethyl)uridine (20).** The crude foam from above (240 g) was added to EtOH (2 L) and the mixture warmed to 35 °C to dissolve the solid. The solution was cooled to 15 °C and NaBH<sub>4</sub> (18.8 g, 0.497 mol) was added in portions over 10 min (the temperature increased to 25 °C). After 30 min the unreacted NaBH<sub>4</sub> was quenched with acetone (80 mL, 1.1 mol) and the solvent was removed by rotary evaporation. The residue was partitioned between EtOAc (2 L) and water (1.5 L). The pH of the aqueous phase was adjusted to 3-4 with 1 N HCl (610 mL). The organic phase was washed twice with a saturated aqueous solution of NaCl (1 L) and dried with Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was removed by rotary evaporation to give 251 g of 20 as a crude foam (55% purity,<sup>45</sup> 49% yield from 18 $\alpha$ /18 $\beta$ ). It was not

possible to purify alcohol **20** by crystallization so the crude product was used directly in the next step. A sample was purified by flash chromatography (5% MeOH/CHCl<sub>3</sub>) for analysis. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.78 (br s, 1H), 2.18–2.21 (m, 1H), 2.30–2.35 (m, 1H), 2.57–2.67 (m, 1H), 3.45 (dd, *J* = 3.3, 10.8 Hz, 1H), 3.55–3.70 (m, 3H), 3.96–3.98 (m, 1H), 5.35 (d, *J* = 8.2 Hz, 1H), 6.08 (dd, *J* = 3.2, 6.9 Hz, 1H), 7.23–7.50 (m, 15H), 7.95 (d, *J* = 8.2 Hz, 1H), 8.60 (br s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 36.4, 40.3, 62.4, 63.4, 82.7, 85.4, 87.4, 101.7, 127.3 (3C), 127.9 (6C), 128.6 (6C), 140.4, 143.2 (3C), 150.4, 163.6; IR (CHCl<sub>3</sub>) 3396, 3103, 1687, 1450, 1272, 1116 cm<sup>-1</sup>; UV (EtOH): λ<sub>max</sub> 263 nm, ε 8048; MS (FD) *m/z* 485. Anal. Calcd for C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>: C, 71.89; H, 5.83; N, 5.78. Found: C, 71.66; H, 6.08; N, 5.93.

**3'-[(Acetyloxy)methyl]-2',3'-dideoxy-5'-O-(triphenylmethyl)uridine (21)** Acetic anhydride (152 mL, 1.61 mol) was added dropwise over 20 min to a cooled solution of crude **20** (743.5 g, 53% purity, 0.810 mol), triethylamine (224 mL, 1.61 mol), and dimethylaminopyridine (1.84 g, 0.015 mol) in EtOAc (3.7 L) while maintaining the temperature below 20 °C. After stirring at this temperature for 1 h, 1 N HCl (1.5 L) was added slowly while maintaining the temperature below 25 °C. The phases were separated and the organic phase was washed with saturated solutions of NaHCO<sub>3</sub> (1.5 L) and NaCl (2 x 1.5 L) and was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, removal of the solvent by rotary evaporation afforded 770 g of **21** (53% purity,<sup>46</sup> 95% yield) as an amorphous foam. It was not possible to purify **21** by crystallization so the crude product was used directly in the next step. A sample was purified by flash chromatography (4% MeOH/CHCl<sub>3</sub>) for analysis. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.90 (s, 3H), 2.23–2.31 (m, 2H), 2.74–2.83 (m, 1H), 3.41 (dd, *J* = 3.3, 10.9 Hz, 1H), 3.64 (dd, *J* = 2.9, 10.9 Hz, 1H), 3.93–3.98 (m, 2H), 4.06 (dd, *J* = 5.7, 11.3 Hz, 1H), 5.27 (dd, *J* = 2.3, 8.1 Hz, 1H), 6.12 (dd, *J* = 2.9, 6.8 Hz, 1H), 7.26–7.46 (m, 15H), 8.01 (d, *J* = 8.2 Hz, 1H), 8.54 (br s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 20.6, 36.6, 36.9, 62.9, 64.0, 83.3, 85.3, 87.5, 101.8, 127.5 (3C), 128.1 (6C), 128.8 (6C), 140.3, 143.2 (3C), 150.3, 163.4, 170.7; IR (KBr) 3200, 3060, 1740, 1680, 1220, 700 cm<sup>-1</sup>; UV (MeOH): λ<sub>max</sub> 263 nm, ε 8750; MS (FD) *m/z* 526. Anal. Calcd for C<sub>31</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub>: C, 70.70; H, 5.74; N, 5.32. Found: C, 70.57; H, 5.82; N, 5.29.

