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A CYCLOPROPANO ANALOG OF 2',3'-DIDEOXYCYTIDINE: STEREOSELECTIVE FORMATION OF A [3,1,0] BICYCLIC SYSTEM *via* HOMOLOGOUS FERRIER REACTION

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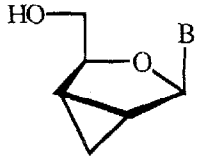
Summary: A synthesis of 2',3'-α-methylene-2',3'-dideoxycytidine is described in which the [3,1,0] bicyclic system and the glycosidic linkage were constructed simultaneously.

Reverse transcriptase inhibitors have thus far proven to be the most effective therapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS)[1]. The most promising agents of this class of drugs are 2',3'-dideoxynucleosides, such as 3'-deoxy-3'α-azidothymidine (AZT) and 2',3'-dideoxycytidine (ddC),[2] which are capable of undergoing 5'-phosphorylation by host kinases but teleologically incapable of DNA chain continuation.

As part of our program concerned with finding new types of dideoxynucleosides with anti-HIV activity,[3] we sought to develop a new strategy for three-membered ring construction which could allow us to prepare a novel type of nucleosides, 2',3'-α-methylene-2',3'-dideoxynucleosides **1**. In order to construct the bicyclic system, we could start either from a five-membered ring or from a three-membered ring. However, neither approach assures selective formation of the desired α-stereoisomer. Therefore, we chose to start with the six-membered perimeter of this [3,1,0] bicyclic ring system.



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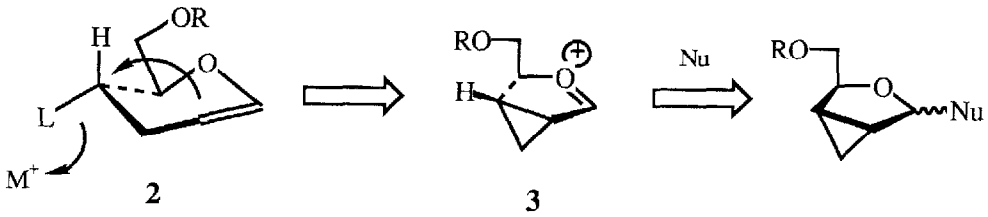
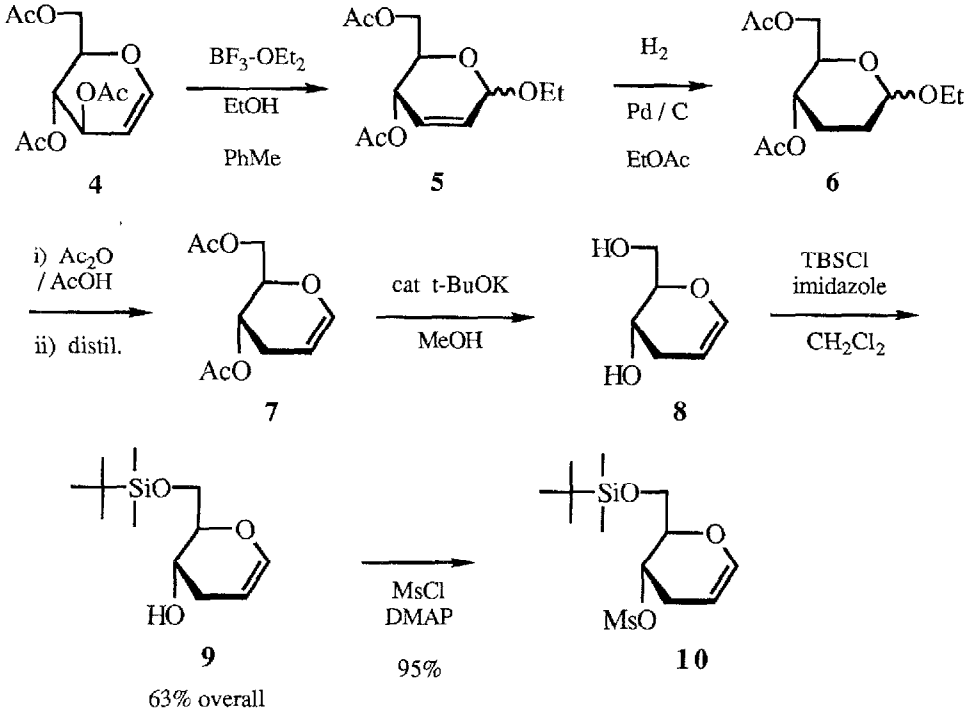


