Pergamon

Tetrahedron Letters, Vol. 37, No. 43, pp. 7717-7720, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01732-7

Practical Route to D-Manno and D-Gluco Azasugars From C_2 Symmetric Bis-aziridines

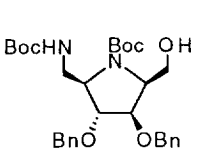
Isabelle McCort, Annie Duréault*, Jean-Claude Depezay

Université René Descartes, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques associé au CNRS
45 rue des Saints-Pères, 75270 Paris Cedex 06, France

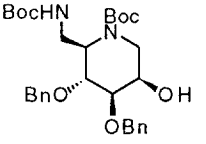
Abstract: 6-Amino-2,5-imino-D-glucitol **2** and 6-amino-1,5-imino-D-mannitol **3**, substituted by a free hydroxyl group, have been synthesized from the conformationally flexible *N*-Boc bis-aziridine **1**. Regioselective ring-opening of **1** by acetic acid is a straight way towards **2**, while reaction of **1** with water or allylic alcohol under ytterbium triflate catalysis produces selectively the azapyranose **3**. Nitrous deamination carried out on the cyclic carbamate-protected pyrrolidine **4** leads to a 1:1 mixture of both 2,5-imino-D-glucitols **5** and **6** bearing a free hydroxyl substituent either at C-1 or at C-6.

Both highly oxygenated pyrrolidines and piperidines constitute an important family of glycosidase and glycosyltransferase inhibitors[1]. Pseudodisaccharides have potential of much specificity[2], therefore pseudodisaccharides in which iminoalditols are linked to other sugars by non-hydrolysable links are the targets of considerable synthetic efforts[3]. Azasugars bearing a free hydroxyl substituent at a well defined position might be used for the construction of complex glycosides.

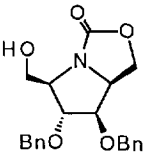
Starting from the conformationally flexible *N*-Boc bis-aziridine **1**, we have carried out the syntheses of 6-amino-2,5-imino-D-glucitol **2**, 6-amino-1,5-imino-D-mannitol **3** and two selectively protected forms of 2,5-imino-D-glucitol (**5** and **6**), precursors of a potent inhibitor of α-and β-glucosidases[4].



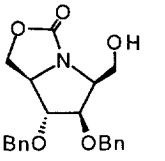
2



3



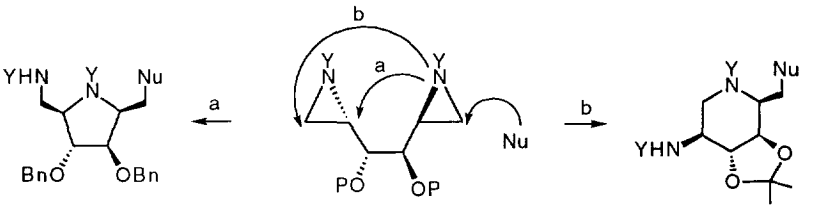
5



6

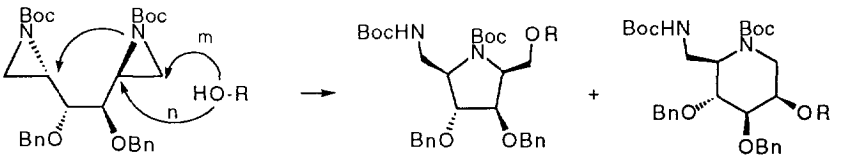
N-Activated bis-aziridines derived from D-mannitol are versatile building blocks for the synthesis of enantiomerically pure polyfunctionalized nitrogen heterocycles. Aziridine ring-opening by nucleophiles proceeds with S_N2 characteristics in aprotic solvents, with complete selectivity at the primary carbon even in the

presence of Lewis acids. Subsequent nitrogen intramolecular heterocyclization via a *6-endo* process provides access to highly hydroxylated piperidines of L-ido configuration[5], while a *5-exo* cyclization leads to pyrrolidines of D-gluco configuration[6]. The regioselectivity of the intramolecular heterocyclization depends on the flexibility of the aziridine carbon chain. With conformationally flexible bis-aziridines (P=CH_2Ph) the cyclization step follows almost exclusively the more favorable *5-exo* process (scheme 1).



Scheme 1

The opening of 3,4-di-O-benzyl bis-aziridines by various nucleophiles enables the synthesis of differently functionalized pyrrolidines, only the Et_2AlCN mediated alkylation of **1**[6b] had been found to occur principally at the secondary carbon. We report here the reaction of bis-aziridine **1** with hydroxylated reagents (acetic acid, allylic alcohol and water), used as polar co-solvents. The opening of **1** takes place at both C-1 and C-2 already at room temperature, it proceeds with S_N1 characteristics with a selectivity which depends on the catalyst, as outlined on scheme 2. The introduction of the hydroxylated group at C-1 provides after nitrogen intramolecular cyclization the tetrasubstituted pyrrolidine **2** of D-gluco configuration (path m), while nucleophilic attack at the secondary carbon leads to piperidine **3** of D-manno configuration via a *6 exo tet* process (path n).