**3'-[(Acetyloxy)methyl]-2',3'-dideoxy-5'-O-(triphenylmethyl)cytidine (22).** Phosphorus oxychloride (287 mL, 3.08 mol) was added dropwise over 15 min to a slurry of 1,2,4-triazole (943 g, 13.7 mol) in acetonitrile (3 L) while maintaining the temperature below 5 °C. Triethylamine (1.82 L, 13.06 mol) was then added dropwise over 30 min while maintaining the temperature below 15 °C. The cooling bath was removed and the crude **21** prepared above (765 g, 53% purity, 0.767 mol) was added to the slurry in one portion and rinsed in with acetonitrile (800 mL). After stirring for 3 h, the reaction was quenched by the addition of ammonium hydroxide (3.8 L) over 30 min while maintaining the temperature below 30 °C. The mixture was stirred overnight at 25 °C, diluted with CH<sub>2</sub>Cl<sub>2</sub> (4.8 L), and the phases were separated. Water (3.8 L) was added to the organic phase and the pH adjusted to 3.5–4.5 by the dropwise addition of 12 N HCl (2.1 L) while maintaining the temperature below 35 °C. The phases were separated and the organic phase washed again with water (3.8 L). The pH of the aqueous phase was adjusted to 6.5–7.5 with 50% aqueous NaOH (15 mL). The organic phase was separated and was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, removal of the solvent by rotary evaporation afforded 743 g of crude **22** (55% purity,<sup>45</sup> 100% yield) as an amorphous foam. It was not possible to purify **22** by crystallization so the crude product was used directly in the next step. A sample was purified by

flash chromatography (7% MeOH/CHCl<sub>3</sub>) for analysis. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.88 (s, 3H), 2.22-2.40 (m, 2H), 2.68-2.80 (m, 1H), 3.38 (dd, *J* = 3.4, 10.8 Hz, 1H), 3.64 (dd, *J* = 2.5, 10.9 Hz, 1H), 3.93-3.98 (m, 3H), 4.05 (dd, *J* = 5.8, 11.3 Hz, 1H), 5.29 (d, *J* = 7.4 Hz, 1H), 6.13 (dd, *J* = 2.7, 6.6 Hz, 1H), 7.27-7.47 (m, 15H), 8.18 (d, *J* = 7.3 Hz, 1H); IR (CHCl<sub>3</sub>) 3417, 3010, 1740, 1649, 1598, 1532, 1491, 1479, 1246 cm<sup>-1</sup>; MS (FD) *m/z* 526. Anal. Calcd for C<sub>31</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>: C, 70.84; H, 5.95; N, 8.00. Found: C, 71.06; H, 6.24; N, 8.30.

**2',3'-Dideoxy-3'-hydroxymethyl-5'-*O*-(triphenylmethyl)cytidine (23).** Potassium carbonate (97.6 g, 0.71 mol) was added to a solution of crude **22** (743 g, 55% purity, 0.773 mol) in MeOH (3.7 L) and the slurry was stirred at room temperature for 3 h. When the reaction was complete, water (2.0 L) and CH<sub>2</sub>Cl<sub>2</sub> (2.7 L) were added and the pH of the aqueous phase adjusted to 6.8-7.2 with 12 N HCl (125 mL). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (1 L), the phases were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (800 mL). The combined organic fractions were dried over MgSO<sub>4</sub> and filtered. Removal of the solvents by rotary evaporation afforded 675 g of crude **23** (49% purity,<sup>45</sup> 88% yield) as an amorphous foam. It was not possible to purify **23** by crystallization so the crude product was used directly in the next step. A sample was purified by flash chromatography for analysis (10% MeOH/CHCl<sub>3</sub> then increased to 20% as the product began to elute). Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.16-2.25 (m, 1H), 2.35-2.56 (m, 2H), 3.38 (dd, *J* = 3.5, 10.8 Hz, 1H), 3.50-3.59 (m, 2H), 3.94-3.97 (m, 1H), 5.37 (d, *J* = 7.3 Hz, 1H), 6.02-6.05 (m, 1H), 7.17-7.53 (m, 17H), 8.03 (d, *J* = 7.5 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 37.4, 40.3, 62.1, 63.4, 82.6, 86.5, 87.3, 94.1, 127.3 (3C), 128.0 (6C), 128.7 (6C), 141.4, 143.5 (3C), 155.9, 165.5; IR (KBr) 3600-2900, 1644, 1527, 1489 cm<sup>-1</sup>; UV (MeOH): λ<sub>max</sub> 206 nm, ε 46744; 273 nm, ε 7830. MS (FD) *m/z* 484 (M<sup>+</sup>). Anal. Calcd for C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>: C, 72.03; H, 6.05; N, 8.69. Found: C, 71.88; H, 6.07; N, 8.76.