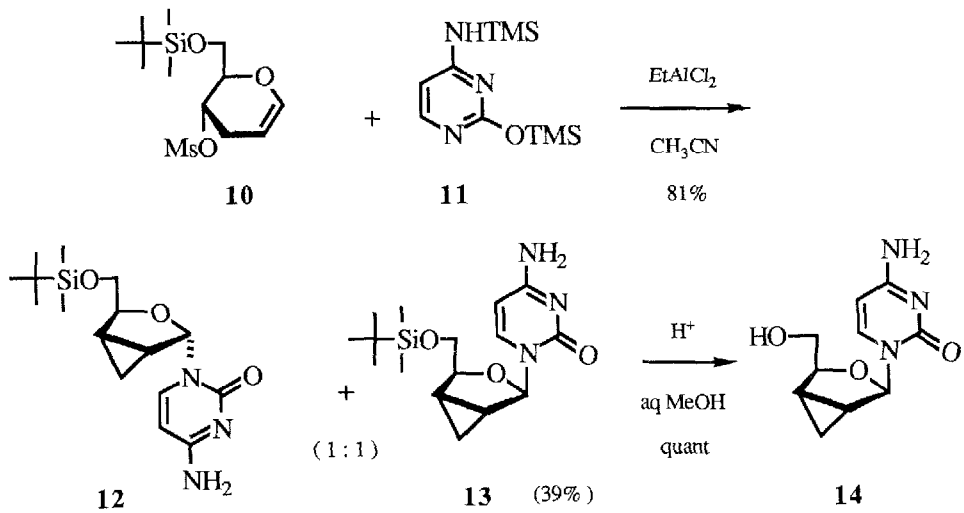
2 3

Our synthesis plan centered on compound **2** with its enol ether and a leaving group at C-4. The enol ether could displace the leaving group in a S_N2 like manner to form the bicyclic cation **3** with the desired stereochemistry, and which could be trapped by a nucleophile. If the nucleophile is a pyrimidine or purine base, we could obtain the desired nucleoside in one step. The implementation of this plan starts with tri-O-acetyl-D-glucal **4**, from which the key precursor **10** is prepared in 60% overall yield. The first step (**4** --->**5**) is a Ferrier reaction[4] in which an acetoxy group is replaced by an ethoxy group in a S_N2' like manner.



The crude unsaturated sugar **5** was hydrogenated to give crude dideoxypyranoside **6**. Treatment of **6** with a refluxing mixture of AcOH-Ac_2O overnight followed by distillation at 5 mm Hg[5] afforded the pure deoxyglucal **7**.[6] Hydrolysis to **8** followed by selective protection of the primary hydroxy group afforded pure **9** (after flash chromatography) in 63% overall yield. The secondary hydroxy group was activated as a mesylate to give the key compound **10** in 95% yield.

The mesylate **10** did not react with bis-TMS-cytosine **11** at room temperature. Therefore, more drastic conditions were employed: two equivalents of $EtAlCl_2$ and **11** in refluxing acetonitrile. After 48 hours of reaction, an α/β anomeric mixture (1:1) of nucleosides **12** and **13**[7] was obtained in 81% yield after flash chromatography. The desired β-anomer **13** was easily isolated by recrystallization from $CHCl_3$-MeOH-EtOAc in 39% yield based on **10**. The deprotection of **13** (p-TsOH in aq. methanol, then OH^--resin) afforded the cyclopropano analog of ddC **14**[8] in a quantitative yield.

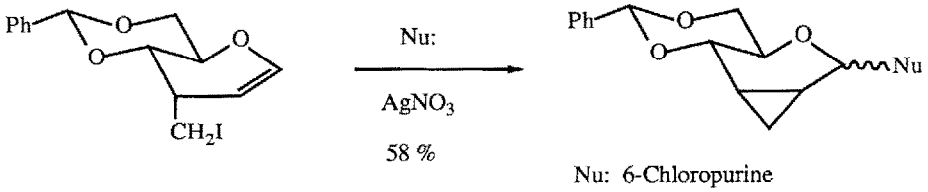


Although compound **14** shows only weak anti-HIV activity, the novel, stereoselective bicyclic system-forming process[9] described here promises to provide an efficient route to a variety of cyclopropano analogs of dideoxynucleosides.

Acknowledgement. The encouragement and advice provided by Dr. David L. Coffen is greatly appreciated.

References and Notes:

1. R. Dagani, *C&E News*, 1987, November 23, p. 41.
2. T. R. Webb, H. Mitsuya, S. Broder, *J. Med. Chem.*, 1988, *31*, 1475 and references cited therein.
3. M. Okabe, R.-C. Sun, S. Y.-K. Tam, L. J. Todaro, D. L. Coffen, *J. Org. Chem.*, 1988, *53*, 4780.
4. R. J. Ferrier, N. Prasad, *J. Chem. Soc. (C)*, 1969, 570.
5. After the treatment of **6** in AcOH-Ac_2O, the ethoxy group of **6** was replaced by an acetoxy group along with the formation of **7**. The acetoxy group was eliminated during distillation; bath temp. 105-140° at 5 mm Hg. Use of a strong acid, such as p-TsOH, leads to decomposition of **7**.
6. Alternatively, compound **7** can be prepared by $LiAlH_4$ reduction of **5** (refluxing dioxane) followed by acetylation. B. Fraser-Reid, B. Radatus, *J. Am. Chem. Soc.*, 1970, *92*, 6661.
7. The stereochemistry of products were assigned on the basis of their ^1H NMR spectra; **12**: $J_{1',2'}$=3.1 Hz, $J_{3'4'}$=0 Hz. **13**: $J_{1',2'}$=0 Hz, $J_{3',4'}$=0 Hz.
8. **14**: mp 230°C (dec); $[\alpha]_D$ -36.0° (c=0.49, MeOH); UV (water) 270 nm (ε 8,640); NMR (DMSO-d_6) δ 0.32 (dt, J=4.6 and 4.3 Hz, 1H), 0.91 (dt, J=4.6 and 8.2 Hz, 1H), 1.88 (m, 2H), 3.40 (m, 2H), 3.92 (t, J=5.8 Hz, 1H), 4.96 (t, J=5.4 Hz, 1H), 5.70 (d, J=7.4 Hz, 1H), 5.84 (s, 1H), 7.08 (bs, 1H), 7.15 (bs, 1H), 7.84 (d, J=7.4 Hz, 1H). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C 53.81; H, 5.87; N,18.82. Found: C, 53.74; H, 5.81; N, 18.84.
9. A related reaction has been described, in which a [4,1,0] bicyclic system was constructed from a six-membered ring. S. Y.-K. Tam, B. Fraser-Reid, *Can. J. Chem.*, 1977, *55*, 3996.



Nu: 6-Chloropurine

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