Tetrahedron Letters, Vol. 34, No. 28, pp. 4555-4558, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A New Procedure for the Synthesis of Azasugars

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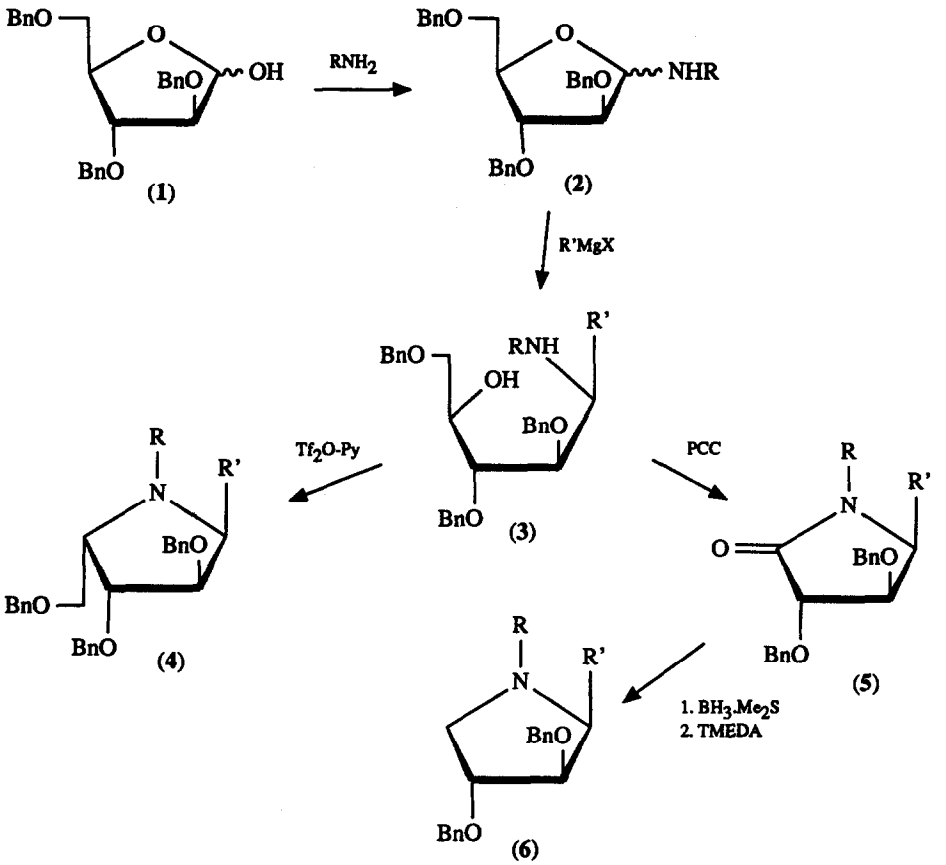
Abstract. Reaction of the commercially available 2,3,5-tri-O-benzyl-D-arabinose with a primary amine (RNH_2) affords the arabinofuranosylamine **2**, which on treatment with a Grignard reagent stereoselectively gives the aminoalcohol **3**. **3** is an useful precursor of azasugars: it is converted into the pyrrolidine **4** by treatment with Tf_2O-Py, whereas by oxidation with PCC it affords the lactam **5** which can be reduced to the corresponding amine **6**.

The "azasugars", molecules structurally related to sugars in which the ring oxygen is replaced by the nitrogen of an amino group, have attracted considerable interest due to their ability to inhibit glycosidases.[1] In fact glycosidase inhibitors have shown remarkable therapeutic potentialities in the treatment of metabolic diseases such as diabetes mellitus,[1,2] in the inhibition of tumoral metastasis,[3] and as antiviral agents, in particular against the human immunodeficiency virus (HIV).[4] Recent studies have shown that some azasugars, such as castanospermine and deoxynojirimycin, inhibit the interaction between the viral envelope glycoprotein (gp120) and the cell protein receptor (CD4), which is required to initiate an infective cycle.[4] Two glucosidases (I and II) and two mannosidases (IA and IB) are involved in the biosynthesis of gp120.[5] It has been shown that the glucosidases are in general inhibited by azasugars which are structurally similar to glucose, while the best inhibitors of mannosidases are structurally quite different from mannose, this is the case of some pyrrolidine derivatives.[6] It has also been observed that the anti-HIV activity of these glycosidase inhibitors is improved by the presence of a lipophilic substituent, such as a butyl group linked to the nitrogen of the azasugars.[7] In other cases[8] an alkyl substituent is linked to the carbon of the azasugar adjacent to the nitrogen, the "anomeric" carbon, so that an "aza-C-glycoside" is formed.

