Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5095-5098, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01033-7

One Step Synthesis of Sulfur and Nitrogen Linked Aza-disaccharide Precursors from D-Mannitol Derived Bis-aziridines

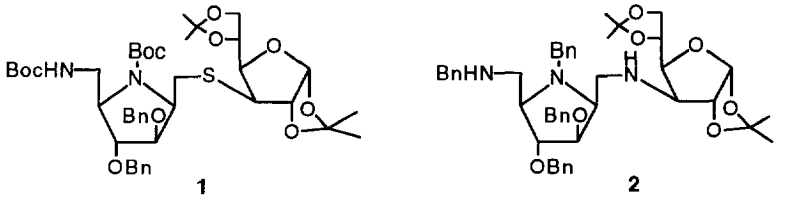
Laurence Campanini, Annie Duréault *, Jean-Claude Depezay

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 *:* Carbon-nitrogen and carbon-sulfur linked pseudodisaccharides incorporating an hydroxylated pyrrolidine type glucosidase inhibitor have been prepared. These new azasugar-containing disaccharides result from the nucleophilic opening of D-mannitol derived bis-aziridines either by 3-deoxy-3-amino-D-glucose or by 3-deoxy-3-thio-D-glucose. Copyright © 1996 Published by Elsevier Science Ltd

Polyhydroxylated pyrrolidines and piperidines are a class of potent inhibitors of glycosidases[1], though simple azasugars that mimic a monosaccharide often act as broad spectrum inhibitors. Different natural products and synthetic analogs that contain an aglycon moiety attached to a glycosyl cation mimetics act as selective inhibitors[2]. Dideoxy-iminoalditols linked to other sugars by non-hydrolysable links have potential of much specificity, and different approaches towards such complex glycosides have already been reported[3].

We report here the synthesis of pseudodisaccharides in which a five-membered azasugar of D-gluco configuration is bonded at C-3 of D-glucose. In these new azadisaccharides, the interglycosidic oxygen atom that is present in natural glucans has been replaced either by a sulfur atom (**1**) or by an amino group (**2**) .

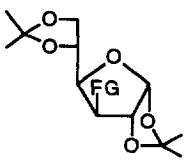


Scheme 1

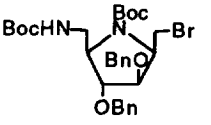
2,5,6-trideoxy-6-amino-2,5-imino-D-glucitol, the 6-amino analog of a potent inhibitor of α-and β-glucosidases[4] is the unnatural glycosyl moiety of **1** and **2.** The synthesis of these pseudodisaccharides can be achieved by coupling activated hydroxypyrrolidines with glucose derivatives. Still more effective is the

preparation of the bisubstrates **1** and **2** through nucleophilic opening followed by intramolecular aminocyclization of D-mannitol derived bis-aziridines[5], either by 3-deoxy-3-thio-D-glucose **3** or by 3-deoxy-3-amino-D-glucose **4**.

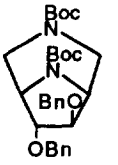
3[6] and **4**[7] were prepared as described, in three steps starting from diacetone-D-allose. The synthesis of the five-membered deoxyazasugar of D-gluco configuration **5**, substituted by a bromo group at the pseudo anomeric position, was achieved following our recently reported strategy[8] (scheme 2).



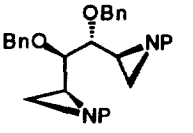
3: FG = SH **4**: FG = NH_2



5



6

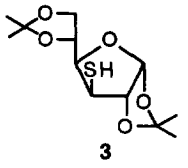


7a: P=Boc **7b**: P=Bn

Scheme 2

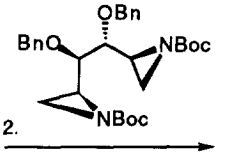
Coupling of the bromosubstituted pyrrolidine **5** with the sodium salt of 3-thio glucose **3** leads to thioether **1** in about 40% yield, together with variable amounts of the *N*-Boc diazabicyclo (3.2.1) octane **6**. **6** results from intramolecular conversion of **5** in basic medium[8].