1 **2** **3**

R = $COCH_3$	**a**	55%	27%
R = CH_2-CH=CH_2	**b**	i 32% ii 27%	38% 55%
R = H	**c**	27%	50%

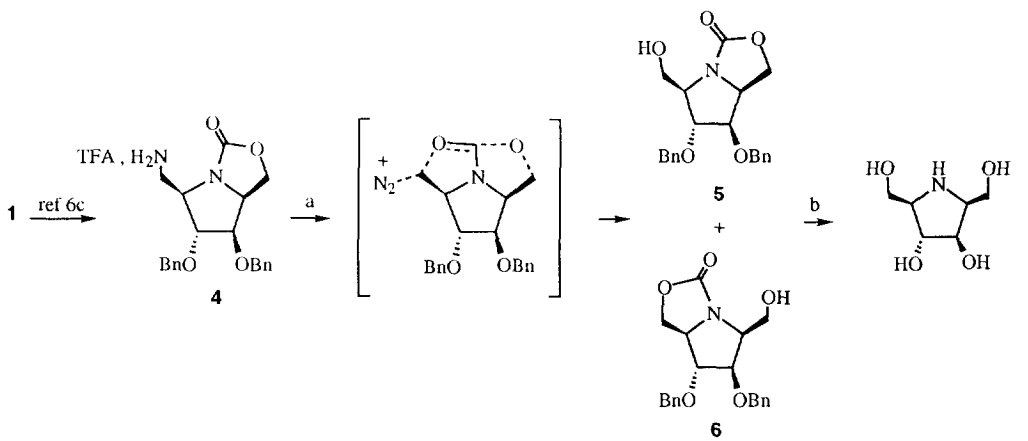
a. AcOH, 20°C, 2h; b. i) CH_2=CH-CH_2OH, $BF_3.Et_2O$, 20°C, 2h ; ii) CH_2=CH-CH_2OH, $Yb(OTf)_3$ 10% mmol, 20°C, 2h; c. HOH, THF, $Yb(OTf)_3$ 10%mmol, 20°C, 20h.

Scheme 2

The reaction of **1** with acetic acid results in the selective one step preparation of the azafuranose **2a**. **2a** is formed in 55% yield besides 27% of the azapyranose **3a**. Transesterification with catalytic amounts of

MeONa in MeOH yields quantitatively the pyrrolidine **2c**[7] bearing a free hydroxyl group at C-1. **2c** was found identical to the compound which results of the oxidation and pummerer rearrangement of the 1-phenylthio pyrrolidine[6d]. The opposite regioselectivity is achieved during the reaction of **1** with alcohols or with water. The ring-opening of *N*-Boc-aziridines by alcohols proceeds with S_N1 characteristics with a selectivity which depends on the Lewis acid[8]. We show in the present study that $Yb(OTf)_3$ strongly catalyzes the opening of bis-aziridine **1** even in water medium, producing a 2:1 mixture of **3** and **2** in high overall yield (**2b+3b**: 82%; **2c+3c**: 77%)[7]. A higher selectivity for the attack at the secondary carbon of the aziridine ring is observed in comparison with the BF_3-Et_2O catalyzed reaction, while rigorous effort in excluding moisture can be avoided[9] (scheme 2).

The introduction of an hydroxyl function at C-1 of the pyrrolidine **2** was our first aim, however it was as well of interest to introduce an hydroxyl group at C-6 in order to obtain the corresponding tetrahydroxy azafuranose. Thus, we have carried out a quick synthesis of two selectively protected forms of 2,5-imino-D-glucitol[4] by the nitrous deamination of the 6-amino-D-gluco azafuranose **4**[7]. The synthesis of the cyclic carbamate-protected pyrrolidine **4** had been reported earlier[6c], resulting from the regioselective opening of **1** with Li_2NiBr_4, followed by Ag^+ promoted intramolecular substitution of the bromide by the *N* Boc group in 75% overall yield.



a) Isoamyl nitrite, Et_3N (0.5eq), THF, 60°C, 1h30, 50%; b) i: H_2, Pd black, AcOH, ii: K_2CO_3, MeOH, reflux, 95%

Scheme 3

We show here that nitrous deamination of **4** with isoamyl nitrite leads in 50% yield to a 1:1 mixture of cyclic carbamate protected pyrrolidines **5** and **6**, which can be chromatographically separated. The amine **4** is reacted as its trifluoracetic salt, in the presence of Et_3N (0.5 equivalent), in order to keep the pH of the reaction mixture superior to 3. The simultaneous formation of both compounds **5** and **6** may result of the nucleophilic attack of a cyclic carbonium intermediate as depicted on scheme 3. The structure of carbamate **5** has been established after debenzylation by comparison with an authentic sample[3b]. Complete deprotection of the **5+6** mixture leads to 2,5-imino-D-glucitol, which analytical spectral data are identical with those previously reported[4].

