Bioorganic & Medicinal Chemistry Letters, Vol.2, No.11, pp. 1419-1422, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

CONCISE SYNTHESIS OF 1-DEOXYMANNOJIRIMYCIN†

Ellen W. Baxter and Allen B. Reitz*

Medicinal Chemistry Department

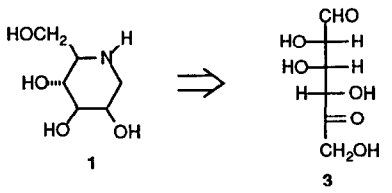
The R. W. Johnson Pharmaceutical Research Institute

Spring House, Pennsylvania 19477 USA

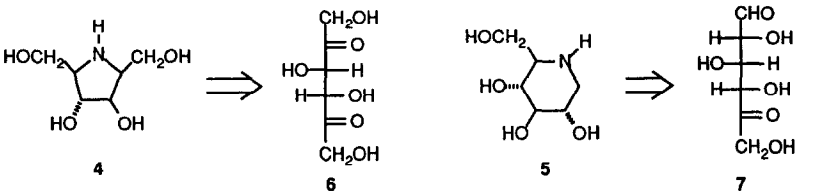
(*Received* 30 *June* 1992)

Abstract: The synthesis of 1-deoxymannojirimycin (**1**) is readily achieved in four steps from 1-methyl-2,3-isopropylidene-D-mannofuranoside (**2**). The key step is a double reductive amination of 5-keto-D-mannose (**3**) using $NaBH_3CN$, entailing a marked divergence in stereocontrol relative to the reported use of catalytic methods.

Azasugars have generated a great deal of interest because they inhibit glycosidase enzymes[1] and may have therapeutic potential as antiviral, anti-HIV, antidiabetic, and anticancer agents.[2-4] A important member of this class of compounds is 1-deoxymannojirimycin (**1**) which inhibits mannosidase I (important in glycoprotein processing) and mammalian fucosidases.[5] A number of syntheses of **1** have been reported,[6,7] many of which employ intramolecular reductive cyclizations under catalytic hydrogenation conditions or azide reductions with subsequent displacements, with suitable protecting-group manipulations. In addition, a number of routes to prepare **1** have utilized enzymatic transformations.[6i-l,p,q,7a] Previously, we reported concise syntheses of 2,5-anhydro-imino-D-glucitol (**4**) and 1-deoxynojirimycin (**5**) by a double reductive amination of 5-keto-D-fructose (**6**) and 5-keto-D-glucose (**7**), respectively.[8a] We have since extended this approach to the preparation of other important natural and unnatural azasugars and have also used model systems to investigate issues of stereocontrol. We describe here the preparation of 1-deoxymannojirimycin (**1**) via the new dicarbonyl sugar 5-keto-D-mannose (**3**).



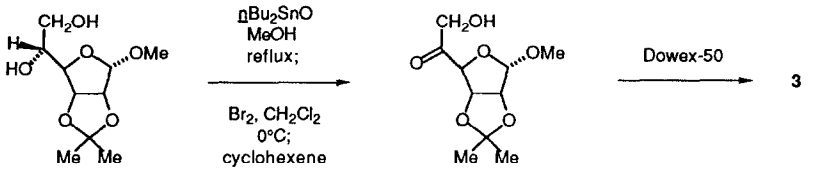
1 **3**



4 **6** **5** **7**

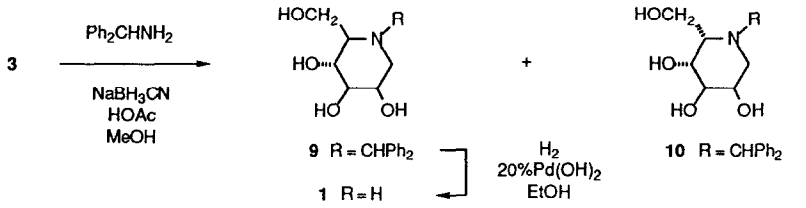
† This paper is dedicated to Prof. Murray Goodman (UC, San Diego) on the occasion of his 65th birthday.

5-keto-D-mannose (**3**) is a logical precursor for making **1** by our methodology. We envisoned that **3** could be readily obtained from 1-methyl-2,3-isopropylidene-D-mannofuranoside (**2**).[9] Selective oxidation[10] of the 5-hydroxyl group of **2** provided ketosugar **8** (70%). Subsequent hydrolysis[11] provided 5-keto-D-mannose (**3**) nearly quantitatively. Unlike 5-keto-D-glucose (**7**), which exists predominantly as a β-pyranose in water (300-MHz H-1 NMR, D_2O), compound **3** exists as a more complex mixture of interconverting forms.