We now describe a new versatile procedure for the synthesis of azasugars, which allows the construction of molecules with different substituents at the nitrogen atom and at the adjacent position, starting from commercially available sugars. The procedure, shown in scheme I, involves the reaction of a protected aldose, 2,3,5-tri-O-benzyl-D-arabinose (**1**), with a primary amine (RNH_2) to afford the corresponding glycosylamine **2**, which is then reacted with a Grignard reagent (R'MgX).[9] The so obtained aminoalcohol **3** can be cyclized by treatment with trifluoromethanesulphonic anhydride, to afford the cyclic amine **4**, or it can be converted into the lactam **5** by treatment with PCC. The lactam **5** can be easily converted into the corresponding amine. In both cases, an azasugar is formed in which R and R' derive respectively from the primary amine and the Grignard reagent, so that different products can be obtained just by changing the structure of these two reagents.

Scheme I

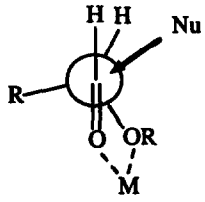


The synthetic strategy involves the formation of a new stereocenter in the Grignard reaction (THF, 20 °C). We observed a good stereoselection in the cases tested: N-benzyl-2,3,5-tri-O-benzyl-D--arabinofuranosylamine (**2**, R = -CH_2Ph) afforded the gluco-isomer **3** (R = -CH_2Ph, R'= -CH=CH_2) in 71 % yield and 88% d.e.;[9] N-hexyl-2,3,5-tri-O-benzyl-D-arabinofuranosylamine (**2**, R = -C_6H_{13}) afforded an isomerically pure product[10] **3** (R = -C_6H_{13}, R'= -C_8H_{17}) (92% yield from **1**). The stereochemical outcome of the reaction is in agreement with a Cram chelation control model (figure I), which results in the formation of the *threo* product, as in general observed by us[11] and others[12] in the reaction of aldoses and their imines[9] with organometallic reagents.[13]

The aminoalcohols **3**, treated with Tf_2O in pyridine afforded the pyrrolidine **4** (73% yield in the case of R = -CH_2Ph, R'= -CH=CH_2; 71% in the case of R = -C_6H_{13}, R'= -C_8H_{17}), the catalytic hydrogenation (Pd/C, EtOH-2N HCl) of which quantitatively afforded the azasugars **7**[14] and **8**.[14]

Figure I

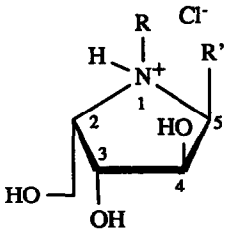
Cram chelation control model for the reaction of aldoses with organometallic reagents



Treatment of **3** with 4 equivalents of PCC (CH_2Cl_2, 4 Å m.s.) afforded the lactam **5** (85% yield in the case of R = -CH_2Ph, R'= -CH=CH_2; 94% yield in the case of R = -C_6H_{13}, -C_8H_{17}). This unusual oxidative degradation allows the access to a new series of azasugars starting from the same precursor. The reaction requires 4 equivalents of PCC, according to the known mechanism of oxidative degradation of ketoses[15] which, however, occurs in very basic conditions.

