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Synthesis of "α-Homogalactostatin" and of its 1,*N*-Anhydro Derivative

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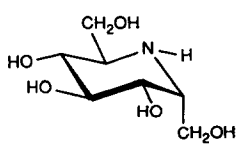
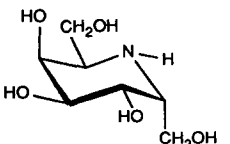
Summary: *α-Homogalactostatin* **2** *was prepared in 10 steps from 2,3,4,6-tetra-O-benzyl-D-galactose by way of a Wittig chain extension and a mercuricyclization. The synthesis of* **2** *was assisted by the unexpected participation of the nitrogen protecting group (benzyl carbamate) during iododemercuration. Intermediate* **10** *was converted in 2 steps into the 1,*N*-anhydro derivative of* **2**, *compound* **3**, *a potential inactivator of galactosidases.*

As stable homologs of 5-amino-5-deoxy-hexopyranoses, piperidine azasugars bearing, at C-1, a hydroxymethyl substituent (e.g. α-homonojirimycin **1**[1]) form a class of "aza-*C*-glycosyl" compounds of increasing importance. Recent studies[2-4] have revealed that these homologs retain much of the powerful biological activity of the parent amino hexoses or imino hexitols as glycosidase inhibitors,[5,6] the presence of the substituent at C-1 being responsible in some cases for a greater selectivity of the inhibitor.[3] The synthesis[7] of the first homoazasugar, **1**, was followed shortly by the discovery of its existence in Nature.[1] Homo analogs of L-fuconojirimycin,[4] mannojirimycin[8,9] and β-nojirimycin[9] have been recently prepared, the latter by way of a chemoenzymatic synthesis, and we have reported very recently the first chemical synthesis of β-homonojirimycin.[10] In this communication, we describe the synthesis of the novel homoazasugar **2**, the α-homo analog of galactostatin (5-amino-5-deoxy-D-galactose), and of its 1,*N*-anhydro derivative **3**, a potential irreversible inhibitor of galactosidases.[11] Both galactostatin[12] and its 1-deoxy derivative[13] are potent inhibitors of α- and β-galactosidases; it is of interest to note that, as in the case of **1**, the synthesis of galactostatin[12a] has preceded its isolation from the fermentation broth of a strain of *Streptomyces lydicus*.[14]



1



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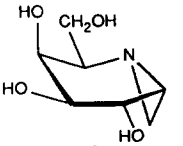
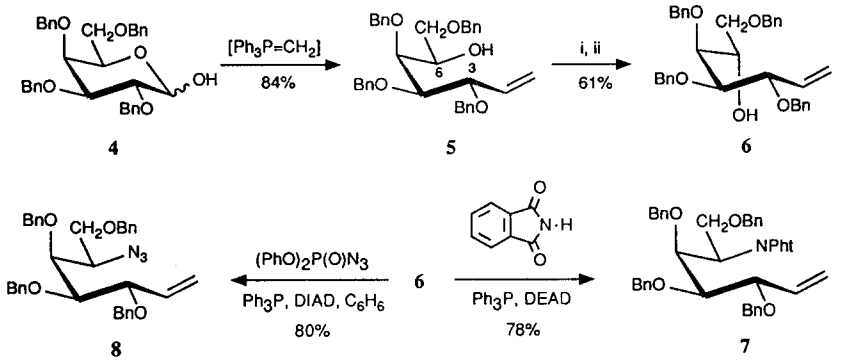


3

C-Glycosyl compounds having a substituted methylene group at C-1 are readily accessible from tetra-*O*-benzyl-hexopyranoses by way of a Wittig chain extension and an internal oxymercuration.[15] The second step is highly stereoselective in the *gluco* and *galacto* series, leading exclusively to an α-*C*-glycosidic linkage. Liu[7] has shown that the cyclisation occurs with the same degree of stereoselectivity when the free OH group

of the intermediate heptenitol was replaced by an NHCOOR group, thus providing access to "aza-α-*C*-glycosyl compounds"; this process constituted the key step of the synthesis of **1**.[7] The procedure developed by Liu to generate the amino heptenitol could not be used for the preparation of the D-*galacto* epimer of **1**: both the reduction of the oxime of the ketone derived from **5** (Scheme 1) and the reductive amination of the same ketone gave, not unexpectedly, the L-*altro* epimer as the major product.[16] We therefore examined substitution processes for the introduction of an amino group at C-6 of the D-*galacto* heptenitol **5**.[17]

