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# Synthesis of β-D-(1→3)-C-linked 1,5,6-Trideoxy-1,5-iminogalactoside of D-altrose Derivatives

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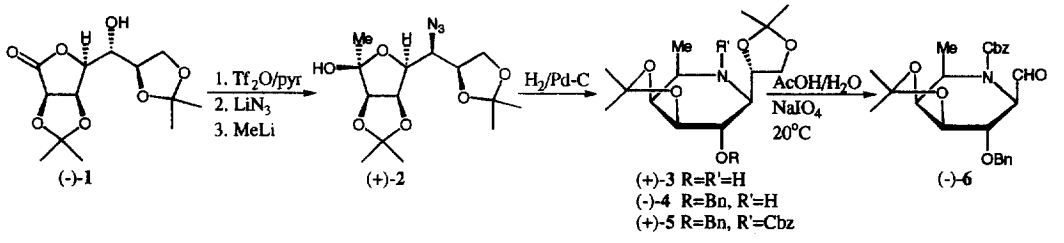
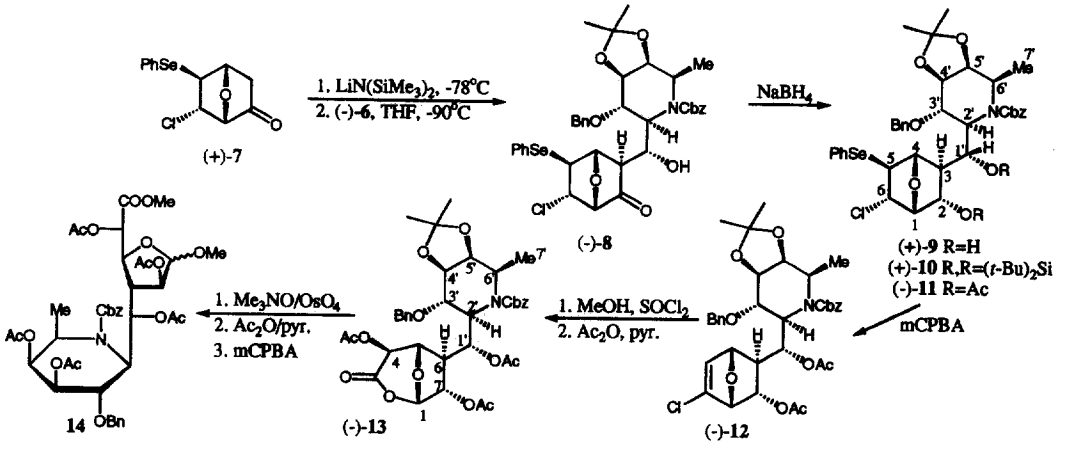
**Abstract**: The title aza-C-disaccharides were obtained through a highly stereoselective cross-aldolisation of a 2,6,7-trideoxy-2,6-imino-D-glycero-L-mannose and a 7-oxanorbornanone derivative.

Inhibition of glycohydrolases[1] may be useful for the treatment of diseases such as diabetes, cancer, viral and bacterial infections and inflammation.[2] Among promising inhibitors one finds polyhydroxypiperidines and pyrrolidines (azasugars).[3] Simple azasugars can inhibit several glycohydrolases. It is thought that selectivity could be improved if the inhibitor would include not only the steric and charge information of the glycosyl moiety but also that of the aglycon which it is attached to. Such inhibitors could be azasugars linked to other sugars through non-hydrolysable links such as in the aza-C-disaccharides. A first example (1,5-dideoxy-1,5-imino-D-mannitol linked at C(6) of D-galactose through a $CH_2$ unit) has been prepared by Johnson and co-workers.[4] We report here the synthesis of a new kind of aza-C-disaccharide in which 1,5,6-trideoxy-1,5-imino-β-galactose is linked at C(3) of D-altrohexouronic acid through a hydroxymethylene unit.




The readily available 2,3:6,7-di-O-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (-)-(**1**)[5] was converted into the azidooctulose derivative (+)-**2** (63%) through esterification ($Tf_2O$/pyr, $CH_2Cl_2$, -20°C), displacement of the corresponding triflate with $LiN_3$ (DMF, 20°C) and addition of MeLi in $Et_2O$/THF.[6] Hydrogenation of (+)-**2** gave the corresponding amine which equilibrated with the corresponding imine resulting from the intramolecular addition to the ulose moiety. The latter was hydrogenated selectively to give (+)-**3** (92%).[6] Benzylation of (+)-**3** (NaH/THF, BnBr, $Bu_4NI$, 20°C, 15 h) gave (-)-**4** (79%).[7] Protection of the amino moiety with benzyl chloroformate (EtOH/$H_2O$, $NaHCO_3$, 20°C) provided (+)-**5** (97%). Treatment with 8:1 AcOH/$H_2O$ and $NaIO_4$ (20°C, 15 h) led to selective hydrolysis of the 7,8-O-isopropylidene group and oxidative cleavage into aldehyde (-)-**6** (94%). Reaction of (-)-**6** with the lithium enolate of ketone (+)-**7** (-90°C, THF, 3.5 h) gave a major aldol product (-)-**8**, isolated in 61% yield, together with 27% of unreacted (+)-**7**. Reduction of (-)-**8** with $NaBH_4$ (1:1 THF/$H_2O$, 0°C) gave diol (+)-**9** (88%), the reaction of which with $(t\text{-Bu})_2Si(OTf)_2$ and 2,6-lutidine ($CHCl_3$, 50°C, 14 h) afforded the dioxysilane (+)-**10** (25%), the $^1$H-NMR spectrum of which showed a vicinal coupling constant of 11.1 Hz between H-C(3) of the 7-oxanorbornane unit and the proton of the silyloxamethylene bridge, thus confirming the structure of the anti aldol (-)-**8** (Zimmerman-Traxler model, *exo* mode of addition). Acetylation of (+)-**9** ($Ac_2O$, pyr, DMAP, $CH_2Cl_2$, 20°C,