**2',3'-Dideoxy-3'-(hydroxymethyl)cytidine Hydrochloride (1).** Anhydrous HCl (44 g, 1.2 mol) was bubbled into a solution of crude **23** (250 g, 49% purity, 0.252 mol) in MeOH (2 L) over 5-30 min while maintaining the temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h. EtOAc (2 L) was added to the slurry and the resulting mixture was stirred at room temperature for 2 h. The slurry was cooled to 0 °C and stirred for 2 h. The precipitate was isolated by filtration and the cake was washed with cold 1:1 MeOH:EtOAc (200 mL) followed by EtOAc (200 mL). The beige solid was then added to EtOAc (300 mL) and the slurry was stirred for 2 h to remove the residual trityl methyl ether byproduct. The solid was filtered, washed with EtOAc, and dried *in vacuo* at 55 °C to afford 39.6 g of **1** (95% purity,<sup>46</sup> 54% yield, 18% yield from **17**) as a beige crystalline solid. Epimeric ratio of **1** was 98:2 (determined by HPLC). mp 153-157 °C. Spectral data: <sup>1</sup>H NMR (D<sub>2</sub>O) δ 2.25-2.40 (m, 3H), 3.60 (d, *J* = 5.5 Hz, 2H), 3.69 (dd, *J* = 5.0, 12.7 Hz, 1H), 3.86 (dd, *J* = 2.7, 12.7 Hz, 1H), 3.97-4.04 (m, 1H), 6.01-6.03 (m, 1H), 6.14 (d, *J* = 7.9 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 35.9, 39.3, 61.1, 61.3, 85.0, 86.5, 93.2, 114.9, 147.0, 159.8; IR (KBr) 3374, 3300, 3108, 3086, 2925, 2885, 2728, 1712, 1690, 1662, 1618, 1274, 1113 cm<sup>-1</sup>; MS (FD) *m/z* 242; UV (EtOH): λ<sub>max</sub> 275, ε 8923. Anal. Calcd for C<sub>10</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>4</sub>: C, 43.25; H, 5.81; N, 15.13; Cl, 12.77. Found: C, 43.57; H, 5.81; N, 15.01; Cl, 13.05. [α]<sub>D</sub><sup>20</sup> +11.5° (*c* 1.01, MeOH).

***N*<sup>4</sup>-Acetyl-5'-*O*-(triphenylmethyl)cytidine (33).** A slurry of *N*<sup>4</sup>-acetyl cytidine **32** (10.0 g, 35.1 mmol) and triphenylmethyl chloride (9.58 g, 34.4 mmol) in pyridine (50 mL) was heated at 45 °C under N<sub>2</sub> for 23 h. When the reaction was complete pyridine was removed by rotary evaporation until approximately 60% of the original reaction weight remained. The resultant viscous reaction solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and water (50 mL) and cooled to 5 °C. The acidity of the mixture was adjusted to pH 4.0 using 12 N HCl (10 mL) while keeping the temperature below 15 °C. The organic layer was concentrated and washed with saturated aqueous NaHCO<sub>3</sub> (50 mL), saturated aqueous NaCl (50 mL) and dried (MgSO<sub>4</sub>). The solvent was removed by rotary evaporation to give a foam that was triturated with MTBE (75 mL) to afford 17.0 g of **33** (77% purity,<sup>47</sup> 71% yield). mp 133 °C. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.17 (s, 3H), 3.46 (bs, 2H), 4.16 (bs, 1H), 4.25 (bs, 1H), 4.40 (s, 2H), 5.88 (s, 2H), 7.14-7.6 (m, 16H), 8.29 (d, *J* = 7.09 Hz, 1H), 9.64 (bs, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 24.9, 62.3, 70.2, 76.2, 84.2, 87.5, 92.3, 97.0, 127.4, 128.0, 128.6, 143.2, 144.7, 156.4, 162.6, 170.7; IR (CHCl<sub>3</sub>) 3401, 3064, 1723, 1652, 1557, 1491, 1482, 1381, 1308, 1238, 1106 cm<sup>-1</sup>; UV (MeOH) λ<sub>max</sub> 299 nm ε 6952; 248 nm ε 12816; 207 nm ε 50737. MS (FAB+) *m/z*: 528.3. Anal Calcd for C<sub>30</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>: C, 68.30; H, 5.54; N, 7.96. Found: C, 68.59; H, 5.73; N, 7.98. [α]<sub>D</sub><sup>20</sup> +36.2° (c 1.02, MeOH).

