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# A NEW SYNTHESIS OF 2',3'-DIDEOXYNUCLEOSIDES FOR AIDS CHEMOTHERAPY

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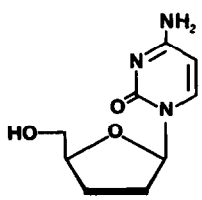
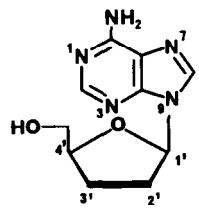
SUMMARY: Dideoxynucleosides were prepared in high optical purity from L-glutamic acid. The condensation reactions between activated 2,3-dideoxypentofuranoses and silylated purines or pyrimidines afforded separable ß/α mixtures of dideoxynucleosides.

2',3'-Dideoxynucleosides have found utility mainly as reagents for DNA sequencing[1], and consequently are commercially available in only small amounts at very high prices[2]. The recent discovery[3] that some dideoxynucleosides selectively inhibit *in vitro* the infectivity and cytopathic effect of the HTLV-III (HIV) virus has sparked renewed interest in this class of compounds, and dideoxycytidine, **1**, is now being clinically evaluated as treatment against Acquired Immune Deficiency Syndrome (AIDS). A general and economically attractive synthesis of dideoxynucleosides has therefore become an important goal.

2',3'-Dideoxynucleosides are typically synthesized from 2'-deoxynucleosides *via* Barton-type deoxygenation reactions[4], or from intact nucleosides by multistep routes involving deoxygenation reactions to 2',3'-unsaturated dideoxynucleosides[5], which are then hydrogenated. Approaches through ketonucleosides[6] and a photoreductive process[7] have also been described.




**1**

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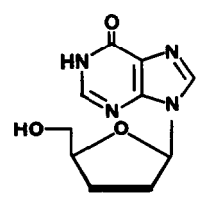
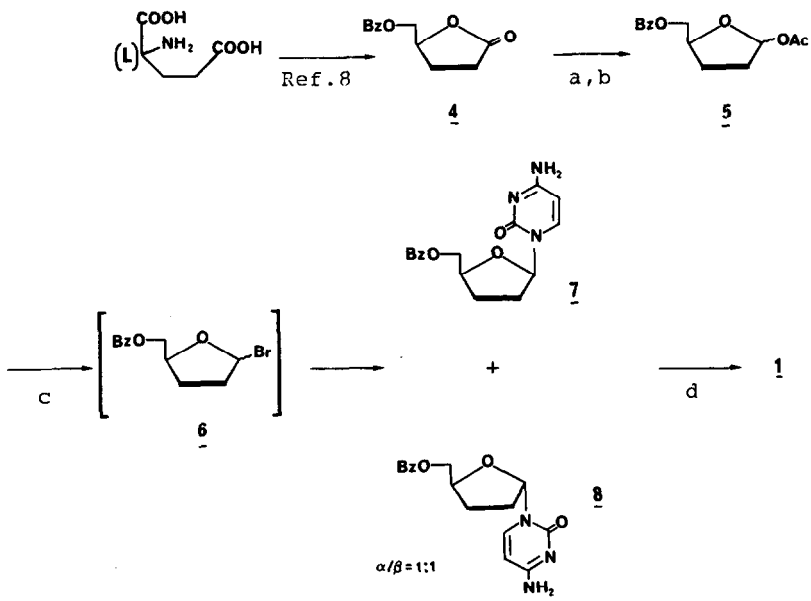



**3**

We envisioned producing dideoxycytidine (ddC), 1, dideoxyadenosine (ddA), 2, and dideoxyinosine (ddI), 3, from a stereochemically less complex, and much cheaper, precursor, i.e. L-glutamic acid (Scheme I).

The known, stereospecific deamination-lactonization reaction, followed by standard manipulations[8], gave lactone 4. Selective reduction[9] with disiamylborane followed by oxidative hydrolysis and acetylation gave a good yield of acetate 5 as a mixture of anomers[10].

