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RAPID SYNTHESIS OF 2',3'-DIDEOXYCYTIDINE (ddC) FROM A SIMPLE ACHIRAL PRECURSOR

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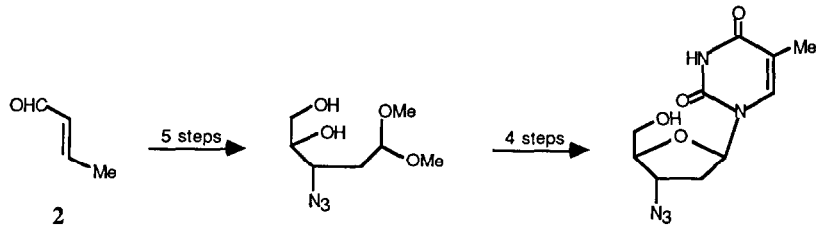
Abstract: The antiviral nucleoside analogue, 2',3'-dideoxycytidine (ddC) **1**, has been synthesized in nine steps and good overall yield from crotonaldehyde **2** via the chiral epoxy alcohol **4** prepared by a Sharpless epoxidation.

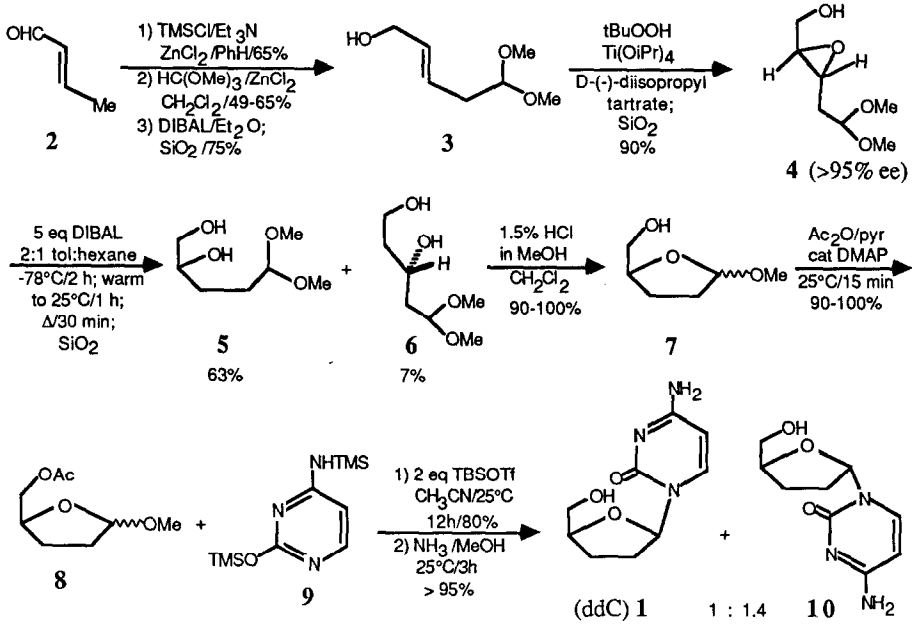
Modified nucleosides often show very potent biological activity. In particular, 2'-deoxynucleosides which do not have the normal hydroxyl group in the 3' position generally show strong antiretroviral properties (e.g., AZT, FdT, ddI, etc.). Among these, one of the most promising candidates for treatment of HIV infections is 2',3'-dideoxycytidine, ddC, **1**.[2,3] Although many syntheses of ddC have been developed, nearly all begin with an intact nucleoside, e.g., cytidine, 2'-deoxycytidine, or 2',3'-dideoxyuridine. To date, only two groups have synthesized **1** from non-nucleosidic materials and both used L-glutamic acid as their starting material.[4] We now report the efficient total synthesis of ddC **1** from simple achiral precursor, crotonaldehyde **2** (Scheme).

We recently reported the efficient conversion of crotonaldehyde **2** into the active anti-AIDS drug AZT by a nine-step route in which the required asymmetry was induced via a Sharpless epoxidation.[5] A three-step sequence (silylation, aldol-type condensation on orthoformate, and aldehyde reduction) was used to prepare (*E*)-5,5-dimethoxy-



2 **AZT**

2-pentenol **3** from crotonaldehyde.[6] Sharpless epoxidation using D-(-)-diisopropyl tartrate afforded up to 90% yield of 2R,3R 3-(2,2-dimethoxyethyl)oxiranemethanol **4** in greater than 95% ee. Addition of this epoxy alcohol **4** in toluene to 5 eq of DIBAL in hexane (-78° C, 2 h; warm to 25° C over 1 h; reflux 1/2 h) produced, after flash chromatography, a 63% yield of the desired 1,2-diol **5** and 7% of the undesired 1,3-diol **6** along with about 10% of the methyl glycoside **7**.[7] Cyclization of **5** to a 1:1 mixture of the α and β anomers of methyl D-2,3-dideoxy-ribofuranoside **7** was effected by our earlier conditions,[5] namely addition of a few drops of 1.5% HCl in methanol to a solution of **5** in dichloromethane at 25° C for 5 min, affording **7** in 90-100% crude yield. Acetylation of the alcohol was easily accomplished giving the acetate **8** in nearly quantitative yield. The ^{1}H NMR data for the two anomers of **8** matched that reported in the literature.[8] Vorbrüggen coupling[9] of **8** with 2 eq of *N,O*-bis(trimethylsilyl)cytosine **9** using 2 eq of *t*-butyldimethylsilyl triflate (TBSOTf) as the promoter in acetonitrile afforded a 65-70% yield (80% corrected for recovered starting material) of 5'-acetyl-2',3'-dideoxycytidine as a 1.4:1 mixture of α:β anomers.[10,11] Removal of the acetate group (methanolic ammonia) afforded a quantitative yield of 2',3'-dideoxycytidine **1** and its α-anomer **10**. The ^{1}H NMR of **1** in D_2O matched that reported in the literature for ddC in this solvent.[12]



Scheme

Thus this route makes ddC **1** available in 9 steps and good overall yield from crotonaldehyde **2**. The use of modified bases in the coupling with **8** should allow for the preparation of various dideoxynucleosides having unusual bases in place of the normal ones. Finally by using the L-enantiomer of the dialkyl tartrate in the epoxidation of **3**, one should be able to easily prepare the L-enantiomer of methyl 2,3-dideoxyribofuranosides such as **7** and **8** and the L-enantiomers of the dideoxynucleosides, some of which, e.g., L-ddC, show moderate activity against HIV in CEM cells.[13] Further work on the preparation of other modified nucleosides is currently underway.[14]

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6. The sequence can be shortened by a step by purchasing 1-(trimethylsilyloxy)-1,3-butadiene (available from Aldrich) rather than preparing it from crotonaldehyde **2**.
7. On a small scale (~50mg), our best yields for this process were 60-65% of **5**, 7-8% of **6**, and 10-12% **7**, thus implying a conversion of **4** into **5** and **7** of 70-77%.
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10. We have not made any attempts to improve the ratio of α:β anomers in this Vorbrüggen coupling by changing the Lewis acid[4b] or by using other derivatives, e.g., the *N*-acetyl derivative, of bis-silylcytosine,[11] methods shown to work in similar systems.

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