**5'-*O*-[Triphenylmethane-1-(2,3-anhydro-β-D-lyxofuranosyl)cytosine (31).** A solution of **33** (219.8 g, 61% purity,<sup>47</sup> 254 mmol) in THF (1 L) was cooled to -30 °C and treated with triethylamine (184 mL, 133.7 g, 1.320 mol), followed by methanesulfonyl chloride (94.3 mL, 139.6 g, 1.22 mol). After stirring at -20 °C for 35 min, the reaction was treated with aqueous 5 N NaOH (610 mL, 3.05 mol) and the resultant two-phased mixture stirred for 22 h at 25 °C. The epoxide **31** precipitated from the reaction mixture when the reaction was complete. The reaction slurry was cooled to 0 ° to 5 °C and neutralized with 5 N HCl (343 mL). The reaction mixture was weighed and the solvent removed *in vacuo* until the weight was reduced by approximately 25%. The resultant slurry was then cooled in an ice bath for 1.5 h and filtered using cold (0-5 °C) water (500 mL) and cold THF (400 mL) as a rinse. The solid was dried *in vacuo* oven at 50 °C to give 111.3 g of **31** (88% purity,<sup>47</sup> 82% yield). mp 155 °C. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.32-3.37 (dd, *J* = 5.67, 9.22 Hz, 1H), 3.46-3.51 (dd, *J* = 5.67, 8.51 Hz, 1H), 3.80 (d, *J* = 2.84 Hz, 1H), 3.98 (d, *J* = 2.84 Hz, 1H), 4.14-4.20 (t, *J* = 1.42 Hz, 1H), 5.65-5.72 (d, *J* = 7.09 Hz, 1H), 6.2 (s, 1H), 7.1-7.6 (m, 16H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 56.2, 56.4, 62.3, 82.8, 87.0, 94.6, 127.2, 127.9, 128.7, 128.8, 142.3, 143.6, 155.9, 165.9; IR (CHCl<sub>3</sub>) 3417, 3063, 3009, 1647, 1599, 1529, 1491, 1449, 1396, 1354, 1278, 1076, 900, 831 cm<sup>-1</sup>. Anal Calcd for C<sub>28</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.86; H, 5.36; N, 8.71. [α]<sub>D</sub><sup>20</sup> +14.0° (c 0.68, MeOH).

**1-[3-Deoxy-3'-*C*-nitrile-5'-*O*-(triphenylmethyl)-β-D-arabinopentofuranosyl]cytosine (35).** To a slurry of lithium hydride (6.07 g, 763 mmol) in THF (910 mL) at 0-5 °C under N<sub>2</sub> was added dropwise acetone cyanohydrin (83.7 mL, 89.8 g, 916 mmol) over 25 min while maintaining a reaction temperature below 5 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 75 min. The lithium cyanide solution was treated with **31** (140 g, 88% purity,<sup>47</sup> 264 mmol) and THF (450 mL) and heated to 65 °C for 2.5 h. On cooling to 0-5 °C the reaction was neutralized with 0.5 N HCl (1.3 L), diluted with EtOAc (2.2 L) and washed with a saturated aqueous solution of NaCl (400 mL). The organic layer was dried (MgSO<sub>4</sub>), and the solvent

removed *in vacuo* to give a solid, which was recrystallized from a 3:1 solution of EtOAc/tol (815 mL, 5 vols). The recrystallized solid was dried in a vacuum oven at 50 °C to give 69.3 g of **35** (87% purity,<sup>47</sup> 46% yield). mp 145 °C. Spectral data: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 3.24-3.40 (m, 2H), 4.23-4.32 (dt, *J* = 3.9 Hz, 1H), 4.72-4.80 (q, *J* = 6.03 Hz, 1H), 5.61-5.63 (d, *J* = 7.09 Hz, 1H), 6.20-6.22 (d, *J* = 5.67 Hz, 1H), 6.28-6.30 (d, *J* = 5.67 Hz, 1H), 7.0-7.5 (m, 17H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 37.5, 62.8, 73.1, 75.7, 84.2, 86.5, 93.1, 118.6, 127.2, 127.9, 128.1, 142.4, 143.2, 155.0, 165.4; IR (CHCl<sub>3</sub>) 3455, 3091, 1675, 1641, 1621, 1525, 1492, 1449, 1294, 1099, 1071, 998 cm<sup>-1</sup>; MS (FD) *m/z* 495 (M+H)<sup>+</sup>. Anal Calcd for C<sub>29</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>: C, 70.43; H, 5.30; N, 11.33. Found: C, 70.70; H, 5.33; N, 11.36. [α]<sub>D</sub><sup>20</sup> +42.7° (c 0.71, MeOH).

