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Synthesis and Inhibition Analysis of Five-Membered Homoazasugars from D-Arabinofuranose via an *SN*2 Reaction of the Chloromethylsulfonate

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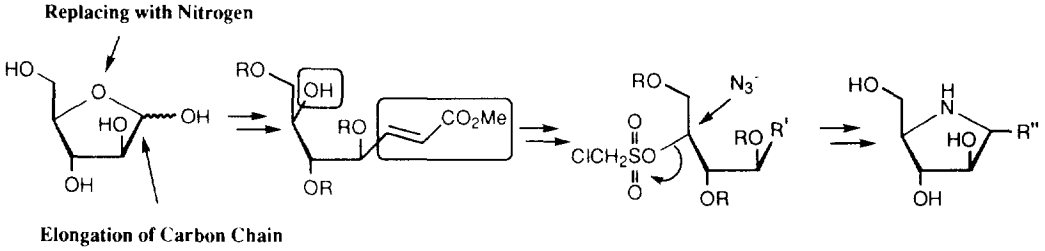
Abstract: Five-membered homoazasugars having a side-chain which can be modified to other functional groups or linked to other aglycon moieties were prepared from 2,3,5-tri-*O*-benzyl-D-arabinofuranose via a favorable *SN*2 reaction of the chloromethylsulfonate with azide. The obtained azasugars were found to be potent inhibitors of the β-glucosidase from sweet almond.

Many synthetic strategies have been reported to prepare five-membered azasugars,[1)] which are proven to be potent inhibitors of glycosidases and in some instances also show synergistic inhibitory activity against glycosyltransferases in the presence of nucleotides such as UDP and GDP.[1b)] Five-membered azasugars having a side chain which can be modified to other functional groups or linked to other aglycon molecules like sugars, peptides and lipids are therefore potentially useful for the development of specific glycosidase or glycosyltransferase inhibitors.

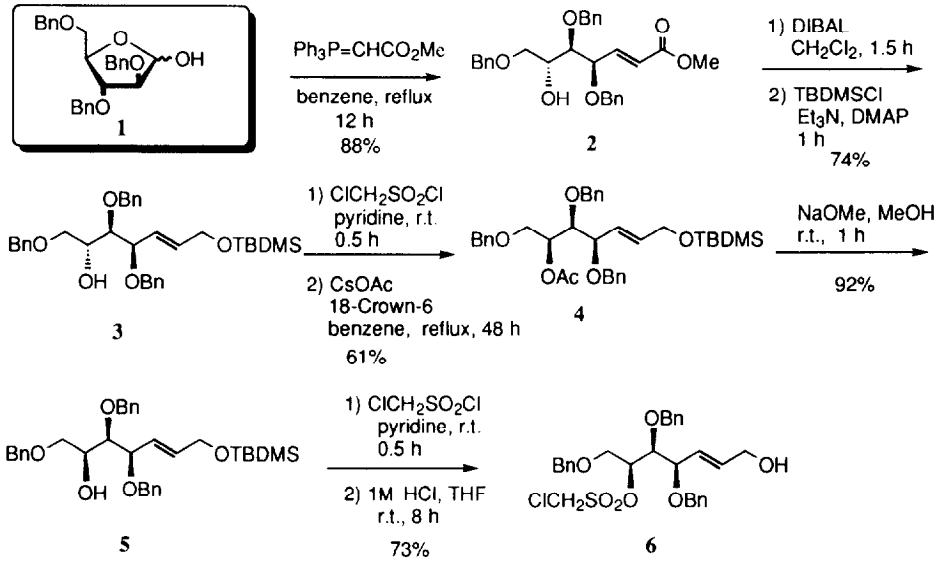


Scheme 1 Strategy for the Synthesis of Five-membered Homoazasugars

Replacing the ring-oxygen of furanoses with nitrogen while retaining the configuration of the other oxygen- and nitrogen-bearing carbons and adding an additional group at the anomeric center should provide this class of azasugars. Wittig reaction would satisfy these requirements, which could add carbon unit at the C-1 position and generate the free hydroxyl group to be replaced by the nitrogen containing group. Changing the secondary hydroxyl

group to the azide group while retaining the *R*-configuration could be achieved by a stepwise double inversion via sulfonate. In this paper, we describe the utility of the chloromethylsulfonyl group as a favorable leaving group of an *SN*2 reaction, and the application of this method to the synthesis of five-membered homoazasugars from D-arabinofuranose.

