

## Efficient Synthesis of 2',3'-Dideoxynucleosides and 2',3'-Dideoxy C-Nucleosides from D-Glucosamine<sup>1</sup>

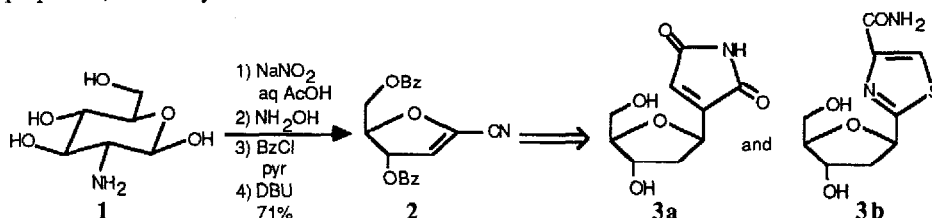
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**Summary:** D-Glucosamine **1** can be easily converted into 2,5-anhydro-6-*O*-benzoyl-3,4-dideoxygluconic acid **6** which can be taken on to both 2',3'-dideoxynucleosides such as dideoxyuridine (ddU) **4** and 2',3'-dideoxy C-nucleosides such as dideoxyformycin B **5** and dideoxyshowdomycin **20**.

Recently we reported the very efficient conversion of the inexpensive starting material D-glucosamine **1** into 2'-deoxy C-nucleosides such as 2'-deoxyshowdomycin **3a** and 2'-deoxytiazofurin **3b**.<sup>3</sup> A key intermediate in this reaction sequence was 2,5-anhydro-3-deoxy-4,6-di-*O*-benzoyl-2,3-didehydroglucononitrile **2**, which was prepared in four steps and 71% overall yield from D-glucosamine **1** (via diazotization-rearrangement, aldoxime formation, perbenzoylation-nitrile formation, and  $\beta$ -elimination of benzoic acid).<sup>3</sup> We now report the conversion of this readily available intermediate **2** into dideoxynucleosides and dideoxy C-nucleosides, such as 2',3'-dideoxyuridine (ddU) **4** and 2',3'-dideoxyformycin B **5**, respectively, via the anhydride dideoxygluconic acid **6** as a key intermediate.

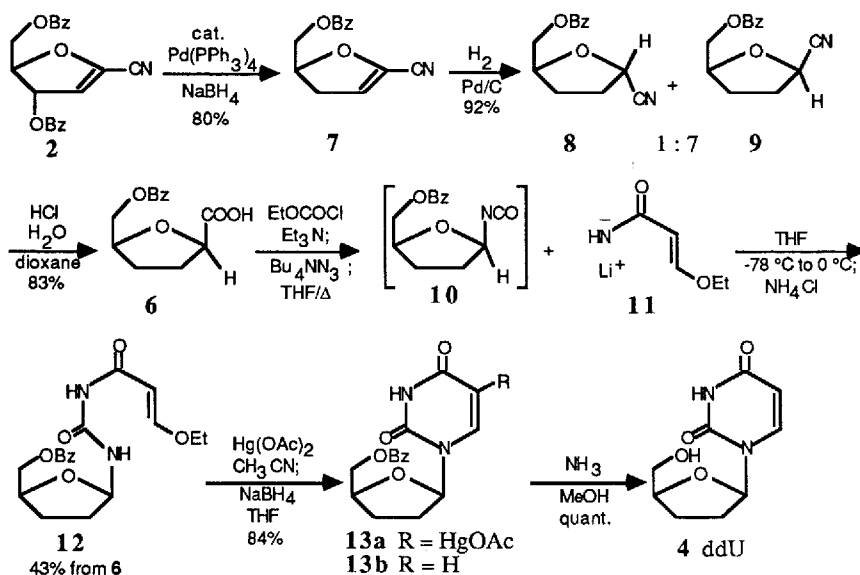
2',3'-Dideoxynucleosides have shown very strong antiviral activity and several compounds, e.g., dideoxycytidine (ddC) and dideoxyinosine (ddI), are under investigation as potential therapeutic agents in the treatment of HIV infections (AIDS).<sup>4</sup> We decided to develop a new route to medicinally quite useful compounds of this sort based on the use of the very inexpensive D-glucosamine **1** as the starting material. In addition, we decided to extend our synthetic scheme to prepare 2',3'-dideoxy C-nucleosides as well.<sup>5</sup>



The key step in our approach involves the deoxygenation of the allylic benzoate **2**. This was accomplished in 80% yield by treatment of **2** with tetrakis(triphenylphosphine)palladium followed by addition of sodium borohydride (use of sodium cyanoborohydride was nearly equally effective) to give in good yield the 2,5-anhydro-6-*O*-benzoyl-2,3-didehydro-3,4-dideoxyglucononitrile **7**. A small amount of an anomeric mixture of the 1-cyano-2-alkenes is also