15 h) afforded (-)-**11** (88%). Oxidation of (-)-**11** with mCPBA ($CH_2Cl_2$, -78 to 20°C) gave (-)-**12** (90%). Double hydroxylation of the chloroalkene (-)-**12** ($Me_3NO/OsO_4$, THF/$H_2O$, $NaHCO_3$) gave the corresponding α-hydroxyketone which was acetylated ($Ac_2O$, pyr., DMAP). Baeyer-Villiger oxidation (mCPBA, $NaHCO_3$, $CH_2Cl_2$, 25°C) provided uronolactone (-)-**13** (67%) which was converted into a mixture of the methyl furanosides **14** (73%) on treatment with MeOH and $SOCl_2$ (0-25°C, 28 h), then with $Ac_2O$/pyr/DMAP (20°C, 14 h).




All the compounds described here were fully characterized by their spectral data and elemental analyses.[7] Deprotection of **14** and biological evaluation will be reported elsewhere.

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[1] See e.g.: Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171-1202; Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319-384; Frank, R. W. *Bioorganic Chem.* **1992**, *20*, 77-88.

[2] See e.g.: Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199-210; Karlsson, G. B.; Butters, T. D.; Dwek, R. A.; Platt, F. M. *J. Biol. Chem.* **1993**, *268*, 570-576 and ref. cited therein.

[3] Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175-3185; Jespersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1778-1779; Wong, C.-H.; Provencher, L.; Porco, J. A.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492-1501 and ref. cited therein.

[4] Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksebati, M. B. *Tetrahedron Lett.* **1994**, *35*, 8991-8994.

[5] Brimacombe, J. S.; Tucker, L. C. N. *Carbohydr. Res.* **1966**, *2*, 341-348; Shing, T. N. M.; Tsui, H. C.; Zhou, Z.-h.; Mak, T. C. W. *J. Chem. Soc., Perkin Trans. I*, **1992**, 887-893.

[6] Details are given in: Baudat, A.; Picasso, S.; Vogel, P. *Carbohydr. Res.* in print.

[7] Data for (-)-**4**: oil, $[\alpha]_D^{25}$ -2 (c 1.5, $CHCl_3$); (+)-**5**: oil, $[\alpha]_D^{25}$ +50 (c 0.93); (-)-**6**: $[\alpha]_D^{25}$ -3 (c 1.4); $^1$H-NMR (400 MHz, $CDCl_3$, 50°C) $\delta_H$ 9.68 (s, HC(1)), 7.36-7.30 (m, 10 H), 5.14 (s, 2 H), 4.78, 4.61 (2d, 11.5, Bn), 4.52 (dq, 7.0, 6.9, HC(6)), 4.49 (d, 7.9, HC(2)), 4.39 (dd, 8.0, 6.9, HC(5)), 4.30 (dd, 7.9, 5.7, HC(3)), 4.05 (dd, 8.0, 5.7, HC(4)), 1.55, 1.36 (2s), 1.27 (d, 7.0, $H_3C$(7)); (-)-**8**: m.p. 138.5-140°C, $[\alpha]_D^{25}$ -8 (c 0.98); (+)-**9**: oil, $[\alpha]^{25}_D$ +17 (c 0.65); (-)-**11**: oil, $[\alpha]_D^{25}$ -9 (c 1.32); (-)**12**: $[\alpha]^{25}_D$ -61 (c 0.74); (-)-**13**: oil, $[\alpha]^{25}_D$ = -56 (c 0.25); $^1$H-NMR (400 MHz, $CDCl_3$, 50°C) $\delta_H$ 7.40-7.27 (m, 10 H), 5.99 (br. s, HC(1)), 5.55 (dd, 6.0, 5.8, HC(1')), 5.18, 5.12 (2d, 12.2, 2 H), 5.17-5.12 (2m, HC(5)), HC(7)), 4.76, 4.55 (2d, 11.1, 2 H), 4.61-4.53 (2m, HC(4), HC(6')), 4.33 (dd, 7.2, 5.8, HC(5')), 4.24 (2dd, 7.8, 5.8, HC(3'), HC(2')), 3.83 (dd, 7.8, 5.8, HC(4')), 2.71 (ddd, 5.4, 4.0, 1.4, HC(6)), 2.12, 2.00, 1.91, 1.54, 1.35 (5s, 5 Me), 1.19 (d, 7.2, $H_3C$(7')) (signal assignments confirmed by COSY-$^1$H-NMR).

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