Scheme I

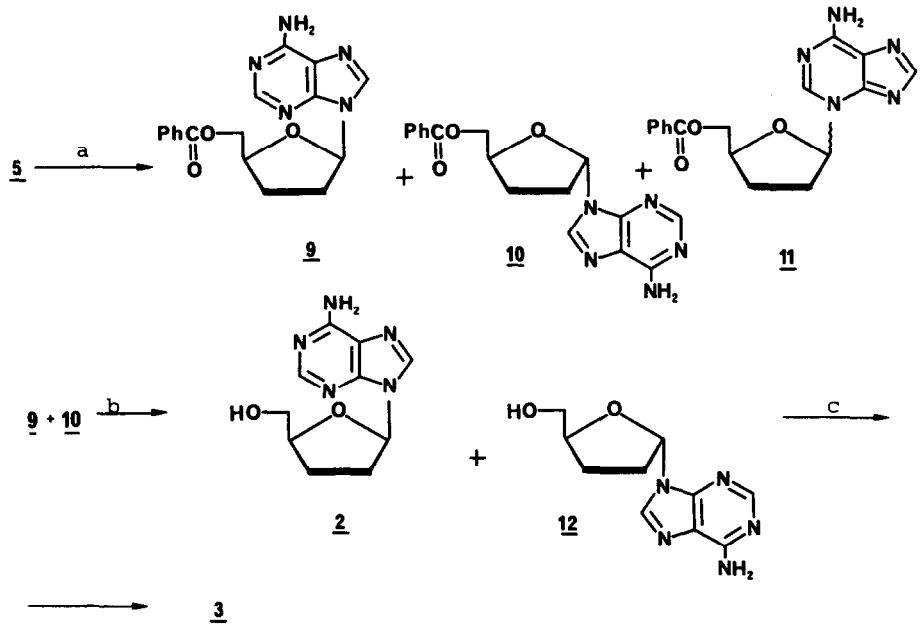



Reagents: (a) disiamylborane, THF, then $H_2O_2$, 50°C; 94% (b) $Ac_2O$, pyridine, RT; 92% (c) $Me_3SiBr$, $CH_2Cl_2$, 0°C, then bis-silylcytosine, -78°C -> RT; 44% yield for 7 after chromatography; (d) $NH_3$/MeOH quant.

Treatment with trimethylsilylbromide[11] cleanly afforded a mixture of anomeric bromides[12] 6. Addition of silylated cytosine to this solution gave a separable mixture[13] of protected ddC and its α anomer in a 1:1 ratio[14]. Standard deprotection afforded ddC[15].

A similar approach (Scheme II) was successful for purine nucleosides. The coupling reaction was carried out at room temperature in order to minimize formation of a side-product, presumably the N-3 alkylation product[16] 11.

Scheme II




Reagents: (a) TMSBr, 0°C; then bis-silyladenine, RT; 63% yield for 9 + 10 (b) $NH_3$, MeOH, RT, quant. yield for 2 + 12 (c) adenosine deaminase, $H_2O$; 33% yield for 3 after crystallization.

Dideoxyinosine, another potentially useful antiviral agent, was prepared by subjecting the mixture of 9 and 10 to a solution of the enzyme adenosine deaminase[17], which quantitatively deaminated the ß-anomer, leaving the α unreacted. Consequently ddI, 3, was obtained by direct crystallization of the reaction crude from methanol[18].

The methodology described in this letter should make a variety of 2',3'-dideoxynucleosides easily available at very low cost.

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2. For example, Aldrich Chemical Company sells 2',3'-dideoxycytidine at $42.00/100 mg.
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10. All new compounds gave satisfactory spectral and analytical data. The α/ß ratio for 5 was 55:45 and was assigned on the basis of NMR considerations. See: K.J. Stone, R.D. Little J.Am.Chem.Soc., 1985, 107, 2495.
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12. Use of 1.2 eq. of TMSBr was needed to achieve >90% conversion. The anomeric protons in the NMR ($CDCl_3$) at δ 6.80; 6.70 (α/ß ~ 60:40) were diagnostic. These anomeric bromides were too unstable for isolation.
13. Separation was effected by preparative reverse phase chromatography (C-18, elution with water/methanol mixtures)
14. The ß/α ratio is very sensitive to the substrate used and the experimental conditions,and some selectivity in favor of the ß anomer can be achieved. We are currently looking for conditions that will maximize this ratio.
15. Dideoxycytidine so obtained had $^1$H-NMR, m.p. and optical rotation in agreement with literature values. See ref. 5a.
16. Assignment was made on the basis of the $^1$H-NMR and UV spectra. Also treatment of isolated 11 with acids gave in variable yield isomerization to the N-9 alkylated compounds 9 and 10. For a precedent, see: M. Miyaki, S. Shimizu Chem.Pharm.Bull., 1970, 18, 732.
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18. Dideoxyadenosine had $[\alpha]_D^{23}$ -25.3° (C 1.00, $H_2O$); lit.[19]: $[\alpha]_D^{25}$ -25.2° (C 1.01, $H_2O$). Dideoxyinosine had IR (KBr) 1700 $cm^{-1}$; UV($H_2O$): $\lambda_{max}$ 240 nm. NMR ($CDCl_3$, 360 MHz) anomeric proton at δ 6.185 (dd, J = 6.8; 3.3 Hz); $[\alpha]_D^{23}$ -28.7° (C 1.00, DMF).
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