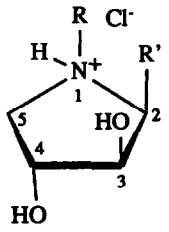
The lactam **5** was reduced to the corresponding amines **6** with $BH_3.Me_2S$ in THF at reflux, followed by treatment of the borate with TMEDA[16] (60% yield in the case or R = -C_6H_{13}, R'= -C_8H_{15}, 76% yield for R = H, R'= -C_2H_5). The deprotection of **6** (H_2, Pd/C, EtOH-2N HCl) afforded quantitatively the azasugars **9**[14] and **10**.[14] Also the lactam **5** (R = -C_6H_{13}, R' = -C_8H_{17}) was deprotected by catalytic hydrogenation (Pd/C, EtOH) to afford quantitatively the lactam **11**.[14]

Figure II



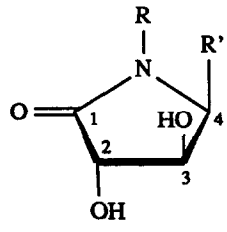
(**7**) R = H, R'= C_2H_5

(**8**) R = C_6H_{13}, R'= C_8H_{17}



(**9**) R = H, R'= C_2H_5

(**10**) R = C_6H_{13}, R'= C_8H_{17}



(**11**) R = C_6H_{13}, R'= C_8H_{17}

In conclusion, the described procedure allows the synthesis of azasugars in a versatile and easy manner. Starting from the same aldose, but employing different amines and Grignard reagents, it is possible to synthesize azasugars which differ in the substituent at the nitrogen and at the adjacent position. Furthermore, the observed oxidative demolition of **3**, with the formation of the lactam **5**, enhances the potentialities of the method. Work is in progress to extend the procedure to different substrates, and to evaluate the biological properties of the products.

Acknowledgments: we thank MURST and CNR "Progetto Finalizzato Chimica Fine II" for the financial support.

