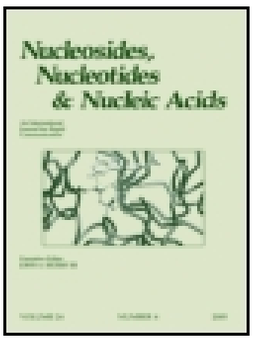


Nucleosides and Nucleotides

ISSN: 0732-8311 (Print) (Online) Journal homepage: http://www.tandfonline.com/loi/lncn19

A Stereoselective Method for the Direct Preparation of 2'-Deoxycytidine

Douglas P. Kjell

To cite this article: Douglas P. Kjell (1997) A Stereoselective Method for the Direct Preparation of 2'-Deoxycytidine, Nucleosides and Nucleotides, 16:3, 301-303, DOI: 10.1080/07328319708001350

To link to this article: http://dx.doi.org/10.1080/07328319708001350

NUCLEOSIDES & NUCLEOTIDES, 16(3), 301-303 (1997)

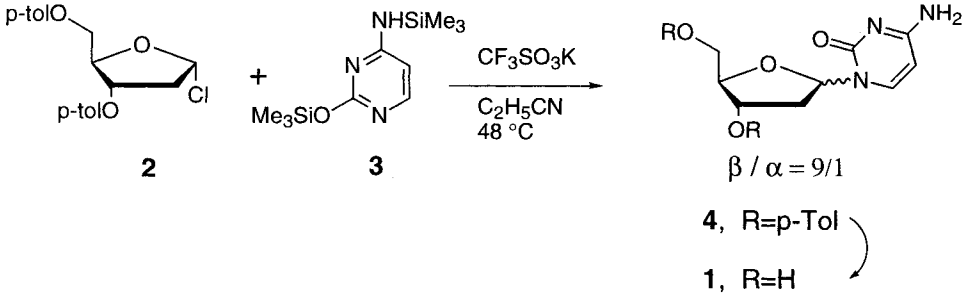
A STEREOSELECTIVE METHOD FOR THE DIRECT PREPARATION OF 2'-DEOXYCYTIDINE

Douglas P. Kjell

Lilly Research Laboratories, Eli Lilly & Co., Lafayette, IN 47902

Abstract: 2'-Deoxycytidine is prepared from 2-deoxy-α-D-ribofuranosyl chloride via novel stereoselective glycosylation conditions.

Deuterated derivatives of nucleosides have been of significant interest since incorporation of these structures into synthetic nucleotides can ease NMR analysis. For example, multiple syntheses of deuterated derivatives of 2'-deoxycytidine (β-**1**) have been reported.[1] These reports all use deuterated derivatives of 2-deoxy-α-D-ribofuranosyl chloride (**2**) as a critical intermediate. However, attempts to directly form the nucleoside via condensation with bis(trimethylsilyl)cytosine (**3**) were not stereoselective.[1b,c,d] Therefore, indirect methods have been developed.[1a] Herein are reported conditions which, using undeuterated **2** as a model for the deuterated derivatives, directly form nucleoside **4** with 9:1 stereoselectivity favoring the β anomer.

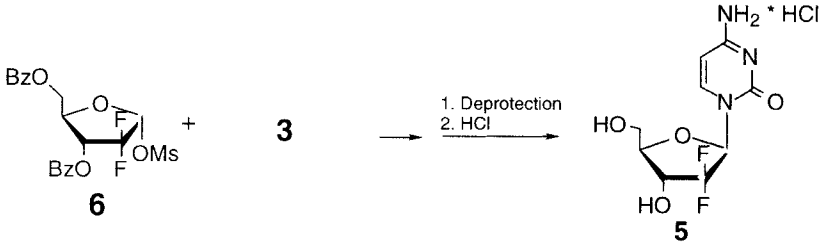


2 **3** β / α = 9/1

4, R=p-Tol

1, R=H

The lack of stereoselectivity in formation of 2'-deoxynucleosides is a recurring problem.[2] Two sets of conditions have been reported for the stereoselective synthesis of 2'-deoxy-2',2'-difluorocytidine (gemcitabine, **5**) from the α-mesylate derivative **6**. The first set of conditions utilizes a very large excess (*ca.* 20 equivalents) of **3** with minimal solvent (usually a moderately polar aromatic such as anisole) at *ca.* 115 °C.[3] A second set of conditions employs less of an excess of **3** in a nitrile solvent at a lower temperature (*ca.* 90°) in the presence of potassium triflate as a catalyst.[4] We were interested in determining if these conditions have general utility. Therefore, the applicability of these conditions to the stereoselectivity problem in the direct synthesis of β-**1** was explored.



