Preparation of Modified Nucleosides from Glucosamine: Rapid and Efficient Formal Total Synthesis of Several 2′-Deoxy *C*-Nucleosides

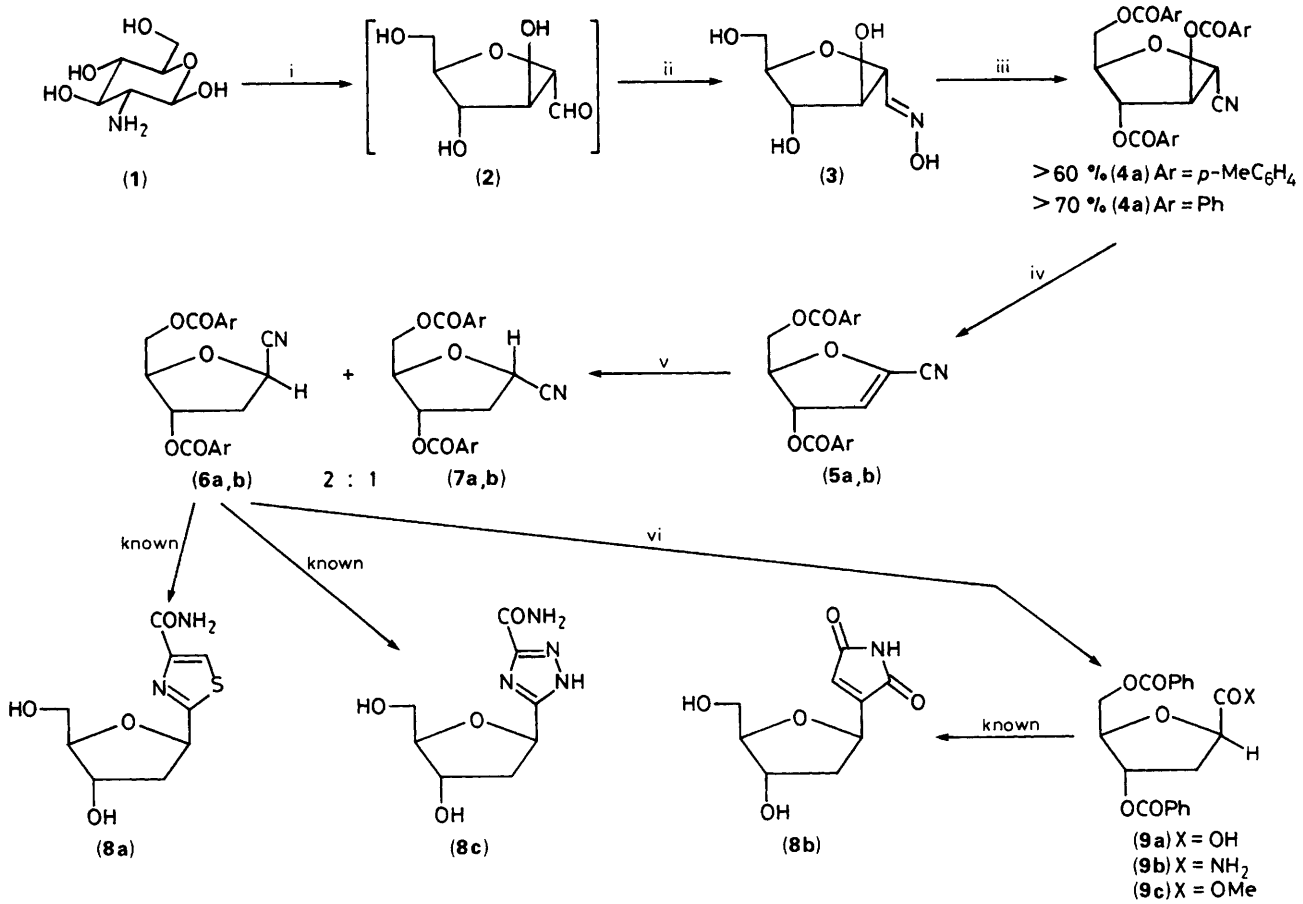
Michael E. Jung,* Ivan D. Trifunovich, John M. Gardiner, and Gary L. Clevenger

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024, U.S.A.

Formal total syntheses of several 2′-deoxy *C*-nucleosides have been accomplished in a short and efficient process using D-glucosamine as the starting material.