References and Notes

1. Truscheit, E, Frommer, W.; Junge, B; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*,744.
2. Creutzfeld, W., Ed. *Proceedings-First International Symposium on Acarbose (Montreux, Oct. 8-11, 1981)*; Excerpta medica: Amsterdam, 1982.
3. Bernacki, R. J.; Niedbala, M. J.; Korytnyk, W. *Cancer Metastasis Rev.* **1985**, *4*, 81.
4. Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature*, **1987**, *330*,74.
5. De Clercq, E. Chemotherapeutic approach of AIDS, Koninklijke Academie voor Geneeskunde van Belgie, **1988**, *2*, 166.
6. Winkler, D. A.; Holan, G. *J. Med. Chem.*, **1989**, *32*, 2084.
7. (a) Karpas, A.; Fleet, G. W.; 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) Liu, P. S.; Hoekstra, W. J.; King, C-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829.
8. See inter alia:(a) Liotta, L. J.; Lee, J.; Ganem, B. *Tetrahedron* **1991**, *47*, 2433. (b) Liu, P. S.; Rogers, R. S.; Kang, M. S.; Sunkara, P. S. *Tetrahedron Lett.* **1991**, *32*, 5853. (c) Mierscough, P. M.; Fairbanks, A. J.; Jones, A. H.; Bruce, I.; Choi S. S.; Fleet, G. W. J., Al-Daher, S. S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10177. (d) Bruce, I.; Fleet, G. W. J.; Cenci de Bello, I.; Winchester, B. *Tetrahedron*, **1992**, *48*, 10191. (e) Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553. (f) Wang, Y-F.; Dumas, D. P.; Wong C-H. *Tetrahedron Lett.* **1993**, *34*, 403.
9. The attack of CH_2=CHMgBr on **2** and the stereochemical outcome of the reaction has been described by us in a procedure directed to the synthesis of C-glycosides: Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1989**, 298.
10. No traces of the isomer were detected by TLC and ^{13}C NMR of the crude reaction product.
11. Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181.
12. (a) Buchanan, J. G.; Edgar, A. R:; Power, M. J. *J. Chem. Soc., Perkin I*, **1974**, 1943. (b) Gupta, C. M.; Jones, G. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 3000. (c) Paulsen, H.; Schüller, M.; Nashed, M. A.; Redlich, H. *Liebigs Ann. Chem.* **1986**, 675. (d) Paulsen, H.; Schüller, M.; Nashed, M. A.; Heitmann, A.; Redlich, H. *Tetrahedron Lett.* **1985**, *26*, 3689. (e) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769.
13. The formation of the *erythro* products, reported by Nagai, N.; Gaudino, J. J.; Wilcox, C. S. *Synthesis* **1992**, 163, is confined to the cases in which the α-hydroxyl group of the aldose is protected as isopropylidene. In these cases probably the protecting group sterically interfere with the chelation.
14. All new compounds gave satisfactory analytical and spectroscopical data. Some selected data:
7 m.p. 174 °C dec.; $[\alpha]_D$ +1.2 (c 1, MeOH). ^{13}C NMR (CD_3OD): ppm 11.62 (Me); 20.86 (CH_2); 59.71 (CH_2O); 65.08, 65.25, 76.60 (1 CHN, 2 CHO). ^1H NMR (CD_3OD): δ 4.18 (bs, H-3); 4.06 (bd, J 3 Hz, H-4); 3.79-3.95 (3 H, m); 3.63 (dt, J 7.5, 3 Hz, H-5); 1.80 (2 H, m, CH_2); 1.05 (t, J 7 Hz, Me).
8 ^{13}C NMR (CD_3OD): (the two protonated forms, epimeric at the nitrogen atom, show different signals) ppm 14.88 (2 Me); 24.00, 24.11, 25.56, 27.55, 27.69, 28.09, 28.39, 30.92, 31.10, 32.95, 33.41 (11 CH_2); 54.55 and 55.54 (CH_2N); 57.67 and 59.87 (CH_2O); 69.63 and 70.27 (CHN); 73.68, 73.79, 74.60, 76.16, 77.09, 77.60 (1 CHN, 2 CHO).
9 m.p. 207-210 °C; $[\alpha]_D$ +10.7 (c 1, MeOH). ^{13}C NMR (D_2O): ppm 13.11 (Me); 21.56 (CH_2); 53.26 (C-5); 66.71 (C-2); 76.94, 77.28 (C-3 and C-4). ^1H NMR (D_2O): δ 4.52 (d, J 5 Hz, H-4); 4.36 (bd, J 3 Hz, H-3); 3.83 (dd, J 8, 3 Hz, H-2); 3.77 (dd, J 12, 5 Hz, H-5a); 3.37 (d, J 12 Hz, H-5b); 1.97 (m, CH_2); 1.18 (t, J 7 Hz, Me).
10 m.p. 110 °C; $[\alpha]_D$ +49.3 (c 1, MeOH). ^{13}C NMR (CD_3OD): ppm 13.75 (2 Me); 22.97, 22.97, 25.01, 25.82, 26.73, 26.73, 29.83, 29.83, 29.83, 31.77, 32.31 (11 CH_2); 56.81, 59.77 (2 CH_2N); 71.44 (CHN); 74.65, 75.06 (2 CH_2O). ^{1}HNMR (CD_3OD): δ 4.23 (d, J 4.3 Hz, H-4); 4.12 (bs, H-3); 3.83 (dd, J 12.7, 4.3 Hz, H-5a); 3.55 (m, H-2); 3.14 (d, J 12.7 Hz, H-5b); 3.03 (m, CH_2N); 2.05-1.02 (22 H, CH_2); 0.91 (t, J 7 Hz, Me); 0.90 (t, J 7 Hz, Me).
11 oil; $[\alpha]_D$ -53.6 (c 1, $CHCl_3$); IR 1750 cm^{-1} (C=O). ^{13}C NMR (CD_3OD): ppm 14.79 (2 Me); 23.95, 24.04, 27.19, 27.90, 28.39, 29.14, 30.70, 30.92, 31.33, 32.95, 33.36 (11 CH_2); 42.54 (CH_2N); 60.40 (CHN); 75.65, 76.50 (CHO); 174.77 (C=O). ^1H NMR (CD_3OD): δ 4.13 (d, J 7 Hz, H-2); 4.10 (t, J 7 Hz, H-3); 3.65 (bq J 7 Hz, H-4); 3.53 (dt, J 14, 8 Hz, CHN); 2.96 (ddd, J 14, 8, 5.5 Hz, CHN); 1.80-1.30 (22 H, CH_2); 0.92 (6 H, m, 2 Me).
15. Green, J. W. in *The Carbohydrates*, Pigman, W.; Horton, D. Ed., Academic press **1980**, *vol. IB*, 1126
16. Brown, H. C.; Choi, M. Y., Narasinhan, S. *J. Org. Chem.*, **1982**, *47*, 3153.

(Received in UK 20 May 1993)