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2,5-Disubstituted Pyrrolidines from D-Mannitol-Derived Bis-Aziridines

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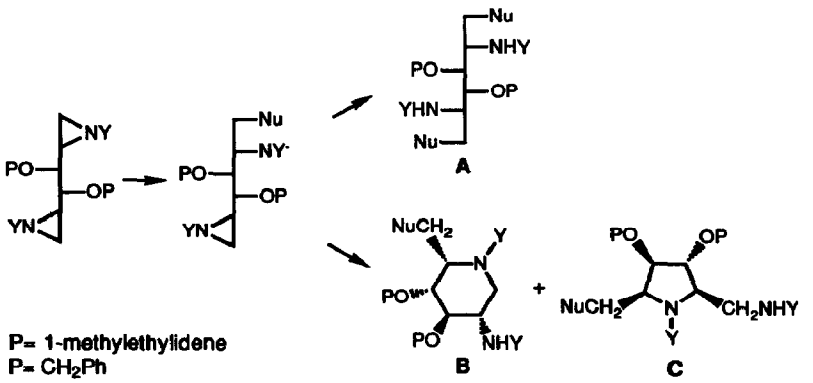
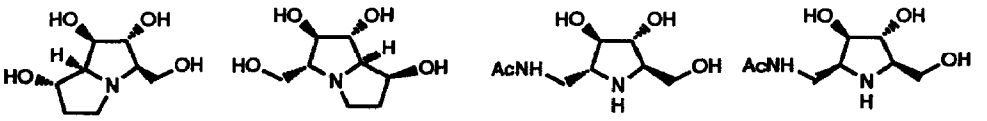
Abstract : *Concise syntheses of 3,4-dihydroxy-2,5-disubstituted pyrrolidines have been achieved starting from D-mannitol-derived flexible L-Ido bis-aziridines. Nucleophilic ring opening of the N-Boc and the N-Cbz activated bis-aziridines by phenylthiolate and azide ions has been studied ; the reaction can be oriented either toward bis-opening (derivative A) or heterocyclization. Heterocyclization leads to a 1:9 mixture of the enantiopure polysubstituted piperidines B and pyrrolidines C.*

We have carried out, starting from D-mannitol, the synthesis of new homochiral C_2 symmetric bis-aziridines which can be used as versatile building blocks in the synthesis of various biologically significant derivatives.

We had previously reported of the synthesis[1] and nucleophilic opening[2] of suitably *N*-activated bis-aziridines derived from 3,4-*O*-isopropylidene-D-mannitol. Nucleophilic opening led after heterocyclization to polysubstituted piperidines **B** possessing four asymmetric centers, close in structure to glycosidase inhibitors. The cyclization followed in this case a *6-endo-tet* process, the C-2, C-3 diol involved in a cyclic acetal preventing the formation of a pyrrolidine ring through a *5-exo-tet*-cyclization mode.



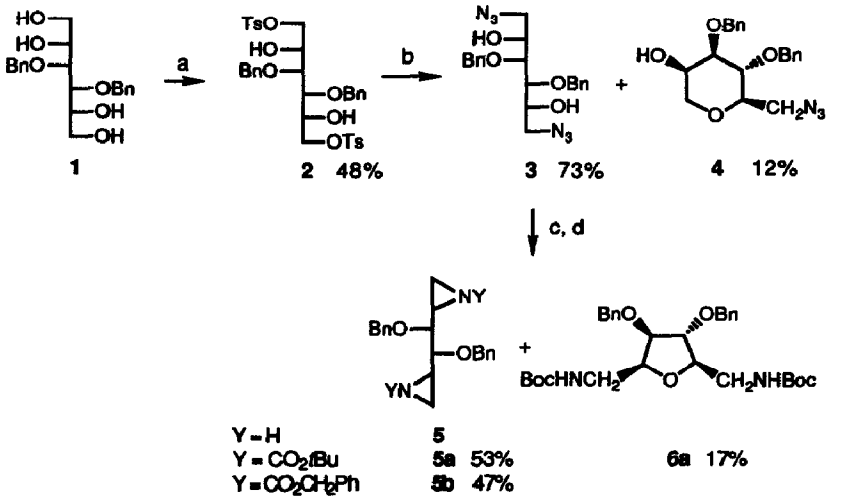
The selective preparation of functionalized pyrrolidines by the same strategy seemed a reasonable goal since, referring to Baldwin's rules, the *5-exo-tet*-cyclization mode is usually more favourable than the *6-endo-tet* process. We report here that bis-aziridines derived from 3,4-di-*O*-benzyl-D-mannitol are precursors of 3,4-dihydroxy-2,5-disubstituted pyrrolidines. Such skeletons are worthwhile synthetic targets since they have the basic structure of several biologically active alkaloids such as alexine[3] or australine[4], inhibitors of many glycosidases. Five membered acetamido azasugars have also recently been shown to be competitive inhibitors of *β-N*-acetylglucosaminase[5].



alexine australine

We anticipated that the nucleophilic ring opening of conformationally flexible bis-aziridines would enable the synthesis of pyrrolidine derivatives substituted at C-2 and at C-5 by two different functions and to this end we carried out the synthesis of bis-aziridine **5** protected at the nitrogen either by a *tert*-butoxycarbonyl (**5a**) or by a benzyloxycarbonyl group (**5b**).

5 was synthesized starting from 3,4-di-*O*-benzyl-D-mannitol **1** itself prepared following a known procedure[6].