We found the reactivity of **2** to be suprisingly low when exposed to 21 equivalents of **3** under the uncatalyzed conditions. Even when the temperature was raised to 125 °C traces of **2** were still visible (by HPLC) after 48 h. The α anomer was formed in moderately greater amounts than the desired β-**4** (β-selectivity 47%).

The potassium triflate catalyzed reaction of **2** with **3** in propionitrile was dramatically faster. α-Chloride **2** was completely consumed within 1 hour when treated with 21 equivalents of **3** and 38 mole % of potassium triflate at 90 °C. Unfortunately, no stereoselectivity was observed. By lowering the reaction temperature we were able to obtain moderate β-selectivity (76 % at 56 °C). Upon further lowering the temperature to 48 °C and increasing to 42 equivalents of **3** we were able to achieve a β-selectivity of 90% for **4**.[5] The mixture of anomers was isolated in 96% yield.[6] The excess cytosine may easily be recovered from the aqueous layer generated in the product isolation.

REFERENCES

1. a) Hodge, R.P.; Brush, C.K.; Harris, C.M.; Harris, T.M. *J. Org. Chem.* **1991**, *56*, 1553-1564;
b) Pathak, T.; Chattopadhyaya, J. *Tetrahedron* **1987**, *43*, 4227-4234;

c) Wu, J.C.; Bazin, H.; Chattopadhyaya, J. *Tetrahedron* **1987**, *43*, 2355-2368;

d) Pathak, T.; Bazin, H.; Chattopadhyaya, J. *Tetrahedron* **1986**, *42*, 5427-5441.

2. Walker, R. T., "Nucleosides" in *Comprehesive Organic Chemistry* , Barton, D. and Ollis, W.D., Eds., vol. 5, Pergamon Press, **1979.**

3. Chou,T.S.; Kjell, D.P.; Grossman, C.S.; Hertel, L.W.; Holmes, R.E.; Jones, C.D.; Mabry, T.E. European patent 0 577 303 A1, 1994.

4. Kjell, D.P. US patent 5 426 183, 1995.

5. Structure β-**4** was assigned by comparison to the ^{1}H-NMR spectrum of the 1'-deutero analogue reported in reference 1a. Compound β-**4** showed an additional resonance at δ 6.83 (dd, H1', $J_{1',2''}$ = 5.7, $J_{1',2'}$ = 7.9). In addition, the anomeric mixture was deprotected by the method of reference 1a, and the major component was shown to be identical to authentic 2'-deoxycytidine.

6. **Preparation of 2'-Deoxy-3',5'-di-O-p-toluoylcytidine (β-4)**

A mixture of cytosine (2.40 g, 21.5 mmol), ammonium sulfate (5 mg, 0.04 mmol), and hexamethyldisilazane (12 mL, 58 mmol) was heated to a gentle reflux (120 - 125 °C). Reflux was maintained until 30 minutes after all solids were consumed. The mixture was then concentrated by distillation until the pot temperature reached 145 °C. The resulting solution of bis(trimethylsilyl) cytosine (**3**) was cooled to 95 °C. Propionitrile (4 mL) was added. Potassium carbonate (0.1 g, 0.72 mmol), propionitrile (2 mL), and triflic acid (0.13 mL, 0.19 mmol) were combined and stirred for 5 minutes. The supernatant was decanted away from the excess potassium carbonate into the silylcytosine mixture. The mixture was cooled to 48 °C. The α-chloride **2** (0.18 g, 0.5 mmol) was added. The reaction was maintained at 48 °C for 1 hour. The reaction was diluted with toluene (10 mL) and poured onto distilled water (30 mL). The two phase mixture was distilled until the pot temperature reached 90 °C. The layers were separated while hot. The organic layer was filtered through silica (first eluting non-polar impurities with toluene, then eluting **4** with methanol). Solvent was removed on a rotary evaporator to give a colorless foam of β-**4** and the α anomer (0.22 g, 0.48 mmol, 96%, ca. 10% the α anomer).

Received October 21, 1996
Accepted January 15, 1997