Owing to the central importance of nucleic acids in all growth and propagation, the nucleosides which comprise them offer a target for structural modification in order to develop new chemotherapeutic agents. In particular, the introduction of modified nucleosides can often affect cell growth in useful medicinal ways. For example, the *C*-nucleosides tiazofurin, showdomycin, pseudouridine, formycin, *etc.*, have shown therapeutically useful antitumour properties, while certain structurally modified nucleosides and simple bases, 5-fluorouracil, ribavirin, AZT (3′-azido-3′-deoxythymidine), are strong antiviral agents.[1] In order to make these and other similar analogues available on a large scale, chemists have worked for years on the development of new methods for their preparation. Of particular importance is that the starting material be inexpensive and available in very large quantities and that the syntheses be short and high yielding. We now report the formal total synthesis of several 2′-deoxy *C*-nucleosides, *e.g.*, 2′-deoxytiazofurin (**8a**), 2′-deoxyshowdomycin (**8b**), and the *C*-nucleoside analogue of 2′-deoxyribavirin (**8c**), by a process in which the key intermediate, 2,5-anhydro-3-deoxymannurononitrile (**6**), is prepared rapidly and efficiently from the readily available D-glucosamine (**1**) (Scheme 1).

Treatment of D-glucosamine hydrochloride (**1**) with sodium nitrite in aqueous acetic acid produced the aldehyde chitose (**2**) in excellent crude yield.[2] Conversion of the aldehyde to the oxime (**3**) was best carried out by treatment of the aldehyde with free hydroxylamine (prepared by treatment of its hydrochloride with sodium methoxide) in methanol for several hours at 25 °C to produce (**3**) in very high crude yield. Treatment of the triol oxime (**3**) with toluoyl or benzoyl chloride in pyridine afforded the triester nitriles (**4a, b**) in good yield.[3] Generally it was best to perform these three steps without isolation of the intermediate aldehyde or triol oxime, going directly from (**1**) to (**4a, b**) in one pot. For example, the overall yield of (**4a**) from (**1**) was routinely 60% for the three steps while that of (**4b**) was greater than 70%. Elimination of



Scheme 1. *Reagents and conditions:* i, $NaNO_2$, HOAc, H_2O; ii, NH_2OH·HCl, NaOMe/MeOH; iii, ArCOCl, pyridine; iv, DBU, CH_2Cl_2, >95%; v, H_2, $Pd/BaSO_4$, EtOH, 65%; vi, HCl/H_2O, dioxane on (**6b**).

the β-acyloxy group was accomplished in >95% yield by treatment of (**4a, b**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the unsaturated nitriles (**5a, b**). Reduction of these unsaturated nitriles could be carried out under several different conditions. However, catalytic hydrogenation proved to be the best process for this transformation. Catalytic hydrogenation of (**5a**) over $Pd/BaSO_4$ in ethanol at 25 °C furnished a 65% yield of a 2:1 mixture of the desired β-anomer (**6a**) and the α-anomer (**7a**). In like fashion, the benzoylated alkenic nitrile (**5b**) produced (**6b**) as the major product. These mixtures of anomers could be separated readily by flash chromatography on silica gel. The structures of (**6a**) and (**7a**) were confirmed by comparison with the data (m.p., NMR) given for these known compounds.[4] It is important to point out that the undesired α-anomers (**7a, b**) can be converted into an approximately 1:1 mixture of the desired β-anomers (**6a, b**) and the α-anomers (**7a, b**) by deprotonation of (**7a, b**) with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) followed by kinetic protonation. Thus with recycling, the overall yield of (**6a, b**) from (**5a, b**) can be much higher. Compound (**6a**) has been converted into 2′-deoxytiazofurin (**8a**) in three steps[5] and into the *C*-nucleoside analogue of ribavirin (**8c**) in three steps,[6] both in good overall yields. We have also been able to hydrolyse the nitrile of (**6b**) to the corresponding acid (**9a**) under the conditions used in ribo series, namely HCl in aqueous dioxane.[7] By carrying out this hydrolysis under milder conditions, we were able to isolate the corresponding primary amide (**9b**) in good yield. As expected, treatment of the acid (**9a**) with diazomethane in methanol/diethyl ether affords the methyl ester (**9c**). Our spectral data for the acid (**9a**) matches that reported for this compound[8] which has already been converted into 2′-deoxyshowdomycin (**8b**) in five steps.[9] Thus these three potentially useful antitumour/antiviral agents (**8a, b, c**) are readily available in reasonable quantities from the inexpensive precursor glucosamine by short sequences using this chemistry.

