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Efficient Synthesis of 2',3'-Dideoxynucleosides and 2',3'-Dideoxy C-Nucleosides from D-Glucosamine[1]

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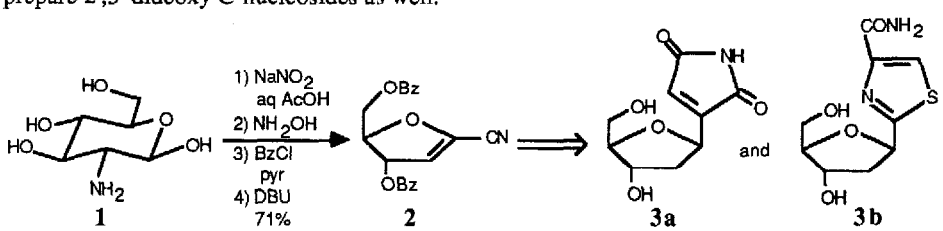
Summary: D-Glucosamine **1** can be easily converted into 2,5-anhydro-6-*O*-benzoyl-3,4-dideoxygluconic acid **6** which can be taken on to both 2',3'-dideoxynucleosides such as dideoxyuridine (ddU) **4** and 2',3'-dideoxy C-nucleosides such as dideoxyformycin B **5** and dideoxyshowdomycin **20**.

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**.[3] A key intermediate in this reaction sequence was 2,5-anhydro-3-deoxy-4,6-di-*O*-benzoyl-2,3-didehydrogluconononitrile **2**, which was prepared in four steps and 71% overall yield from D-glucosamine **1** (via diazotization-rearrangement, aldoxime formation, perbenzoylation-nitrile formation, and β-elimination of benzoic acid).[3] 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 anhydrodideoxygluconic 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).[4] 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.[5]

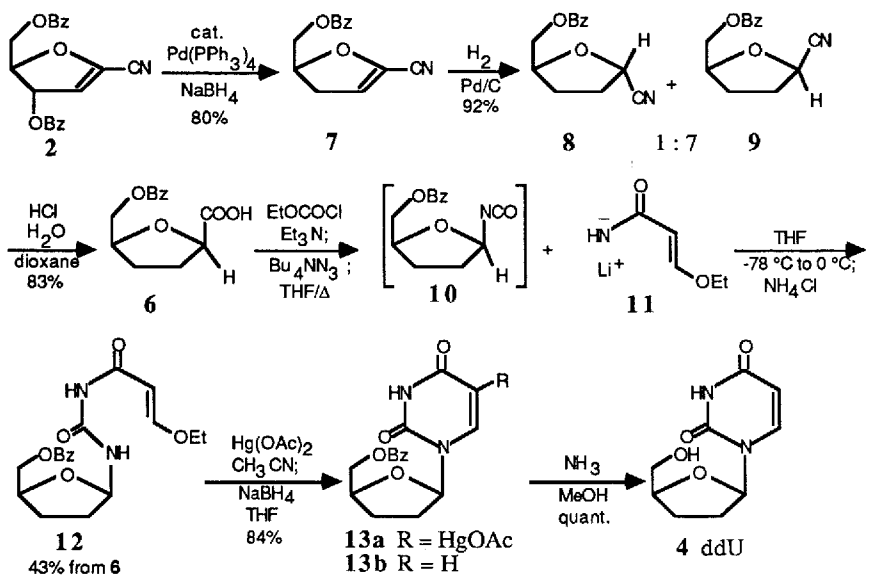


1 2 3a 3b

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-dideoxygluconononitrile **7**. A small amount of an anomeric mixture of the 1-cyano-2-alkenes is also

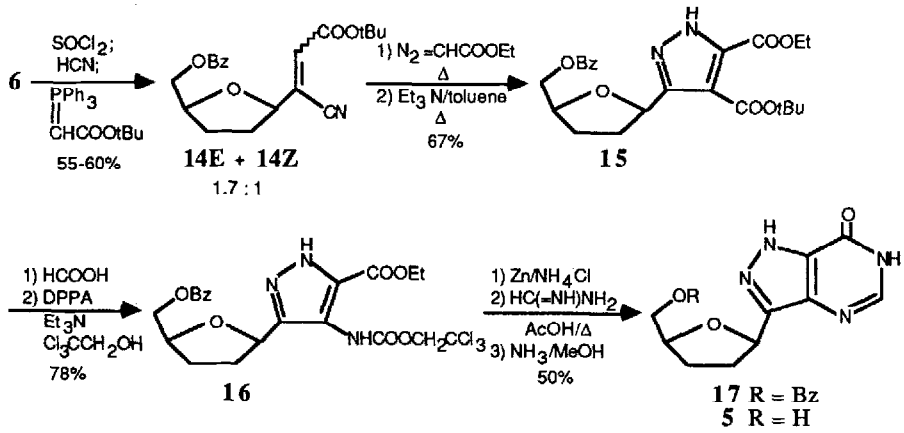
produced. Catalytic hydrogenation of the total mixture over palladium on carbon gave an 92% yield of a 1:7 mixture of the undesired α and the desired β anomers of the dideoxyanhydrogluconononitrile, **8** and **9**, respectively. The stereochemistry of these compounds could not be determined by simple examination of their ^{1}H NMR spectra which are similar and quite complex. The structural assignment was based on spectral data of further derivatives[6] 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[7] 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**.[8] Treatment of a solution of **10** in toluene with the lithium salt of (*E*)-3-ethoxyacrylamide **11** in THF at -78 °C with warming to 0 °C produced only the desired β-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-(acetoxymercurio)-uridine **13a**;[9] reduction with borohydride produced dideoxyuridine benzoate **13b**[10] in 84% yield. Removal of the benzoate (methanolic ammonia) gave a quantitative yield of only the desired β-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**.

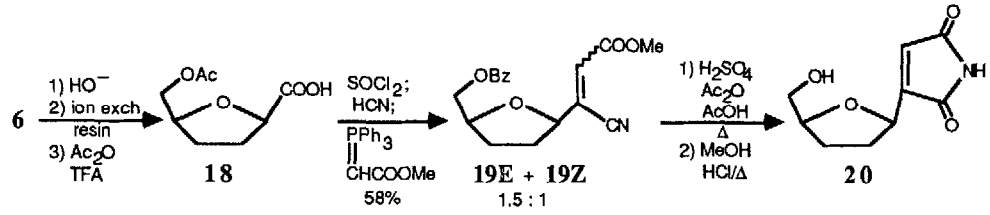


Conversion of **6** to 2',3'-dideoxyformycin B **5** followed the chemistry of Kalvoda.[11] Formation of the acid chloride, condensation with HCN and Wittig reaction of the resulting acyl nitrile produced the cyano ester **14** as a 1.7:1 mixture of (*E*) and (*Z*) stereoisomers in 55-60% yield. Addition 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.[12] 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 β- and α-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.[13]

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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.

3) Jung, M. E.; Trifunovich, I. D.; Gardiner, J. M.; Clevenger, G. L. *J. Chem. Soc., Chem. Commun.*, **1990**, 84. 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_S) from the trans-isomer (C_2) easily by ^{13}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 ^1H 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 ($Pb(OAc)_4$, 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_4T, could be made from D-glucosamine as well. For a different approach to the synthesis of antiviral modified nucleosides such as AZT, ddC and d4T 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.

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