The direct nucleophilic ring opening of the *N*-Boc bis-aziridine **7a** with thiol **3** is a more efficient way towards **1**. Opening of the first aziridine ring takes place already at -20°C, followed by slow intramolecular cyclisation into the thioglucosyl substituted pyrrolidine **1**. Thioether **1** is thus obtained in 50% yield, together with about 30% of recovered **7a** and small amounts of the diamine resulting from **7a** bis-opening. Recovering of the starting material is due to the formation of some disulfide from **3** in the reaction conditions.

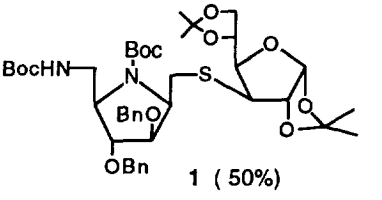


3

1. HNa → 2. **5** (20°C, 4h) → **1** + **6**



3 → 1. HNa → 2. (-20°C, then 4°C 12h)

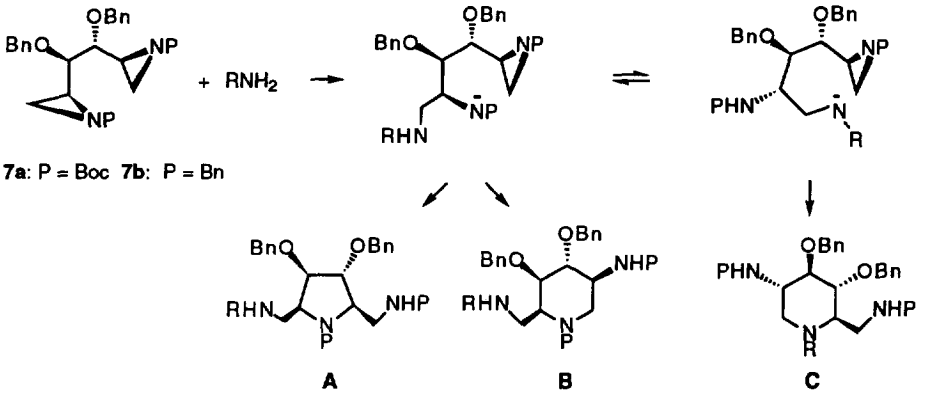


1 (50%)

Scheme 3

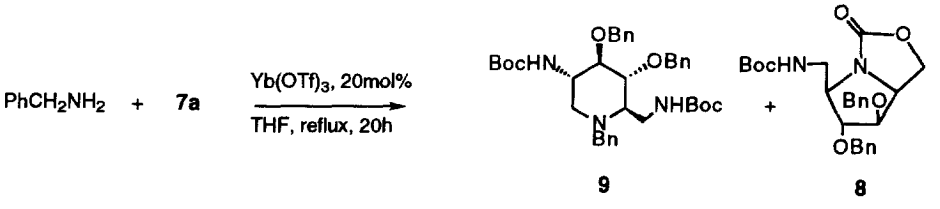
The ring opening of activated aziridines by amines requiring elevated temperatures, the introduction of the amino group is generally best realized by nucleophilic ring opening by sodium azide[9]. The ytterbium triflate catalyzed aminolysis of *N*-protected aziridines such as *tert*-butoxycarbonyl, tosyl, and benzyl aziridines has

been reported recently to proceed under smooth conditions with primary and secondary amines[10]. Actually both *N*-Boc and *N*-Bn bis-aziridines **7a** and **7b** react with primary amines in the presence of 10% or 20% of ytterbium triflate. Nucleophilic opening takes place regioselectively at the primary carbon leading to an α-diamino intermediate apt to cyclize from both nitrogen atoms (scheme 4) and give, either the pyrrolidine **A**[8] (D-gluco), the piperidine **B**[9] (L-ido), or the piperidine **C** (D-gluco).