Scheme 1[a]



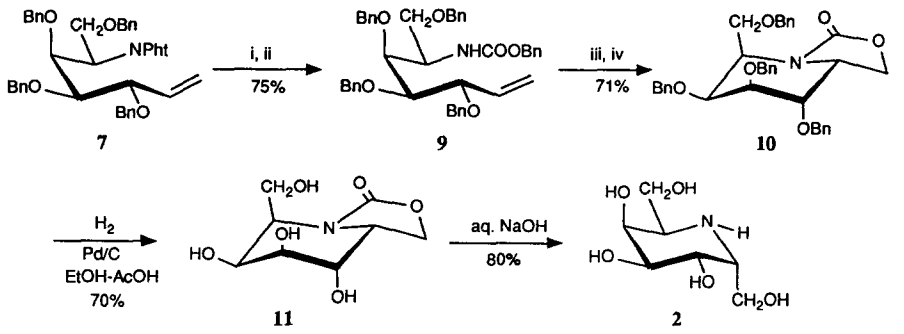
[a]Key: (i) Ph_3P, DEAD, *p*-$O_2NC_6H_4COOH$; (ii) MeONa, MeOH

Substitution reactions at this position are hampered by the extreme tendency of the benzyloxy group at C-3 to participate as an internal nucleophile, a process that leads to substituted tetrahydrofurans.[17] This participation, however, could be avoided when the displacements were performed under Mitsunobu conditions. Thus, the configuration at C-6 of **5** could be inverted in 61% overall yield by reaction with *p*-nitrobenzoic acid[18] in the presence of Ph_3P and DEAD, followed by debenzoylation. The 6-OH group of the resulting L-*altro*-heptenitol **6** could be displaced efficiently, with inversion, by a phthalimido or an azido group, using phthalimide or diphenylphosphoryl azide[19] in the presence of Ph_3P and an azodicarboxylate, to provide the derivatives of a 6-amino-6-deoxy-D-*galacto*-heptenitol, compounds **7** and **8**,[20] respectively.

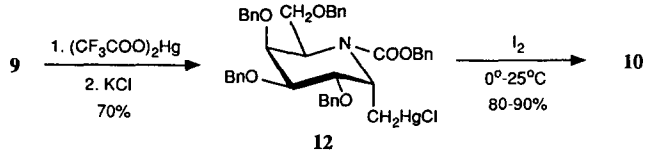
The phthalimido group in **7** was converted into a benzyloxycarbonylamino group in two steps (Scheme 2) and the amino heptenitol carbamate **9** was submitted to mercuricyclisation using mercury trifluoroacetate.[21] The resulting organomercurial was not isolated but treated immediately with iodine in order to achieve iododemercuration. Remarkably, this reaction led to the cyclic carbamate **10** in very good yield (71% from **9**) instead of the expected iodo compound. This is a particularly useful sequence of reactions[22] since it provides directly the α-*C*-glycosidic linkage (no β-epimer detected) with the appropriate functionalization at C-1. Subsequent experiments have shown that other carbamates (*t*-butyl, phenyl instead of benzyl) lead to the same product, and that the participation of the benzyl carbamate also occurs when the intermediate organomercurial (e.g. **12**) is isolated and then treated with iodine.