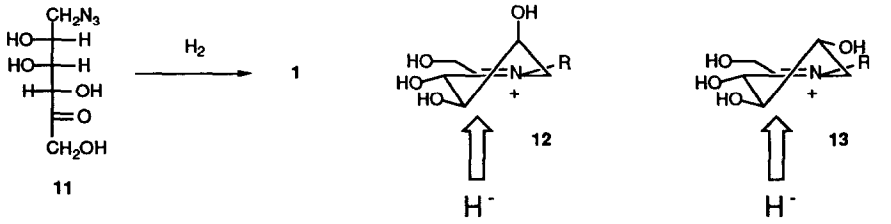
2 **8**

With **3** in hand, the critical double reductive amination was investigated. This transformation was effected with benzhydrylamine and $NaBH_3CN$[12] to produce a 2:1 ratio of piperidines **9** and **10**, having the D-manno and L-gulo configurations, respectively (45%); these were readily separated by chromatography. Hydrogenolysis of **9** followed by treatment with Dowex 50W-X8 resin provided 1-deoxymannojirimycin (**1**, 90%). This material was converted to its HCl salt which was identical to an authentic sample.[13]



The stereocontrol (2:1 D-manno:L-gulo) observed in the double reductive amination of **3** is particularly intriguing in light of our results with 5-keto-D-glucose (**7**), in which the D-gluco product formed in a >95:5 ratio relative to the L-ido isomer.[8a] Substrates **3** and **7** differ only in the configuration at C-2 which is relatively remote from the key stereodetermining reduction. Furthermore, hydrogenation of 1-azido-1-deoxy-5-keto-D-mannose (**11**) using catalytic amounts of noble metals afforded the D-manno product almost exclusively.[6i-l,p,q] In the reduction of **11**, and also of **3**, one can consider the key cyclic iminium ion intermediate to be **12**. In the analogous reduction of **7**, the corresponding reactive species is **13**. The hydroxyl groups are drawn in **12** and **13** largely in the equatorial configuration, but they could also invert to the axial position to relieve $A^{1,2}$ strain with the C-5 hydroxymethyl group.[14] The attack of hydride on **12** and **13** is predicted to occur axially providing mainly the D-manno and D-gluco products respectively. The stereochemistry of reduction is the same in reaction of **13** with either $NaBH_3CN$[8] or with catalytic hydrogenation.[6i-l,p,q] There is some confusion in the literature on this point, as there is a report that the *L-ido (not the L-gluco)* product was obtained upon such a reaction involving the L isomer of **13**, but this stereochemical assignment was determined to be in error.[7d] Alternatively, reduction of **12**

reveals a divergence in the results between the two methods, with the high stereocontrol seen under catalytic conditions (>95:5)[6i-l,p,q] eroding to ca. 2:1 with $NaBH_3CN$. In this case, a seemingly remote hydroxyl group influences the stereochemistry of hydride delivery. Perhaps the hydroxyl at C-2 of **12** is interacting with the hydride reducing agent or **12** can adopt conformations in which the stereocontrol would be altered. Experiments are being conducted with additional dicarbonyl substrates to probe these stereochemical questions in greater detail.



In summary, 1-deoxymannojirimycin (**1**) has been synthesized in four steps with an overall yield of 17%. The key step is a double reductive amination of 5-keto-D-mannose (**3**), which provides a 2:1 mixture of stereoisomers. This result stands in marked contrast to those observed when similar reactions are carried out under catalytic hydrogenation conditions and highlights the mechanistic divergence of these two pathways for the formation of azasugars. Finally, this synthesis of **1** can be readily extended to the synthesis of N-substituted derivatives.

Acknowledgement: We appreciate the advice and encouragement of Dr. Bruce E. Maryanoff.

References and Notes

1. (a) Fleet, G. W. J. *Chem. Brit.* **1989**, 287. (b) Fellows, L. E. *Chem. Brit.* **1987**, 842. (c) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497. (d) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 744.
2. Antiviral: (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 9229. (b) Fleet, G. W. J. et al. *FEBS Lett.* **1988**, *237*, 128. (c) Tyms, A. S. et al. *Lancet* **1987**, 1025. (d) Datema, R.; Olofsson, S.; Romero, P. A. *Pharmacol. Ther.* **1987**, *33*, 221.
3. Anticancer: (a) Spearman, M. A.; Jamieson, J. C.; Wright, J. A. *Expt. Cell Res.* **1987**, *168*, 116. (b) Tsukamoto, K.; Uno, A.; Shimada, S.; Imokaw, G. *Clin. Res.* **1989**, *37A*, 722.
4. Antidiabetic/antiobesity: (a) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (b) *Drugs Future* **1986**, *11*, 1039. (c) Ref. 1c. (d) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539.
5. (a) Legler, G.; Julich, E. *Carbohydr. Res.* **1984**, *128*, 61. (b) Fuhrmann, U.; Bause, E.; Legler, G.; Pleogh, H. *Nature* **1984**, *307*, 755. (c) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.