**3'-Cyano-2',3'-didehydro-2',3'-dideoxy-5'-O-(triphenylmethyl)cytidine (36).** A solution of **35** (5.00 g, 85% purity,<sup>32</sup> 8.6 mmol) in acetonitrile (20 mL) was treated with 1,1'-carbonyldiimidazole (1.97 g, 12.1 mmol) and 4-dimethylaminopyridine (DMAP) (0.12 g, 1.01 mmol). After stirring at 25 °C for 3 h, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with saturated aqueous NH<sub>4</sub>Cl (3 x 50 mL) and saturated aqueous NaCl (50 mL). The organic layer was dried (MgSO<sub>4</sub>), and the solvent was removed *in vacuo* to give 4.71 g of **36** (80% purity,<sup>47</sup> 92% yield). mp 223 °C. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.42-3.60 (dq, *J* = 10.99, 2.33 Hz, 2H), 4.92 (bs, 1H), 5.16-5.18 (d, *J* = 7.09 Hz, 1H), 6.70 (s, 1H), 7.10-7.15 (d, *J* = 2.84 Hz, 1H), 7.27-7.54 (m, 15H), 7.75-7.77 (d, *J* = 7.09 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 61.9, 84.4, 86.9, 89.3, 94.7, 111.4, 117.3, 126.7, 127.3, 127.9, 140.8, 141.2, 142.0, 154.8, 165.1; IR (CHCl<sub>3</sub>) 3065, 3010, 1731, 1662, 1647, 1491, 1449, 1403, 1278, 1118, 1067, 1045, 985 cm<sup>-1</sup>; HRMS (FAB) Calcd for C<sub>29</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub> 477.193300. Found 477.192666. [α]<sub>D</sub><sup>20</sup> +35.7° (c 1.00, MeOH).

**1-[5'-OTriphenylmethyl]-2',3'-dideoxy-3'-C-cyano-β-D-arabinopentofuranosylcytosine (37α/37β).** A solution of **36** (1.00 g, 80% purity,<sup>47</sup> 1.68 mmol) in EtOH (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was cooled to 0-5 °C and treated with NaBH<sub>4</sub> (0.05 g, 2.10 mmol). The reaction was allowed to warm to 25 °C, stirred for 2 h then diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and washed with saturated aqueous NH<sub>4</sub>Cl (2 x 40 mL) and saturated aqueous NaCl (40 mL). The organic layers was dried (MgSO<sub>4</sub>), and the solvent was removed *in vacuo* to give 0.96 g of **37α/37β** (72% purity,<sup>47</sup> 86% yield, α:β, 1:4 mixture by HPLC). The β-diastereomer can be precipitated directly by the following protocol: Treatment of **37** (3.0 g) with 1:1 EtOAc:toluene (30 mL) at 25 °C provided a solution which was concentrated to a white slurry. This was stirred for 3 h and then filtered to give a 2.1 g of a white solid. HPLC analysis indicated a β:α ratio of 99:1. **37β** characterization: mp 157 °C. Spectral data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.35-2.42 (dt, *J* = 3.19 Hz, 1H), 2.74-2.88 (qt, *J* = 7.09 Hz, 1H), 3.24-3.26 (m, 1H), 3.45-3.52 (dd, *J* = 5.32, 9.58 Hz, 1H), 3.66-3.74 (dd, *J* = 5.67, 9.93 Hz, 1H), 4.16-4.24 (q, *J* = 5.67, 10.99 Hz, 1H), 5.74-6.00 (d, *J* = 7.09 Hz, 1H), 6.10-6.16 (dd, *J* = 6.47, 3.55 Hz, 1H), 6.66 (s, 2H), 7.22-7.26 (m, 15H), 7.72-7.72 (d, *J* = 7.45 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 30.8, 37.7, 63.7, 79.4, 86.0, 87.9, 95.1, 118.8, 127.7, 128.4, 129.0, 140.2, 143.7, 166.4; IR (CHCl<sub>3</sub>) 3417, 3064, 3010, 1657, 1531, 1449, 1354, 1281, 1080 cm<sup>-1</sup>; UV (MeOH) λ<sub>max</sub> 270 nm ε 9653; 206 nm ε 55428; MS (FD) *m/z* 479 (M)<sup>+</sup>. Anal

Calcd for  $C_{29}H_{26}N_4O_3$ : C, 72.79; H, 5.48; N, 11.71. Found: C, 72.52; H, 5.51; N, 11.65.  $[\alpha]^{20}_D +50.8$  (c 1.00, MeOH).

**3'-Cyano-2',3'-dideoxy-5'-O-(triphenylmethyl)cytidine (37 $\alpha$ /37 $\beta$ ), a one-pot procedure.** A solution of **35** (2.00 g, 85% purity,<sup>47</sup> 3.4 mmol) in acetonitrile (10 mL), was treated with 1,1'-carbonyldiimidazole (0.79 g, 4.9 mmol) and 4-dimethylaminopyridine (DMAP) (49 mg, 0.4 mmol). The reaction was stirred at 25 °C for 3 h, then diluted with ethyl alcohol (5 mL) and cooled to 0-5 °C. To the resultant solution was added  $NaBH_4$  (0.16 g, 4.2 mmol) and the reaction allowed to warm to 25 °C for 2 h. A 1:4 mixture of  $\alpha$ : $\beta$  3' nitriles (37 $\alpha$ /37 $\beta$ ) was formed as determined by HPLC. The reaction solution was diluted with  $CH_2Cl_2$  (60 mL) and washed with saturated aqueous ammonium chloride (3 x 75 mL). The organic layers were dried ( $MgSO_4$ ), and the solvent was removed *in vacuo* to give 1.77 g of **37** (62% purity,<sup>47</sup> 67% yield).

