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Highly Functionalized Cyclopentanes from Meso Bicyclic Hydrazines. A Rapid Access to Mannosidase Inhibitors

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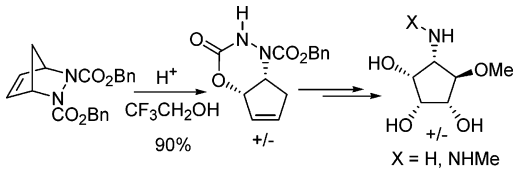
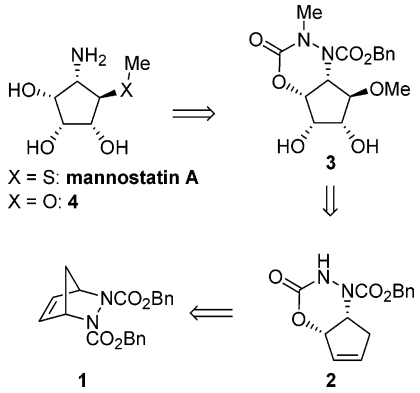


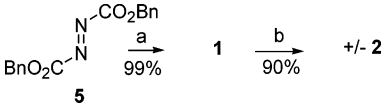
A simple diastereoselective access to amino- and hydrazinocyclopentitols is described. The key step involves a cationic rearrangement of a meso bicyclic hydrazine, followed by two successive stereoselective hydroxylations. Both racemic compounds are micromolar α-mannosidase (Jack bean) inhibitors.

The development of synthetic routes toward highly functionalized aminocyclopentanes has been stimulated by the extensive interest in glycosidases inhibitors these past decades.[1] Since the isolation in 1989 of the α-mannosidases inhibitor, mannostatin A,[2] several strategies have been proposed to have an access to synthetic analogues of this natural product, starting from carbohydrates,[3] inositols,[4] or 1,4-disubstituted cyclopentenes.[5]

SCHEME 1. Retrosynthetic Analysis of Compound 4



SCHEME 2. Acidic Rearrangement of Hydrazine 1[a]



[a] Reagents and conditions: (a) cyclopentadiene, rt. (b) H_2SO_4, CF_3CH_2OH, 20 min.

We have recently described the use of meso bicyclic hydrazine **1** for the straightforward stereoselective preparation of diaminocyclopentanols[6] and substituted 1,4-hydrazinocyclopentenes.[7] We wish to describe here the use of this starting material in the diastereoselective synthesis of polyhydroxylated amino- and hydrazinocyclopentanes and report on their biological activities.

Mannostatin A analogue **4**, with a methoxyl instead of the methylthio group, has recently been described by Ogawa and co-workers to exhibit interesting inhibitory activity of Jack bean α-mannosidase.[8] Scheme 1 outlines our retrosynthetic analysis, for which the key steps are the regio- and stereoselective introduction of three hydroxyl groups from intermediate **2**.

In contrast to strategies involving 5,5-bicyclic cyclopentenic intermediates,[5c,e] the use of a 5,6-bicyclic intermediate should favor a good facial discrimination in the allylic oxidation process, establishing the 1,2-trans configuration. Furthermore, the conformational flexibility of the oxadiazine moiety should be of interest in a directed osmium-catalyzed dihydroxylation,[9] leading to the correct relative configuration of the final compound.

Bicyclic hydrazine is readily available in a large scale (>20 g) from cyclopentadiene (Scheme 2). Although its acid-catalyzed rearrangement into oxadiazine **2** could be conducted under various conditions at a 100-mg scale,[7] the scale-up of this transformation proved to be prob-

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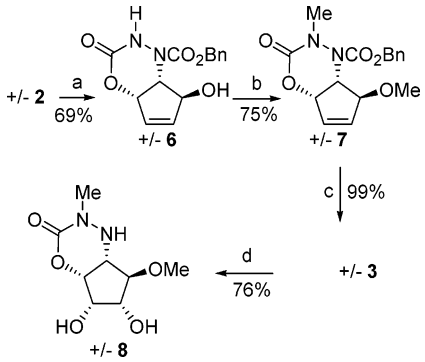
SCHEME 3. Synthesis of Polyhydroxylated Bicyclic Hydrazines[a]

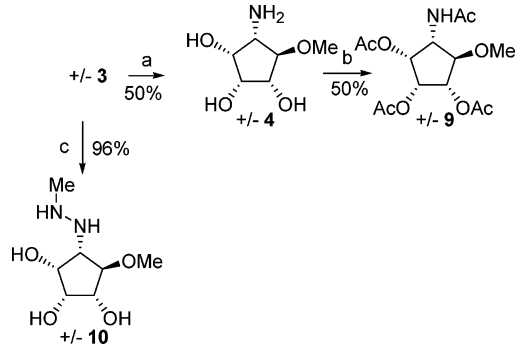


[a] Reagents and conditions: (a) SeO_2, KH_2PO_4, diglyme, 170 °C. (b) KH, MeI, THF. (c) OsO_4, NMO, THF/H_2O. (d) H_2, Pd/C, MeOH.

lematic. Since solvolysis or oligomerization of the transient allylic cation was probably responsible for this difficulty, the rearrangement was investigated in trifluoroethanol.[10] In such a medium, a reproducible 90% chemical yield could be obtained when conducting the reaction on several grams (Scheme 2).