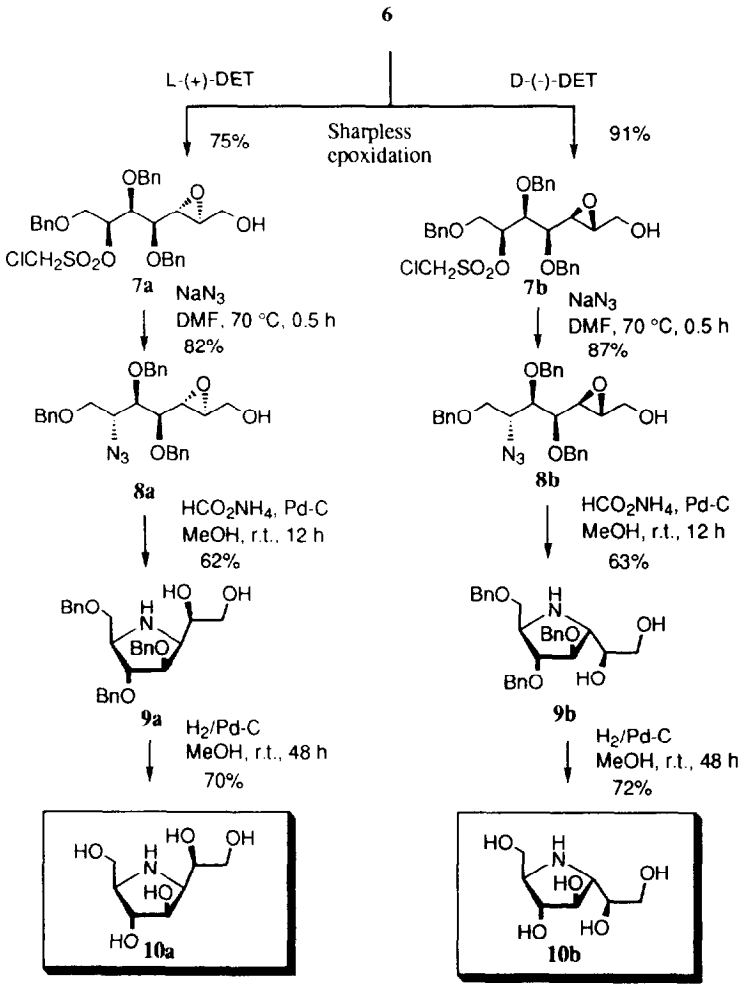
2,3,5-Tri-*O*-benzylarabinofuranose (**1**)[2] was condensed with methyl (triphenylphosphoranylidene)acetate to afford the Wittig product (**2**) with *E*-configuration in 88% yield. The carbomethoxy group of **2** was reduced with di-*iso*-butylaluminum hydride (DIBAL) to the ally alcohol, and the generated primary alcohol was protected by the *t*-butyldimethylsilyl (TBDMS) group to afford compound **3** (overall yield 74%).[3] The mesyloxy group derived from the hindered secondary hydroxyl group of **3** was, however, proved to be a weak leaving group in the *SN*2 reaction by the acetoxy group.[4] Alternatively, the hydroxyl group of **3** was activated to the chloromethylsulfonyl group which was replaced by the acetoxy group to give **4** (overall yield 61%) by reacting with cesium acetate in the presence of 18-crown-6 in refluxed benzene.[5] The acetate **4** was saponified to give the alcohol **5** (92%).[6] The hydroxyl group of **5** with *S*-configuration was chloromethylsulfonated again, and deprotection of the silyl group with 1M hydrochloric acid gave the allyl alcohol (**6**) (overall yield 73%).[7]



Scheme 2

The allyl alcohol (**6**) was epoxidized by Sharpless procedure[8] with (+)- and (-)-diethyl tartarates. Both reactions proceeded by a stereoselective manner to afford the epoxides **7a** (82%) and **7b** (91%) respectively. No corresponding diasteromers were observed by 270 MHz NMR in both epoxidation products. Each of the chloromethylsulfonyloxy groups of **10a** and **10b** was respectively substituted by the azide group smoothly to give compounds

8a[9] (82%) and **8b**[10] (87%) as a sole product. Reduction of the azide group with ammonium formate in the presence of palladium-carbon[11] spontaneously gave five-membered homoazasugars **9a** (62%) and **9b** (63%). Finally the benzyl groups were removed by catalytic hydrogenation on palladium-carbon to give the final compounds **10a**[12] (70%) and **10b**[13] (72%). The obtained azasugars **10a** and **10b** exhibited inhibitory activities at pH 5.0 against the β-glucosidase from sweet almond with *Ki* values of 7.0 and 24.5 μM, respectively.[14]