**2',3'-Dideoxy-3'-formyl-5'-O-(triphenylmethyl)cytidine (38).** A solution of **37** (5.00 g, 10.4 mmol) in  $CH_2Cl_2$  (50 mL) was cooled to -13 °C and DIBAL-H (1.00 M in toluene, 26.1 mL, 26.0 mmol) was added over 10 min maintaining the temperature below -4 °C. The thick reaction mixture was stirred at -10-0 °C for 1 h, then carefully quenched with 1 N HCl (80 mL), maintaining the temperature below 25 °C. The mixture was allowed to completely warm to 25 °C and extracted with 1 N HCl (40 mL) and saturated aqueous NaCl (40 mL). The organic layer was dried ( $MgSO_4$ ) and the solvent removed *in vacuo* to afford 4.53 g of **38** as a foam. The foam was redissolved in  $CH_2Cl_2$  (45 mL) and silica gel (20 g) was added to the solution. The mixture was stirred overnight at room temperature. The silica gel was filtered off and rinsed with 200 mL of MeOH/ $CH_2Cl_2$  mixture (1:3). The filtrate was concentrated to dryness and the residue (4.35 g) redissolved in  $CH_2Cl_2$  (30 mL). EtOAc (10 mL) was added dropwise to the solution to precipitate the product. The slurry was stirred at room temperature for 4 h, cooled at 0 °C for 1 h and then filtered. The product was washed with 5 mL of 1:1  $CH_2Cl_2$ /EtOAc and dried overnight *in vacuo* at 50 °C to afford 2.97 g (59%) of **38** as a 93:7 mixture of epimers (determined by  $^1H$  NMR). mp 116-121 °C (dec). Spectral data:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  2.20-2.80 (m, 2H), 3.20-3.62 (m, 3H), 4.34-4.39 (m, 1H), 5.40 (d,  $J$  = 7.1 Hz, 1H), 6.08-6.15 (m, 1H), 7.17-7.44 (m, 17H), 7.75 (d,  $J$  = 7.3 Hz, 1H), 9.50 (s, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  34.6, 50.4, 63.2, 79.8, 86.2, 94.2, 127.5, 128.1, 128.6, 140.9, 143.3, 155.8, 165.6, 171.4, 198.7; IR (KBr) 2928.3, 1724.6, 1643.6, 1490.2, 1448.7, 1280.9, 1074.5  $cm^{-1}$ ; UV (MeOH)  $\lambda_{max}$  206 nm,  $\epsilon$  48549; 274 nm,  $\epsilon$  8459; MS (FD)  $m/z$  482 (100%,  $M^+$ ).  $[\alpha]^{20}_D +62.71^\circ$  (c 0.66,  $CHCl_3$ ).

**2',3'-Dideoxy-3'-hydroxymethyl-5'-O-(triphenylmethyl)cytidine (23).** To a solution of **38** (2.50 g, 5.20 mmol) in  $CH_2Cl_2$  (12 mL) was added EtOH (12 mL) and the solution was cooled to 2 °C.  $NaBH_4$  (0.09 g, 2.0 mmol) was added in one portion. The reaction mixture was stirred for 30 min at 0-5 °C. The solution was then stripped to a residue which was partitioned between  $CH_2Cl_2$  (25 mL) and aqueous 1 M sodium bisulfate solution (15 mL). The aqueous layer was separated and the organic layer washed with saturated aqueous sodium bicarbonate (15 mL). The organic layer was dried ( $MgSO_4$ ) and the solvent removed *in vacuo* to give 2.08 g (83%) of **23** as a foam. Spectral data:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  ppm 2.16-2.23 (m, 1H), 2.32-2.56 (m, 2H), 3.34-3.44 (m, 1H), 3.45-3.62 (m, 2H), 3.94-3.97 (m, 1H), 5.41 (d,  $J$  = 7.4 Hz, 1H), 6.02-6.05 (m, 1H), 7.17-7.53 (m, 17H), 8.03 (d,  $J$  = 7.4 Hz, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  ppm 37.4, 40.3,



62.1, 63.4, 82.6, 86.5, 87.3, 94.1, 127.3, 128.0, 128.6, 128.7, 141.4, 143.5, 155.9, 165.5; IR (KBr) 3339.2, 2872.4, 1643.6, 1489.2, 1448.7, 1281.9, 1114.0  $\text{cm}^{-1}$ ; UV (MeOH):  $\lambda_{\text{max}}$  206 nm,  $\epsilon$  46743; 273 nm,  $\epsilon$  7830. MS (FD)  $m/z$  484 ( $M^+$ ). Anal. Calcd for  $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_4$ : C, 72.03; H, 6.05; N, 8.69. Found: C, 72.06; H, 6.17; N, 8.58.  $[\alpha]_{\text{D}}^{20} +55.68^\circ$  ( $c$  0.29, MeOH).

