Tetrahedron: Asymmetry Vol. 4, No. 6, pp. 1203-1204, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

SIMPLE AND STEREOSELECTIVE CHEMOENZYMATIC SYNTHESIS OF AN α-C-MANNOSIDE

Francesco Nicotra,* Luigi Panza, Giovanni Russo and Alessia Verani
Dipartimento di Chimica Organica e Industriale
Centro per lo Studio delle Sostanze Organiche Naturali del C.N.R.
via Venezian 21, I-20133 Milano, Italy

(*Received* 25 *February* 1993)

Abstract: Aldolase-catalyzed reaction of D-ribose 5-phosphate with dihydroxyacetone phosphate and reduction of the product with triethylsilane affords an α-C-D-mannopyranoside (**3**), through a stereoselective procedure which does not require any protective step.

The importance of C-glycosides, due to their biological properties and their use as chiral building blocks, is now well documented. In particular α-C-mannosides have recently shown inhibitory activity towards the receptor-mediated adhesion of *E. coli* to host cells,[1] a process that is essential for infectivity; and mannosidase inhibitors are potential anti-HIV agents.[2] Many synthetic procedures of C-glycosylation have been reported[3] which, however, are often of little practical interest, as they require many steps, are time-consuming and give low yields of the desired product.

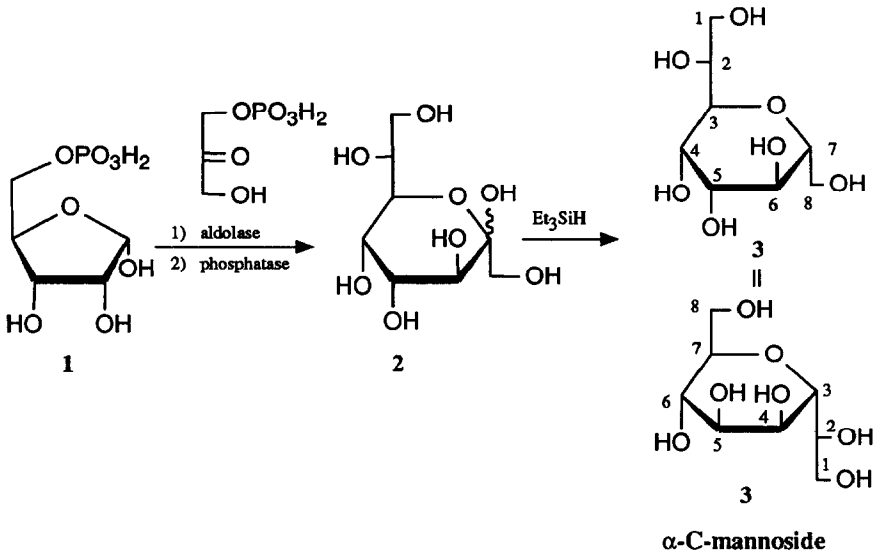
We decided to investigate the possibility to synthesize C-mannosides through a short stereoselective process which does not require any protective step, employing an aldolase to extend the skeleton of the sugar in a stereoselective manner, and then reducing the obtained ketal **2** (Scheme).

Ribose 5-phosphate disodium salt (**1**) (5 mmol) was condensed with dihydroxyacetone phosphate[4] employing rabbit muscle aldolase (RAMA) as described by Whitesides et al.[5] After dephosphation,[5] the D-*glycero*-D-*allo*nonulose **2**[6] was isolated by dialysis and preparative HPLC (LiChrosorb-NH_2, 7μm; MeCN-H_2O 80/20)(74 % yield), and then reduced by reaction with bistrimethylsilyltrifluoroacetamide, trimethylsilyltriflate and triethylsilane in acetonitrile.[7] The reduction afforded stereoselectively[8] the α-C-mannoside **3**[9] (L-*allo*-D-*erythro*-3,7-anhydro-octitol) in 70 % yield after HPLC purification (LiChrosorb-NH_2, 7μm; MeCN-H_2O 80/20). This two-pot procedure affords stereoselectively the α-C-mannoside **3** in 52% overall yield.

In conclusion, the idea to exploit an aldolase to lengthen the skeleton of a sugar, combined with the possibility to reduce one-pot in non protected form the lengthened glyculose,outlines an easy stereoselective

way to obtain C-glycosides without employing any protective step. The described results are an example of application of this idea; work is in progress to extend this procedure to to synthesis of other C-glycosides.

Scheme



α-C-mannoside

References and notes

1 Bertozzi, C.; Bednarski, M. *Carbohydr. Res.* **1992**, *223*, 243.
2 Winkler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084.
3 See *inter alia* Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.*, **1982**, *104*, 4976; Pougny. J-R.; Nassr, M. A. M.; Sinay, P. *J. Chem. Soc., Chem. Commun.*, **1981**, 375; Reed, L. A.; Ito, Y.; Masamune, S.; Sharpless, K. B. *J. Chem. Soc.*, **1982**, *104*, 6468; Giese, B.; Dupuis, J.; Leising, M.; Nix, M.; Lindner, H. J. *Carbohydr. Res.*, **1987**, *171*, 329; Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.*, **1988**, *53*, 4181; and references cited therein.
4 Obtained in situ from D-fructose 1,5-bisphosphate with Triose Phosphate Isomerase (ref. 3).
5 Bednarski, M. D.; Waldmann, H. J.; Whitesides, G. M. *Tetrahedron Letters*, **1986**, *48*, 5807.
6 **2**, mixture of anomers, oil, ^{13}C NMR (D_2O) (major isomer): ppm 63.56 (2 t), 72.88 (2 d), 75.83 (d), 76.80 (d), 81.22 (d), 102.50 (s). MS (FAB) *m/e* 263 (M^+ + Na). Anal. Calcd For $C_8H_{16}O_8$: C, 40.00; H, 6.71. Found: C, 40.31; H. 6.95.
7 Bennek, J. A.; Gray G. I. R. *J. Org. Chem.*, **1987**, *52*, 892.
8 The configuration at C-7 of **3** was inferred from the ^1H NMR chemical shifts and coupling constants, which are unjustifiable for its 7-epimer which must assume a $^4C_1$ conformation. Moreover, this configuration is expected from the stereochemical outcome of the anomeric hydroxyl group reduction.[3a]
9 **3**, oil, $[\alpha]_D$ +6.6 (c 1, MeOH); ^1H NMR (300 MHz, D_2O): δ 3.68 (dd, J 12 and 7 Hz, H-1a), 3.76 (dd, J 12 and 7 Hz, H-8a), 3.78-3.85 (3 H, m, H-1b, H-2 and H-3), 3.86 (dd, J 12 and 4 Hz, H-8b), 3.96 (dd, J 4 and 5 Hz, H-4), 4.12 (dt, J 7, 4 and 2 Hz, H-7), 4.18 (dd, J 4 and 2 Hz, H-6), 4.27 (dd, J 4 and 2 Hz, H-5); ^{13}C NMR (D_2O): ppm 62.84 (t), 65.23 (t), 73.91 (d), 75.13 (d), 79.78 (d), 80.31 (d), 83.85 (d), 87.69 (d). MS (FAB) *m/e* 247 (m^+ + Na). Anal. Calcd for $C_8H_{16}O_7$: C, 42.86; H, 7.19. Found: C, 42.57; H, 7.39.

Acknowledgment. We thank the M.U.R.S.T. for the financial support and Mr. Enrico Caneva and Mr. Sergio Crippa for the NMR Spectra .