Compound **10** was debenzylated by catalytic hydrogenolysis, to afford **11**,[23] and the cyclic carbamate function of **11** cleaved using aqueous NaOH,[24] thus completing the synthesis of α-homogalactostatin **2**.[25]

Scheme 2[a]

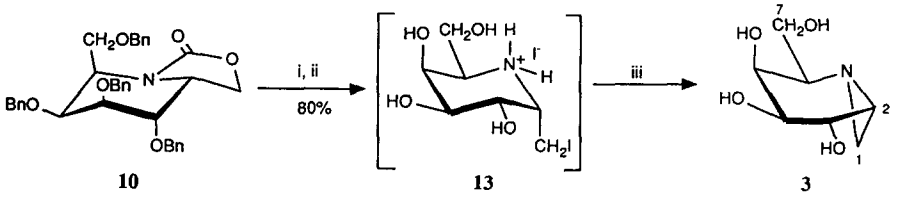


[a]Key: (i) NH_2NH_2, Δ; (ii) BnOCOCl, K_2CO_3; (iii) $(CF_3COO)_2Hg$, THF; (iv) I_2, 0°→25°C



The availability of **10** gave access to the 1,*N*-anhydro derivative of **2**, compound **3**. Aziridines of this type are of special interest as potential active-site directed inactivators of glycosidases: Ganem[11] has provided evidence that the inactivation of green coffee bean α-galactosidase by the 6,*N*-anhydro derivative of 1,5-dideoxy-1,5-imino-D-galactitol was due to the formation of an ester linkage between an active site carboxylic acid function and the inactivator. This class of compound remains however largely unexplored.[10,24,26] The conversion of **10** into **3** was achieved as follows: treatment of **10** with trimethylsilyl iodide at elevated

Scheme 3[a]



[a]Key: (i) Me_3SiI, 80-90°C, MeCN; (ii) H_2O; (iii) K_2CO_3, H_2O

temperature[27] followed by aqueous processing of the reaction mixture afforded the deprotected iodo ammonium salt **13**. On reaction with potassium carbonate, compound **13** underwent ring closure and gave **3**[28] in essentially quantitative yield (NMR). Compound **3** is the first example of an aziridine of this type having a constitution and a configuration closely related to that of an α-glycoside. The evaluation of the activity of **2** and **3** as glycosidase inhibitors is in progress.

Acknowledgments. Support of this research by a grant from the National Institutes of Health (DK 35766) is gratefully acknowledged.

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23. Mp 210°C (dec.); $[\alpha]_D^{18}$ – 36.1° (*c* 0.36, H_2O); ^{13}C-NMR (90 MHz, D_2O): δ 50.47, 56.28 (C-2, 6), 58.43, 64.88 (C-1,7), 65.03, 69.79, 71.34 (C-3–5), 160.65 (CO).
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25. Compound **2** was purified by ion-exchange chromatography [Amberlite IR-120 (H^+)-resin, elution with 10% aq. NH_3]. ^{13}C-NMR (D_2O): δ 54.82, 56.63 (C-2,6), 56.75, 60.74 (C-1,7), 68.27, 68.37, 70.80 (C-3–5).
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27. At room temperature, debenzylation only occurred, thus giving **11**.
28. ^{13}C-NMR (D_2O containing K_2CO_3): δ 33.83, 37.32 (C-1,2), 63.11, 66.05, 68.44, 70.92, 72.47 (C-3–7). ^{1}H-NMR (360 MHz; ref. internal CH_3OD, δ 3.35): δ 1.72 (d, 1H, $J_{1A,1B}$ ~ 0, $J_{1A,2}$ 4.8, H-1A), 2.11 (d, 1H, $J_{1B,2}$ 6.0, H-1B), 2.47 (q, 1H, $J_{2,3}$ 6.4, H-2), 2.79 (dt, 1H, $J_{5,6}$ ~ 1.5, $J_{6,7A} \cong J_{6,7B} \cong 7$, H-6), 3.45 (dd, 1H, $J_{3,4}$ 9.1, $J_{4,5}$ 2.0, H-4), 3.79 (ABX, 2H, H-7A, 7B), 3.96 (narrow t, 1H, H-5), 4.37 (dd, 1H, H-3). Compound **3** appears to be indefinitely stable in basic aqueous solution.

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