**2',3'-Dideoxy-3'-(hydroxymethyl)cytidine Hydrochloride (1).** A solution of **23** (0.92 g, 72% purity,<sup>47</sup> 1.4 mmol) in methanol (8 mL) was cooled to 0 °C and anhydrous HCl was bubbled into the reaction for 5-10 seconds. The reaction was allowed to come to room temperature over 2 hr during which time the product precipitated. The reaction mixture was diluted with EtOAc (8 mL) and the reaction stirred 15 minutes before the solid was collected by vacuum filtration and washed with EtOAc (5 mL) to give 0.33 g of **1** as a white solid (92% purity,<sup>47</sup> 80% yield) and as a 95:5 mixture of epimers (determined by HPLC). mp 153-157 °C. Spectral data:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ )  $\delta$  2.25-2.40 (m, 3H), 3.60 (d,  $J = 5.5$  Hz, 2H), 3.69 (dd,  $J = 5.0, 12.7$  Hz, 1H), 3.86 (dd,  $J = 2.7, 12.7$  Hz, 1H), 3.97-4.04 (m, 1H), 6.01-6.03 (m, 1H), 6.14 (d,  $J = 7.9$  Hz, 1H), 8.13 (d,  $J = 8.0$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  35.9, 39.3, 61.1, 61.3, 85.0, 86.5, 93.2, 114.9, 147.0, 159.8; IR (KBr) 3373, 3107, 2895, 1711, 1663, 1545, 1385, 1273, 1113, 1056  $\text{cm}^{-1}$ ; UV (EtOH):  $\lambda_{\text{max}}$  275,  $\epsilon$  8923. MS (FD)  $m/z$  242. Anal. Calcd for  $\text{C}_{10}\text{H}_{16}\text{ClN}_3\text{O}_4$ : C, 43.25; H, 5.81; N, 15.13; Cl, 12.77. Found: C, 43.39; H, 5.66; N, 14.91; Cl, 12.85.  $[\alpha]_{\text{D}}^{20} +86.8$  ( $c$  1.01, MeOH).

**2',3'-Dideoxy-3'-hydroxymethylcytidine (1) by hydroformylation:** To a 100 mL stainless steel bomb (Parr 4591 Micro Reactor®) was charged 1.0 g of **46** (3.4 mmol, 1.0 equiv), 50 mg of  $\text{Rh}(\text{CO})_2\text{acac}$  (0.19 mmol, 0.056 equiv) and 200 mg of triphenylphosphine (0.76 mmol, 0.22 equiv). The reagents were dissolved in 50 mL of dry THF. The bomb was pressurized to 80 psi with a 1:1 mixture of  $\text{H}_2$  and CO and heated to 60 °C for 48 h. to afford *N*<sup>4</sup>-Acetyl-5'-*O*-acetyl-2',3'-dideoxy-3'-formylcytidine **47** in 32% yield as determined by  $^1\text{H}$  NMR analysis using dimethyl terephthalate ( $\delta$  8.10 (s, 4H) in  $\text{THF}-d_8$ ) as an internal standard. Spectral data:  $^1\text{H}$  NMR (300 MHz,  $\text{THF}-d_8$ )  $\delta$  2.05 (s, 3H), 2.13 (s, 3H), 2.37 (m, 1H), 2.81 (m, 1H), 3.12 (m, 1H), 3.90-4.10 (m, 2H), 4.20-4.40 (m, 1H, d, 1H,  $J = 7.4$  Hz), 5.98 (m, 1H), 8.07 (d, 1H,  $J = 7.4$  Hz), 9.63 (s, 1H), 10.05 (bs, 1H). The THF was removed *in vacuo* and the residue triturated with toluene (2 x 30 mL) to remove the triphenylphosphine and triphenylphosphine oxide. The residue was dissolved in 10 mL of EtOH, cooled to 0 °C and treated with  $\text{NaBH}_4$  (235 mg, 6 mmol). The reaction was allowed to warm to rt for 1 hour, then recooled 0 °C and treated with acetone to destroy excess  $\text{NaBH}_4$ . The reaction was neutralized with 1.0 *N* HCl and the solvent removed *in vacuo* to afford 1.46 g of material which was purified by column chromatography (75  $\text{CH}_2\text{Cl}_2$ : 25 MeOH: 2  $\text{Et}_3\text{N}$  to 35  $\text{CH}_2\text{Cl}_2$ : 15 MeOH: 1  $\text{Et}_3\text{N}$ ) to afford 164 mg of **1** as a 94:6 ratio of  $\alpha$ : $\beta$  epimers (20 % yield from **46**). Spectral data:  $^1\text{H}$  NMR ( $\text{MeOD}-d_4$ )  $\delta$  2.00-2.15 (m, 1H), 2.23-2.40 (m, 2H), 3.58 (dd, 2H,  $J = 2.4$  Hz,  $J = 5.6$  Hz), 3.71 (dd, 1H,  $J = 4.2$  Hz,  $J = 12.4$  Hz), 3.88 (m, 2H), 5.84 (d, 1H,  $J = 7.4$  Hz), 6.02 (m, 1H), 8.10 (d, 1H,  $J = 7.4$  Hz); ( $\text{D}_2\text{O}$ )  $\delta$  2.20-2.41 (m, 3H), 3.65 (d, 2H,  $J = 5.5$  Hz), 3.73 (dd, 1H,  $J = 5.5$  Hz,  $J = 12.5$  Hz), 3.89 (dd, 1H,  $J = 2.8$  Hz,  $J = 12.5$  Hz), 4.0 (m, 1H), 6.03 (d, 1H,  $J = 7.6$  Hz), 6.09 (dd, 1H,  $J = 4.0$  Hz,  $J = 6.5$  Hz), 7.91 (d, 1H,  $J = 7.6$  Hz);  $^{13}\text{C}$  NMR ( $\text{EtOH}-d_6$ )  $\delta$  36.9, 40.5, 62.1, 62.2, 85.0, 86.6, 94.4, 141.7, 157.1, 166.6.  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ )  $\delta$  35.6, 40.7,