A modification (reduced selenium oxide, shorter reaction time, nonaqueous workup) of Trost and Van Vranken conditions for allylic oxidation led to the desired alcohol in 69% yield in a complete regio- and stereoselective manner. Assignment of the relative configuration of the newly created stereogenic center was based on the assumption that selenium dioxide would add from the convex face of the bicyclic oxadiazine system to give alcohol **6**. *O*- and *N*-methylation of compound **6** led to oxadiazine **7**. Osmium-catalyzed dihydroxylation afforded compound **3** in a quantitative manner. The diastereoselectivity of this transformation proved to be difficult to establish, since NMR of compound **3** revealed a complex mixture of conformers. Removal of the benzylcarbamate group by hydrogenolysis led to **8** as a single compound, with no detectable isomers by ^1H and ^{13}C NMR, indicating that the dihydroxylation occurred in a fully stereoselective manner.Completion of the synthesis could be achieved by a one-step reductive cleavage of the benzyloxycarbonyl group, the hydrazine bond, and hydrolysis of the carbazate moiety, leading to the final aminocyclitol **4** in 50% yield. Chemical correlation with compound **9**, previously described by Ogawa and co-workers, was performed by peracetylation and comparison of spectral data, confirming the stereochemical assignment of the final compound (Scheme 4).[11] The racemic mixture exhibited an IC_{50} value of 1.4 μM in a standard Jack Bean α-mannosidase inhibitory essay with a *p*-nitrophenyl α-D-

SCHEME 4. Final Deprotection Step[a]



[a] Reagents and conditions: (a) Li, NH_3, −33 °C. (b) Ac_2O, pyridine. (c) LiOH, THF/H_2O.

mannopyranoside as a substrate. Interestingly, hydrazinocyclopentitol **10** could also be obtained in good yield. This compound showed a surprising activity with an IC_{50} value of 3.6 μM in the same test. Although some cyclic hydrazines are known to be good glycosidase inhibitors,[12] such an activity for exocyclic hydrazinocyclopentitols is, to the best of our knowledge, unprecedented.

In conclusion, a stereoselective synthesis of compound **4** has been performed in 6 steps and 23% overall yield from diazodicarboxylate **5**. This new route, involving an easily available bicyclic hydrazine as a key intermediate, not only enables the fast preparation of aminocyclopentitols of known biological activity but can also lead to a new class of glycosidase inhibitors. Racemic hydrazine **10**, obtained in a 44% yield from diazodicarboxylate **5**, proved to be quite active as a mannosidase inhibitor and could serve as an interesting scaffold for the elaboration of more complex heterocycle-substituted cyclopentitols.[13] Finally, since the absolute configuration is known to be crucial for mannosidases inhibitory activities,[14] an increase of the biological activity in both series can be expected when working with enantiopure material having the "natural" configuration. The preparation of enantiomerically pure oxadiazine **2** is under investigation.

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Supporting Information Available: Experimental procedures and characterizations of compounds **2**, **3**, **4**, **6**, **7**, **8**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Acetic acid 2,3-diacetoxy-5-acetylamino-4-methoxy-cyclopentyl ester 9:** ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.08 (s, 6H), 2.10 (s, 3H), 3.42 (s, 3H), 3.76 (t, J = 5.0 Hz, 1H), 4.57 (ddd, J = 9.0, 6.3, 5.0 Hz, 1H), 5.14 (t, J = 5.0 Hz, 1H), 5.34 (dd, J = 6.3, 4.0 Hz, 1H), 5.46 (dd, J = 5.0, 4.0 Hz, 1H), 5.77 (d, J = 9.0 Hz, 1H). Literature (ref 8) ^1H NMR: 2.04 (s, 3H), 2.08 (s, 6H), 2.10 (s, 3H), 3.42 (s, 3H), 3.77 (t, J = 4.6 Hz, 1H), 4.57 (ddd, J = 9.0, 6.1, 4.6 Hz, 1H), 5.14 (t, J = 4.6 Hz, 1H), 5.34 (dd, J = 6.1, 3.9 Hz, 1H), 5.46 (dd, J = 4.6, 3.9 Hz, 1H), 5.82 (d, J = 9.0 Hz, 1H).

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