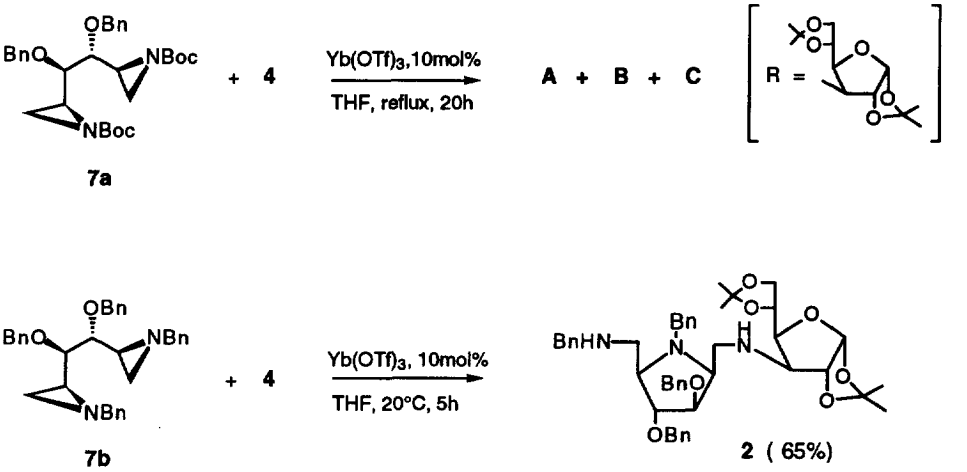
Scheme 4

When the *N*-Boc bis-aziridine **7a** is submitted to $Yb(OTf)_3$ catalyzed opening by benzylamine the piperidine **9** of D-gluco configuration is formed exclusively in about 20% yield. The reaction is slow in refluxing THF, goes with degradation of the aziridine and leads besides **9**, to various amounts of oxazolidinone **8**. The piperidine **9** is formed via a *6-exo-tet* aminocyclization process, while the formation of **8** results from the catalyzed rearrangement of **7a** with participation of the Boc substituent[8].



Scheme 5

Nucleophilic opening of the *N*-Boc bis-aziridine **7a** by aminoglucose **4** in refluxing THF leads to a mixture of type **A** glucosyl substituted pyrrolidine and of both piperidines **B** and **C**. **A** is formed in about 25% yield together with small amounts of **B** and **C**, and with degradation products. With the *N*-benzyl aziridine **7b**, there is as expected no competitive formation of any of the *N*-glucosyl piperidines; the reaction is achieved at 20°C and gives the pseudo disaccharide **2** as a single product in 65% yield.



Scheme 6

Nucleophilic opening of bis-aziridines with thio or aminosugars is an efficient method for the synthesis of pseudodisaccharides. The scope of the reaction is being extended to various sugars.

Acknowledgment: We are grateful to Roussel-Uclaf for financial support of this work.

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.
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.
4. Liu, K.K.-C.; Kajimoto, T.; Chen, L.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.*, **1991**, *56*, 6280-6289.
5. Fitremann, J.; Duréault , A.; Depezay, J.C. *Tetrahedron* , **1995**, *51*, 9581-9594.
6. Risbood, P.A.; Phillips, T.S.; Goodman, L. *Carbohydr. Res.*, **1981**, *94*, 101-107.
7. Whistler, R.L.; BeMiller, J.N. *Methods in Carbohydrate Chemistry*, **1972**, *VI*, 220-222.
8. Campanini, L.; Duréault , A.; Depezay, J.C. *Tetrahedron Lett.*, **1995**, *36*, 8015-8018.
9. Duréault , A.; Tranchepain, I.; Depezay, J.C. *J. Org. Chem.* **1989**, *54*, 5324-5330.
10. Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.*, **1994**, *35*, 7395-7398.

(*Received in France* 10 *April* 1996; *accepted* 23 *May* 1996)