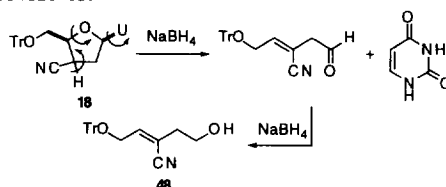
48.8, 62.5, 63.0, 84.5, 86.8, 96.5, 142.3, 158.3, 168.8; IR (KBr) 3424.9, 1645.6, 1489.6, 1108.5  $\text{cm}^{-1}$ ; MS [FAB Exact Mass M+H] Calcd for  $\text{C}_{10}\text{H}_{15}\text{O}_4 + \text{H}$ : 242.1141; Found: 242.1140

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38. HPLC conditions for analysis of **16**, **17**, **18α**, and **18β**: Supelco LC-ABZ (25 cm), 40 °C, gradient of 50% acetonitrile/50% 10 mM phosphate buffer (pH 7) for 3 min, increase to 80% acetonitrile over 12 min and hold for an additional 5 min, 1.5 mL/min, 210 nm. *t<sub>R</sub>* = 6.3 min (**16**), 7.0 min (**18β**), 7.1 min (**18α**), 7.9 min (**17**). Purities determined vs. standards of known purity.
39. The product is a single compound by HPLC which contains 3.4% EtOAc and 5.6% toluene (by wt., <sup>1</sup>H NMR).
40. The product contains 2.8 mol% related impurities (HPLC), 7.2% toluene, and 2.3% EtOAc (by wt., <sup>1</sup>H NMR).
41. The ratio of **18α** and **18β** can be determined either by <sup>1</sup>H NMR (**18α**, doublet at 5.40 ppm; **18β**, doublet at 5.60 ppm) or by HPLC (see Ref 36).
42. The product is a single isomer which contains 8% EtOAc (by wt., <sup>1</sup>H NMR).
43. A reference sample of **18α** was prepared in 63% yield by reduction of the phenylthionocarbonate derivative of **16** (tris(trimethylsilyl)silane, AIBN, toluene, 80 °C, 2 h).

44. The solvent volumes and the inverse quench are critical to avoid a gelatinous suspension of aluminum salts upon workup.
45. HPLC conditions for analysis of **20**, **21**, **22**, and **23**: Supelco LC-ABZ (25 cm), 40 °C, gradient of 40% acetonitrile/60% 12 mM phosphate buffer (pH 7) for 5 min, increase to 60% acetonitrile over 10 min and hold for an additional 10 min, 1.5 mL/min, 210 nm.  $t_R$  = 10.8 min (**23**), 13.2 min (**20**), 14.8 min (**22**), 16.9 min (**21**). Purities determined vs. standards of known purity.
46. HPLC conditions for **1**: Supelco LC-ABZ (25 cm), 40 °C, gradient, 100% 25 mM phosphate buffer (pH 7) for 1 min, increase to 40% acetonitrile over 20 min, 1.5 mL/min, 205 nm and 275 nm.  $t_R$  = (7.3 min, **1**), 6.7 min (*C*-3'  $\beta$ -isomer), 5.3 min (*C*-1' $\alpha$ -isomer).
47. HPLC conditions for analysis of **33**, **34**, **31**, **35**, **36**, **37**, **23**, and **1**: Supelcosil LC-ABZ (25 cm), gradient of 40% acetonitrile/60% pH 7 phosphate buffer for 5 min to 70/30 over 5 min, hold for 5 min at 70/30 then return to 40/60 over 5 min, 1.5 mL/min, 210 nm. Purities determined vs. standards of known purity.

(Received in USA 14 March 1997; revised 2 May 1997; accepted 5 May 1997)