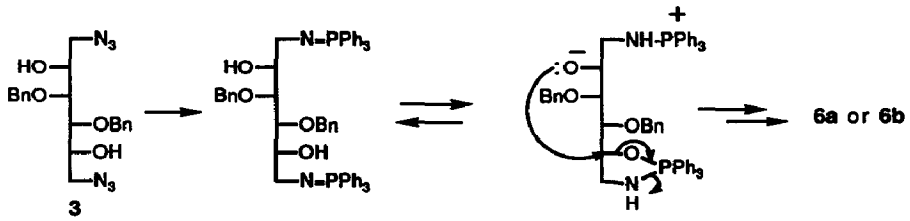
a) TsCl, pyridine, 0°C. b) NaN_3, DMF, 70°C, 5h. c) Ph_3P, $PhCH_3$,35°C 2h, then 85°C, 8h.
d) $(CO_2tBu)_2O$, Et_3N, THF, 0°C to rt, 3h; or: $ClCO_2CH_2Ph$, Et_3N, CH_2Cl_2, 0°C to rt, 3h.

The tetrol **1** was transformed into the corresponding diazidodiol **3** by sodium azide substitution of the corresponding primary ditosylate **2**, itself prepared in 48% yield by conventional manner. Sodium azide substitution of **2** effected at 70°C during 5 hours resulted in 73% of **3** besides 12% of the 1,6-dideoxy-6-azido-D-mannopyranose **4**. **4** results from the competitive attack, allowed by the conformational flexibility of the carbon chain of the secondary hydroxyle group on the primary tosylate.

When reacted with triphenylphosphine, as previously described for the 3,4-di-*O*-isopropylidene derivative[1], the diazidodiol **3** led to a mixture of the expected *N*-H bis-aziridine **5** and of the furan **6**. Both derivatives were isolated in their *N*-protected form; the *N*-Boc bis-aziridine **5a** and *N*-Cbz bis-aziridine **5b** in respectively 53% and 47% yield, and the *N*-Boc-2,5-diaminomethyl-3,4-dihydroxyfuran **6a** in 17% yield. *N*-Cbz-dihydroxyfuran **6b** is formed together with **5b**,but has not been purified.

The structure of the furanose **6a** was established by its ^{1}H and ^{13}C NMR spectral data. It does not possess the C_2 symmetry but the configuration of D-glucose and therefore occurs with inversion of configuration at C-2 of D-mannitol.

The formation of the furan **6** from the diazidodiol **3** derived bis-iminophosphorane could result from a competitive decomposition, allowed by the flexibility of the carbon chain, of the intermediate oxazaphospholidine as depicted in the scheme.



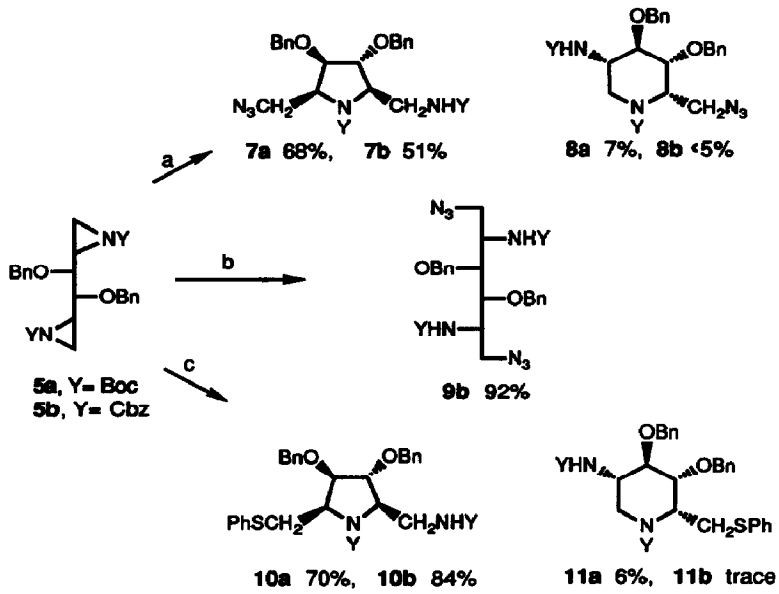
We have carried out the nucleophilic ring opening of the *N*-Boc and *N*-Cbz activated bis-aziridines by azide and phenylthiolate ions.

When the reaction is effected in an aprotic medium, the nucleophilic opening of the first aziridine ring is followed by an intramolecular aminocyclization leading to the formation of a piperidine or pyrrolidine derivative. We found that in each case the formation of the pyrrolidine ring largely prevailed.

Sodium azide nucleophilic ring opening of **5a** or **5b** when effected in DMF in the presence of 10% of tetrabutylammonium iodide led to the pyrrolidines **7a** and **7b** in respectively 68% and 51% yield; starting from **5a** the piperidine **8a** was also isolated in 7% yield.

The reaction was oriented toward bis-opening by using guanidinium azide as nucleophile, the bis-aziridine **5b** led thus to the bis-amino derivative **9b** very mildly in 92% yield. In this reaction the guanidinium ion acted as the proton donor.

When reacted with sodium phenylthiolate, **5a** led to a 10:1 mixture of the pyrrolidine **10a** and of the piperidine **11a**, which where isolated in respectively 70% and 6% yield. The aziridine **5b** led to **10b** in 84% yield, and to traces of the corresponding piperidine **11b**.



a) from **5a**: NaN_3, $IN(Bu)_4$ 10%, DMF, 65°C, 20h; from **5b**: NaN_3, $IN(Bu)_4$ 10%, DMF, 65°C, 4h
b) N_3^- $H_2N^+=C(NH_2)_2$, 60°C, 20h. c) PhSh, HNa, DMF, 20°C,3h.

Conformationally flexible D-mannitol-derived bis-aziridines are versatile precursors of attractive homochiral tetrasubstituted azafuranoses with D-glucose configuration.

References and Notes

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7. All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses.

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