Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 7, pp. 893-896, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00135-2

DIHYDROXYPYRROLIDINES C-LINKED TO GALACTOSE. TOTAL SYNTHESIS OF A SPECIFIC INHIBITOR OF α-MANNOSIDASES

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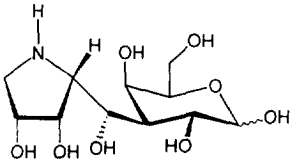
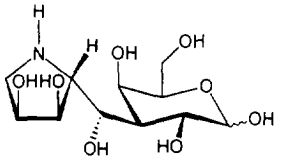
Abstract: New disaccharide mimics connecting 4-amino-4-deoxyerythrofuranose at C(1) to position C(3) of galactose through a CH(OH) link have been prepared as racemates and tested toward 25 commercially available glycohydrolases. One of them (**2**) is a moderate but specific (43% of inhibition at 1mM) inhibitor of jack bean α-mannosidase.

Glycosidases are key enzymes in the biosynthesis and processing of glycoproteins, which are macromolecules involved in recognition (cell-cell, host-pathogene interactions) and in control of biological mechanisms and structures.[1] Thus, substances able to inhibit the biosynthetic pathway of glycoproteins have become important as potential antibacterial, antiviral, antimetastatic, antidiabetes, antihyperglycemic, antiadhesive, or immunostimulatory agents.[2,3] In particular, the specific inhibition of individual N-linked glycoprotein processing α-mannosidases by nitrogen analogues of mannopyranose[4] and mannofuranose[5] may provide a useful anticancer strategy.[6] Polyhydroxylated pyrrolidines (five-membered azasugars) have shown to be potent inhibitors of glycosidases.[7,8] Being monosaccharide mimics they often lack specificity. It is believed that imino-C-disaccharides which link an iminosugar to another sugar through a carbon link[9-12] should mimick both the glycon and the aglycon during the glycoside cleavage and because of that, should be more specific glycosidase inhibitors. Furthermore, because of the carbon link, they should resist acidic and enzymatic hydrolyses. These systems are also expected to become useful tools in glycobiology.[2]



1



2

We report here the total synthesis of the new disaccharide mimics **1** and **2** connecting 4-amino-4-deoxyerythrofuranose at C(1) to position C(3) of galactose through a CH(OH) link. They are the first examples of imino-C-furanosides of hexoses. We have tested them (in their racemic form) as potential inhibitors of 25 commercially available glycosidases and have found that **2** which has the relative configuration of α-mannose for its C-4-amino-4-deoxyerythrofuranoside moiety is an α-mannosidase inhibitor and does not inhibit the other glycohydrolases whereas isomer **1** was completely inactive toward all the enzymes assayed.

The Diels-Alder adduct (±)-**3** of furan to 1-cyanovinyl acetate[13] can be converted into all kinds of carbohydrates and analogues.[14] Starting from enantiomerically pure 1-cyanovinyl esters[15] diastereomerically pure adducts (+)-**4** and (-)-**5** ("naked sugars of the first generation")[14,15] are obtained readily, allowing one to prepare the targeted sugar mimics in both their enantiomeric forms with the same ease. Recently we have

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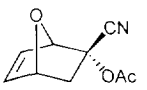
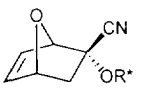
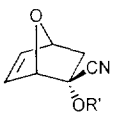
reported the conversion of (±)-**3** into the branched-chain galactose derivative **6**.[16] We have now found a simple way to convert **6** into the two aza-C-disaccharides **1** and **2**.