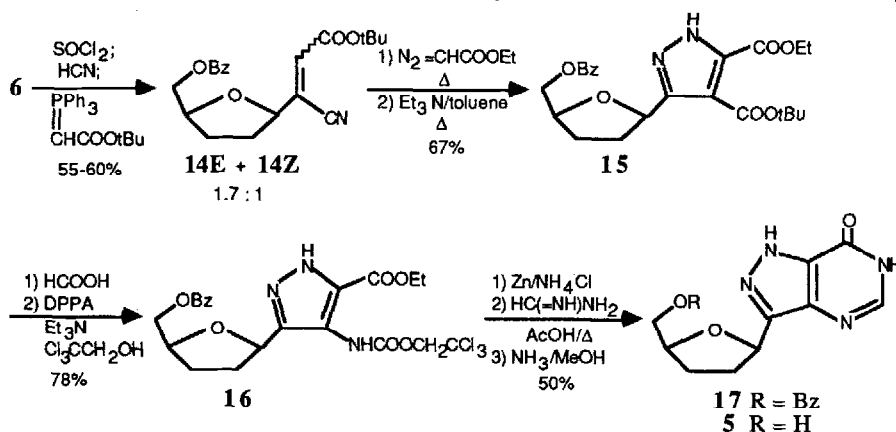
produced. Catalytic hydrogenation of the total mixture over palladium on carbon gave an 92% yield of a 1:7 mixture of the undesired  $\alpha$  and the desired  $\beta$  anomers of the dideoxyanhydroglucononitrile, **8** and **9**, respectively. The stereochemistry of these compounds could not be determined by simple examination of their  $^1\text{H}$  NMR spectra which are similar and quite complex. The structural assignment was based on spectral data of further derivatives<sup>6</sup> and on the ultimate conversion of **9** into 2',3'-dideoxyuridine **4**. Acidic hydrolysis of the nitrile of **9** by the conditions of Bobek and Farkaš<sup>7</sup> gave the key acid **6** in 83% yield. Conversion of this acid functionality into a uracil group would complete the synthesis of ddU **4** while its conversion to a pyrazolopyrimidine would afford dideoxyformycin B **5**. These were accomplished as follows.

Treatment of **6** in dichloromethane with ethyl chloroformate and triethylamine, followed by addition of tetra-*n*-butylammonium azide, isolation of the crude acyl azide, addition of THF, and heating gave the isocyanate **10**.<sup>8</sup> Treatment of a solution of **10** in toluene with the lithium salt of (*E*)-3-ethoxyacrylamide **11** in THF at  $-78^\circ\text{C}$  with warming to  $0^\circ\text{C}$  produced only the desired  $\beta$ -acyl urea **12** in 43% overall yield from **6**. Formation of the final bond was effected by reaction of **12** with mercuric acetate in refluxing acetonitrile which gave the 5-(acetoxymercuro)-uridine **13a**;<sup>9</sup> reduction with borohydride produced dideoxyuridine benzoate **13b**<sup>10</sup> in 84% yield. Removal of the benzoate (methanolic ammonia) gave a quantitative yield of only the desired  $\beta$ -anomer, namely dideoxyuridine (ddU) **4**. Thus this novel dideoxynucleoside is available in only 10 steps and fair overall yield (13.4%) from D-glucosamine **1**.

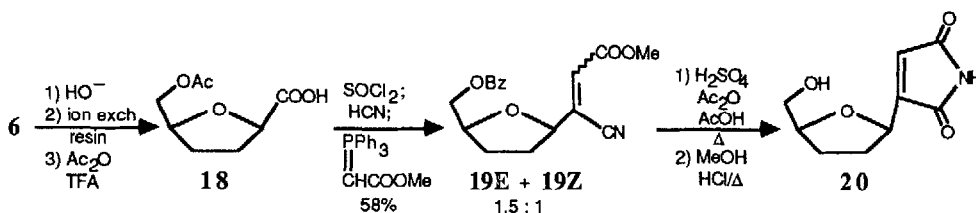


Conversion of **6** to 2',3'-dideoxyformycin B **5** followed the chemistry of Kalvoda.<sup>11</sup> Formation of the acid chloride, condensation with HCN and Wittig reaction of the resulting acyl nitrile produced the cyano ester **14** as a 1.7:1 mixture of (*E*) and (*Z*) stereoisomers in 55-60% yield. Addition of ethyl diazoacetate to either isomer of **14** followed

by heating with triethylamine in toluene (to eliminate HCN) afforded the pyrazole diester **15** in good yield (67% from the *E*-isomer, 60% from the *Z*-isomer). Removal of the *t*-butyl group and heating the acid with diphenylphosphoryl azide, 2,2,2-trichloroethanol and base furnished the carbamate **16** in 78% yield. Reductive removal of the protecting group and condensation with formamidine and acetic acid produced the desired 5-*O*-benzoyl-2',3'-dideoxyformycin B **17** in 56% yield. Final hydrolysis of the benzoate afforded 2',3'-dideoxyformycin B **5** in 95% yield. To show the generality of this method, we have also converted **6** into 2',3'-dideoxyshowdomycin **20** by an extension of the method used for the parent C-nucleoside.<sup>12</sup> Hydrolysis of the benzoate of **6** and reacylation with acetic anhydride furnished the acetate **18**, which was converted via the acyl nitrile to a 1.5:1 mixture of (*E*)- and (*Z*)-isomers of the cyano ester **19** in 58% yield. Cyclization of **19E** with sulfuric acid and acetic anhydride in acetic acid at 100° C followed by treatment



with methanolic HCl gave the desired dideoxyshowdomycin **20** in 50% yield as a 3:1 mixture of  $\beta$ - and  $\alpha$ -anomers. We are presently having **5** and **20** tested for antiviral and antitumor activity and will report those results in due course.