It should be pointed out that this is one of the first syntheses of *C*-nucleoside derivatives that utilizes all six carbons of a hexose starting material in preparing the key six-carbon intermediate, *e.g.*, (**6**). Normally most syntheses of *C*-nucleoside derivatives start with ribose (which is itself prepared from glucose in several steps, the key one being loss of a carbon atom) and add one carbon (usually cyanide on the derived protected robosyl bromide).[10,11] Further transformations of these intermediates are currently underway.

We thank the National Institutes of Health (AI-26692) for their generous financial support. M. E. J. is a Gold Shield Faculty Awardee. I. D. T. is the BASF Graduate Fellow, UCLA, 1988—89.

Received, 9th August, 1989; Com. 9/03384J

References

1 There are many reviews on synthetic antiviral agents, especially those which are active against AIDS. For a brief overview, see R. K. Robins, *Chem. Eng. News,* 1986, **64** (4), and references cited therein; R. Dagani, *ibid.*, 1987, **65** (26), 25; M. M. Mansuri and J. C. Martin, *Annu. Rep. Med. Chem.*, 1988, **23**, 161, and earlier volumes in this series.

2 For an overview of the deamination of amino hexoses, see S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, 1976, **33**, 111, especially pp. 114—119 and references cited therein.

3 We believe that our preparation of (**4b**) is clearly superior to the known literature route to (**4b**) (Ar = Ph) which starts with the relatively expensive D-arabinose and proceeds *via* Koenigs–Knorr reaction of the arabinosyl bromide tribenzoate. G. Barnathan, T. Huynh Dinh, A. Kolb, and J. Igolen, *Compt. Rend.*, 1972, **274C**, 2192; *Eur. J. Med. Chem.-Chim. Ther.*, 1976, **11**, 67; P. J. Marshall, M. L. Sinnott, P. J. Smith, and D. Widdows, *J. Chem. Soc., Perkin Trans. 1*, 1981, 366.

4 A. Kolb, T. Huynh Dinh, and J. Igolen, *Bull. Soc. Chim. Fr.*, 1973, 3447.

5 P. C. Srivastava, R. K. Robins, F. Takusagawa, and H. M. Berman, *J. Heterocycl. Chem.*, 1981, **18**, 1659; P. C. Srivastava, M. V. Pickering, L. B. Allen, D. G. Streeter, M. T. Campbell, J. T. Witkowski, R. W. Sidwell, and R. K. Robins, *J. Med. Chem.*, 1977, **20**, 256.

6 T. Huynh Dinh, J. Igolen, E. Bisagni, J. P. Marquet, and A. Civier, *J. Chem. Soc., Perkin Trans. 1,* 1977, 761; A. Kolb, C. Gouyette, T. Huynh Dinh, and J. Igolen, *Tetrahedron,* 1975, **31**, 2914; Igolen and co-workers have used compound (**6a**) to prepare a large number of 2′-deoxy-*C*-nucleosides; for leading references, see: T. Huynh Dnh, R. S. Sarfati, C. Gouyette, J. Igolen, E. Bisagni, J.-M. Lhoste, and A. Civier, *J. Org. Chem.*, 1979, **44**, 1028; Acton and colleagues have converted (**6a**) into several purine-like *C*-nucleosides; for leading references, see: E. M. Acton and K. J. Ryan, *ibid.*, 1984, **49**, 528.

7 M. Bobek and J. Farkas, *Collect. Czech. Chem. Commun.*, 1969, **34**, 247.

8 L. J. S. Knutsen, B. D. Judkins, R. F. Newton, D. I. C. Scopes, and G. Klinkert, *J. Chem. Soc., Perkin Trans. 1,* 1985, 621.

9 A. M. Mubarak and D. M. Brown, *Tetrahedron Lett.*, 1981, 683.

10 For a review of *C*-nucleoside syntheses, see S. R. James, *J. Carbohydr., Nucleosides, Nucleotides,* 1979, **6**, 417.

11 Since the completion of our work, two other groups have reported approaches to *C*-glycosides using conceptually similar ring contractions: G. W. J. Fleet and L. C. Seymour, *Tetrahedron Lett.*, 1987, **28**, 3015; A. Kaye, S. Neidle, and C. B. Reese, *ibid.*, 1988, **29**, 1841, 2711.