6. (a) Leontein, K.; Lindberg, B.; Lonngren, J. *Acta Chem. Scand. B* **1982**, *36*, 515. (b) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1984**, *25*, 4029. (c) Ref. 5a. (d) Fleet, G. W. J.; Smith, P. W. *Tetrahedron Lett.* **1985**, *26*, 1469. (e) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123. (f) Setoi, H.; Takeno, H.; Hashimoto, M. *Chem. Pharm. Bull.* **1986**, *34*, 2642. (g) Fleet, G. W. J.; Fellows, L. E.; Smith, P. W. *Tetrahedron* **1987**, *43*, 979. (h) Broxterman, H. J. G.; Neefjes, J. J.; van der Marel, G. A.; Pleogh, H. L.; van Boom, J. H. *J. Carbohydr. Chem.* **1988**, *7*, 593. (i) Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem. Int. Ed. Eng.* **1988**, *27*, 716. (j) Pederson, R. L.; Kim, M.-J.; Wong C.-H. *Tetrahedron Lett.* **1988**, *29*, 4645. (k) Pederson, R. L.; Wong C.-H. *Heterocycles* **1989**, *28*, 477. (l) von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F., III; Pederson, R. L.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924. (m) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319. (n) Idem, Ibid., 327. (o) Ikota, N. *Heterocycles* **1989**, *29*, 1469. (p) Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926. (q) de Raadt, A.; Stutz, A. E. *Tetrahedron Lett.* **1992**, *33*, 189.

7. (a) For the preparation of the mirror image of **1** see references 7b and 7c. (b) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6678. (c) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280. (d) The original error was the reported conversion of **1b** to **4b** in reference 7b, along with the corresponding mechanistic arguments. This was corrected differently in footnote 7 of reference 7c and in an errata (*J. Am. Chem. Soc.* **1991**, *113*, 9009). Prof. Wong has informed us that the latter errata is the accurate one.

8. (a) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777. (b) For the use of other hydride sources see: Koebernick, W.; DE 3,049,446 (Dec. 30, 1980); U.S. Patent 4,611,058 (Sept. 9, 1986).

9. Randall, M. H. *Carbohydr. Res.* **1969**, *11*, 173.

10. (a) Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979**, *101*, 5839. (b) Tsuda, Y.; Hanajima, M.; Matshuhira, N.; Okuno, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, *37*, 2344.

11. Kiely, D. E.; Fletcher, H. G., Jr. *J. Org. Chem.* **1969**, *34*, 1386.

12. (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Jones, T. H.; Franko, J. B.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1980**, *21*, 789. (c) Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597.

13. Compound **1** was converted to its HCl salt. This material was identical to the commercially available hydrochloride salt of 1-deoxymannojirimycin (Sigma) by 300-MHz H-1 NMR (D_2O) and mass-spectral analysis. Compounds **8** and **9** were characterized by NMR, TLC, mass spectroscopy, and optical rotation. Characterization for **8**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 3 H), 1.43 (s, 3 H), 2.96 (t, J = 5.0 Hz, 1 H), 3.35 (s, 3 H), 4.48 (d, J = 4.7 Hz, 1 H), 4.52 (d, J = 5.4 Hz, 1H), 4.59 (m, 2 H), 5.01 (dd, J = 5.8, 4.1 Hz, 1 H), 5.04 (s, 1 H); $[\alpha]_D^{25}$ = -2.1 (c = 1.00, CH_2Cl_2). Characterization for **9**: (300 MHz, CD_3COCD_3): δ 2.44 (dd, J = 12.0, 3.9 Hz, 1 H), 2.75-2.95 (m, 2 H), 3.50 (d, J = 6.7 Hz, 1 H), 3.64 (br s, 1 H), 3.72 (br t, J = 5.2 Hz, 1 H), 3.89 (br s, 3H), 3.95-4.10 (m, 3 H), 5.43 (s, 1H), 7.14-7.33 (m, 6 H), 7.50 (d, J = 7.1 Hz, 2 H), 7.56 (d, J = 7.4 Hz, 2 H); $[\alpha]_D^{25}$ = +4.0 (c = 1.00, MeOH).

14. Anet, F. A. L. in "The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds," Rabideau, P. W., Ed.; VCH Publishers: New York, 1989, pp. 1-45.

15. Stevens, R. V. in "Strategies and Tactics in Organic Synthesis," Lindberg, T., Ed.; Academic Press: San Diego, 1984, pp. 275-298.