In summary, dideoxynucleosides and dideoxy C-nucleosides can be prepared from D-glucosamine by a direct route that may be applicable to other substituted derivatives.<sup>13</sup>

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### References and Notes

- 1) This work was presented in part at the 8th ICOS meeting, Helsinki, Finland, July 1990, abstract 1.123.
- 2) BASF Graduate Fellow, UCLA, 1988.

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For an earlier similar approach, see: Jung, M. E.; Clevenger, G. L. *Tetrahedron Lett.* **1991**, 32, 6089.
- 4) For reviews on the use of dideoxynucleosides in the treatment of AIDS, see: a) Norbeck, D. W. *Ann. Rep. Med. Chem.* **1990**, 25, 149. b) Yarchoan, R.; Mitsuya, H.; Broder, S. *Ann. Rep. Med. Chem.* **1988**, 23, 253. c) Mansuri, M. M.; Martin, J. C. *Ann. Rep. Med. Chem.* **1988**, 23, 161; *Ann. Rep. Med. Chem.* **1987**, 22, 147.
- 5) For reviews of C-nucleoside syntheses, see: a) James, S. R. *J. Carbohydr., Nucleosides, Nucleotides* **1979**, 6, 417. b) Buchanan, J. G. *Prog. Chem. Org. Nat. Prod.* **1983**, 44, 243. c) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, 22, 1. For synthesis and testing of some 2',3'-dideoxy C-nucleosides, see among others: d) Chu, C. K.; Shinazi, R. F.; Arnold, B.; Cannon, D. L.; Doboszewski, B.; Bhadti, V. S.; Gu, Z. P. *Biochem. Pharmacol.* **1988**, 37, 3543. e) Tam, S.; Holman, M.; Klein, R. S.; Mitsuya, M.; Broder, S. *Nucleosides Nucleotides* **1989**, 8, 1109.
- 6) Preparation of the bis-Mosher's esters of the corresponding diols allowed us to tell the cis-isomer (C<sub>5</sub>) from the trans-isomer (C<sub>2</sub>) easily by <sup>13</sup>C NMR. Jung, M. E.; Trifunovich, I. D. manuscript in preparation.
- 7) Bobek, M.; Farkaš, J. *Collect. Czech. Chem. Commun.*, **1969**, 34, 247.
- 8) The isocyanate **10** could be isolated as a solution in toluene and was shown by <sup>1</sup>H NMR to be only the desired β-anomer (i.e., no racemization had occurred in the Curtius process). Treatment of **10** with ammonia produced the corresponding urea in 60% overall yield from **6**.
- 9) We are currently investigating the use of the 5-bromomercurio compound (prepared from **13a** and sodium bromide) to prepare 5-substituted derivatives of ddU, e.g., various 2-substituted ethyl and vinyl systems. For leading references to similar chemistry, see: Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, 100, 8106; Bergstrom, D. E.; Ruth, J. L. *J. Am. Chem. Soc.* **1976**, 98, 1587; *J. Carbohydr., Nucleosides, Nucleotides* **1977**, 4, 257; Jones, A. S.; Verhelst, G.; Walker, R. T. *Tetrahedron Lett.* **1979**, 4415.
- 10) This benzoate **13b** can be prepared from **6** by a much shorter route by a Hunsdiecker-type oxidation (Pb(OAc)<sub>4</sub>, PhH, Δ, 3h) to give in 68% yield the anomeric acetate as a mixture of α- and β-anomers. Vorbrüggen coupling of this mixture with bis(TMS)uracil gives the benzoate **13b** along with an equal amount of the undesired α-anomer.
- 11) Kalvoda, L. *Collect. Czech. Chem. Commun.* **1978**, 43, 1431.
- 12) Kalvoda, L. *J. Carbohydr., Nucleosides, Nucleotides* **1976**, 3, 47.
- 13) Studies are underway to see if other nucleophiles, e.g., azide, fluoride, thiophenyl, etc., could be substituted for hydride in the conversion of **2** into **4**. If successful, 3α-substituted derivatives, e.g., AZT, FdT, d<sub>4</sub>T, could be made from D-glucosamine as well. For a different approach to the synthesis of antiviral modified nucleosides such as AZT, ddC and d<sub>4</sub>T from non-carbohydrate precursors, see: a) Jung, M. E.; Gardiner, J. M. *J. Org. Chem.* **1991**, 56, 2614. b) Jung, M. E.; Castro, C.; Gardiner, J. M. *Tetrahedron Lett.* **1991**, 32, 5717. c) Jung, M. E.; Gardiner, J. M. *Tetrahedron Lett.* submitted for publication.