Scheme 3

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References and Notes

1. (a) Nishimura, Y. *Stud. Nat. Prod. Chem.* **1992**, *10*, 495 and references cited. (b) Ichikawa, Y.; Lin, Y.-C.; Dumas, D. P.; Shen, G.-J.; Garcia-Junceda, E.; Williams, M. A.; Bayer, R.; Ketcham, C.; Walker, L. E.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 9283. (c) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182.
2. Purchased from Sigma.
3. ^{1}H-NMR ($CDCl_3$) δ 0.08 (6H, s, $SiCH_3$), 0.89 (9H, s, $C(CH_3)_3$), 2.74 (1H, d, J=4.9 Hz, OH), 3.55 (3H, m, H-5, H-7), 3.93 (1H, m, H-6), 4.04 (1H, m, H-4), 4.12 (2H, m, H-1), 5.75 (2H, m, H-2, H-3), 7.20~7.40 (15H, m, aromatic).
4. Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555.
5. Shimizu, T.; Nakata, T., Further investigation of the present reaction will be reported in due course.
6. Compound **5** was also prepared from **4** via oxidation of the secondary alcohol of **3** with DMSO-Ac_2O followed by reduction of the obtained ketone with sodium borohydride at -78°C in the presence of $CeCl_3 \cdot 7H_2O$. However, this sequence produced 16% of diastereomer, and the two diastereomers could not be separated in the further stages.
7. ^{1}H-NMR ($CDCl_3$) δ 1.70 (1H, bd, OH), 3.56 (1H, dd, J=3.0, 11.6 Hz, H-7), 3.66 (1H, dd, J=7.0, 11.6 Hz, H-7), 3.68 (1H, dd, J=5.0, 5.0 Hz, H-5), 4.04 (1H, dd, J=5.0, 7.6 Hz, H-4), 4.12 (2H, m, H-1), 4.50 (1H, d, J=11.9 Hz, $ClCH_2SO_3$), 4.67 (1H, d, J=11.9 Hz, $ClCH_2SO_3$), 4.99 (1H, ddd, J=3.0, 5.0, 6.9 Hz, H-6), 5.65 (1H, dd, J=7.6, 15.8 Hz, H-3), 5.95 (1H, ddd, J=5.0, 5.0, 15.8 Hz, H-2), 7.20-7.40 (15H, m, aromatic).
8. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *51*, 1922. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
9. ^{1}H-NMR ($CDCl_3$) δ 2.97 (1H, m, H-2), 3.08 (1H, dd, J=2.0, 6.3 Hz, H-3), 3.46 (1H, dd, J=2.6, 6.3 Hz, H-4), 3.60 (1H, m, H-7), 3.70 (3H, m, H-1, H-5), 3.80 (2H, m, H-6, H-7). IR 2200 cm^{-1}.
10. ^{1}H-NMR ($CDCl_3$) δ 2.92 (1H, m, H-2), 3.29 (2H, m, H-3, H-4), 3.50 (1H, m, H-1), 3.66 (1H, dd, J=2.6, 7.3, H-5), 3.70 (3H, m, H-1, H-7), 3.80 (1H, m, H-6). IR 2170 cm^{-1}.
11. Gartiser, T.; Selve, C.; Delpuech, J.-J. *Tetrahedron Lett.* **1983**, *24*, 1609.
12. ^{1}H-NMR (CD_3OD) δ 3.01 (1H, m, H-4), 3.17 (1H, dd, J=4.0, 7.3 Hz, H-1), 3.60~3.75 (4H, m, H-5, H-2'), 3.80~3.90 (2H, m, H-1', H-3), 4.05 (1H, dd, J=1.3, 4.0 Hz, H-2). Mass TOF Mass: 193 (M^+), 216 (M^++Na^+), ($C_7H_{15}NO_5$ 193).
13. ^{1}H-NMR (CD_3OD) δ 3.00 (2H, m, H-1, H-4), 3.55~3.75 (4H, m, H-2', H-5), 3.69 (1H, m, H-1'), 3.79 (1H, dd, J=6.3, 6.6 Hz, H-2 or H-3), 4.04 (1H, dd, J=6.3, 6.6 Hz, H-2 or H-3). Mass TOF Mass: 193 (M^+), 216 (M^++Na^+), ($C_7H_{15}NO_5$ 193).
14. The inhibition constants were determined in 0.1 M acetate buffer, pH 5.0 using *p*-nitrophenyl-β-D-glucopyranoside as substrate.

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