In conclusion we have shown that ytterbium triflate catalyzes efficiently the opening of bis-aziridine **1** with water or alcohols, allowing the preparation of polyhydroxylated pyrrolidines or piperidines bearing a free hydroxyl substituent. Application of this work towards the preparation of aziridinyl pyrrolidines, as potential irreversible glucosidase inhibitors[10], and azasugar bisubstrates is currently in progress.

REFERENCES AND NOTES

1. (a) Winchester, B.; Fleet, G.W. *Glycobiology*, **1992**, *2*, 199-210. (b) Look, G.C.; Fotsch, C.H.; Wong, C.-H. *Acc. Chem. Res.*, **1993**, *26*, 182-190. (c) Nishimura, Y. "Glycosidase and Glycosyltransferase Inhibitors" in "Studies in Natural Products Chemistry", Atta-ur-Rahman, Ed.; Elsevier: Amsterdam **1992**, Vol. 10, p. 495.
2. (a) Liu, P.S. *J. Org. Chem.*, **1987**, *52*, 4717-4721. (b) Anzeveno, P.B.; Creemer, L.J.; Daniel, J.K.; King, C.-H.R.; Liu, P.S. *J. Org. Chem.*, **1989**, *54*, 2539-2542.
3. (a) Johnson, C.R.; Miller, M.W.; Golebiowski, A.; Sundram, H.; Ksebati, M.B. *Tetrahedron Lett.*, **1994**, *35*, 8991-8994. (b) Wong, C.-H.; Provencher, L.; Porco, Jr., J.A.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D.H. *J. Org. Chem.* **1995**, *60*, 1492-1501. (c) Campanini, L.; Duréault , A.; Depezay, J.C. *Tetrahedron Lett.*, **1996**, *37*, 5095-5098.
4. Liu, K.K.-C.; Kajimoto, T.; Chen, L.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.*, **1991**, *56*, 6280-6289.
5. Duréault, A.; Tranchepain, I.; Depezay, J.C. *J. Org. Chem.*, **1989**, *54*, 5324-5330.
6. (a) Fitremann, J.; Duréault , A.; Depezay, J.C. *Tetrahedron Lett.*, **1994**, *35*, 1201-1204. (b) Fitremann, J.; Duréault , A.; Depezay, J.C. *Synlett,* **1995**, 235-237. (c) Campanini, L.; Duréault , A.; Depezay, J.C. *Tetrahedron Lett.*, **1995**, *36*, 8015-8018. (d) Fitremann, J., Ph.D. Thesis, Université Paris 6, **1995**.
7. **2c**: ^{13}C NMR (63 MHz, $CDCl_3$) δ: 28.36, 28.42 (CH_3), 42.2 (C-6), 61.9, 62.5 (C-2, C-5), 63.0 (C-1), 72.2, 72.7 ($O\underline{C}H_2Ph$), 79.2, 81.4 ($\underline{C}(CH_3)_3$), 82.0, 82.6 (C-3, C-4), 127.7, 128.0, 128.2, 128.5, 128.6, 136.9, 137.5 (C_{arom}), 156.1, 156.3 (CO).
3c: ^{13}C NMR (63 MHz, $CDCl_3$) δ: 28.32, 28.41 (CH_3), 38.9 (C-1), 40.9 (C-6), 52.7 (C-5), 64.4 (C-2), 71.2, 73.4 ($O\underline{C}H_2Ph$), 73.7, 77.3 (C-3, C-4), 79.3, 80.2 ($\underline{C}(CH_3)_3$), 127.6, 127.8, 128.3, 128.4, 128.7, 137.2, 137.7 (C_{arom}), 155.8, 155.85 (CO).
4: $[\alpha]_D$ +26 (c 1.0, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ: 3.37 (m, 1H), 3.49 (m, 1H), 3.64 (s, 1H), 3.89 (s, 1H), 3.99 (d, J=10Hz, 1H), 4.26-4.46 (m, 5H), 4.55 (AB, J=12Hz, 1H), 4.57 (AB, J=12Hz, 1H), 7.1-7.4 (m, H_{arom}, 10H), 8.25 (brs, 3H, NH_3^+).
8. Ho, M.; Chung, J.K.K.; Tang, N. *Tetrahedron Lett.*, **1993**, *34*, 6513-6516.
9. Kobayashi, S. *Synlett,* **1994**, 689-701.
10. Tong, M.K.; Ganem, B. *J. Am. Chem. Soc.*, **1988**, *110*, 312-313.

(*Received in France* 22 *July* 1996; *accepted* 6 *September* 1996)