(±)-**3**



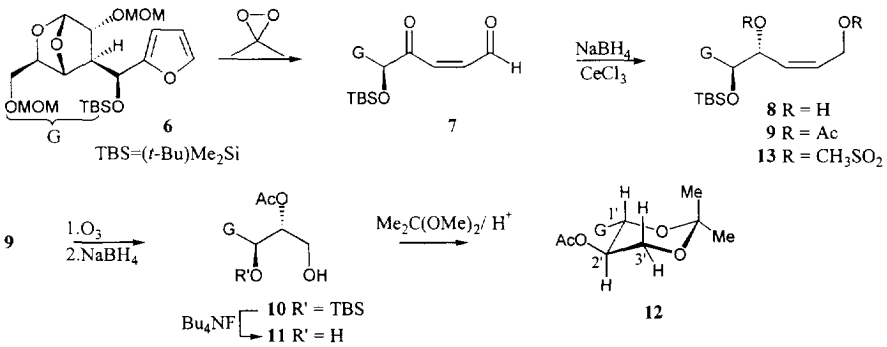
(+)-**4a**, **4b**



(-)-**5a**, **5b**

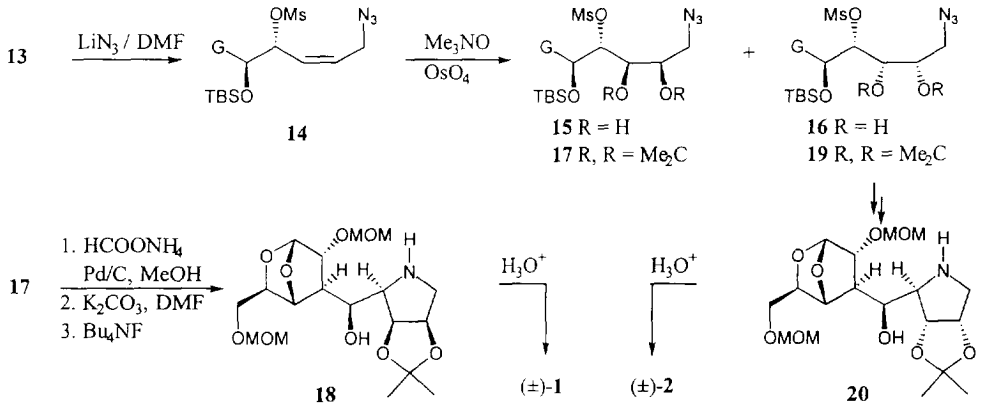
a) R* = (4S)-camphanoyl[15a]
R' = (4R)-camphanoyl[15a]
b) R* = SADO(Et)[15b]
R' = RADO(Et)[15b]

Oxidation of **6** with dimethyldioxirane (0.09 molar in acetone, 0°C, 15 h) led to the γ-oxo-(Z)-enal **7** which was not isolated but directly reduced under Luche's conditions[17] ($NaBH_4$, $CeCl_3$, MeOH, 0°C) to produce the enediol **8**[18] in 65% yield. The relative configuration of the secondary allylic alcoholic center was established in the following way. Acetylation of **8** (Ac_2O/pyridine, DMAP, 20°C, 15 h) gave diacetate **9** (90%) which was treated with ozone (anh. MeOH, -78°C) first, then with $NaBH_4$ (-78 to 20°C). This furnished alcohol **10** (67%). Desilylation of **10** with Bu_4NF (THF, 0-20°C, 5 min) liberated the diol **11** (78%) which was converted into the acetonide **12** (90%) on treatment with $Me_2C(OMe)_2$ (DMF, TsO^-PyrH^+, 20°C, 15 h). The 400 MHz ^{1}H-NMR spectrum of **12** showed typical vicinal coupling constant ^3J(Haxial-C(1'), Haxial-C(2')) = 7.2 Hz and NOE's between the signals of H-C(1'), Haxial-C(3') and one of the acetonide methyl groups.



Esterification of enediol **8** with CH_3SO_2Cl (Et_3N, CH_2Cl_2, -78°C, 5 min) gave the dimesylate **13**, an unstable compound that was treated with LiN_3 (DMF, 0°C, 45 min) to yield the azide **14**. Without purification, **14** was allowed to react with Me_3NO and a catalytic amount of OsO_4 (0.1 M/CCl_4) in 4:1 THF/H_2O (20°C, 20 h). This led to a mixture of diols **15** and **16** that were separated and purified by flash column chromatography on silica gel and isolated in 37% and 17% yield (based on enediol **8**), respectively. The major diol **15** was protected with $Me_2C(OMe)_2$ (camphorsulfonic acid, 20°C, 5 h) to provide **17** (79%). Reduction of the azide **17** with $HCOONH_4$ in the presence of 10% Pd on charcoal[19] (MeOH, 20°C, 1 h) followed by treatment with anhydrous K_2CO_3 (DMF, 50°C, 20 h) and then with Bu_4NF (anh. THF, 0-20°C, 1 h) provided the partially protected aza-C-disaccharide **18**[20] (79%, based on **17**) the configuration of which was established by 400 MHz ^{1}H-NMR with the help of double irradiation experiments and 2D NOESY spectra. Under similar conditions, diol **16** was converted into **19** (73%) and **20**[21] (54% based on **19**). Acidic hydrolysis of **18** (3N HCl/H_2O, 25°C, 3 h) gave a 2:3 mixture of α- and β-DL-galactopyranose derivatives (**1** · **HCl**). Under similar

conditions, **19** led to a 35:15:30:20 mixture of α-, β-galactopyranose, α-, and β-galactofuranose derivatives (**2** · **HCl**).



At 1 mM concentration (above acidic solutions buffered just before use), the imino-C-disaccharide **1** did not inhibit the following enzymes :[22] α-glucosidases (maltases) from yeast, rice; α-glucosidase (isomaltase) from baker yeast; amyloglucosidases from *Aspergillus niger, Rhizopus* mold; β-glucosidases from almonds, *Caldocellum saccharolyticum*; α-galactosidases from coffee beans, *Aspergillus niger, Escherichia coli*; β-galactosidases from *E. coli*, bovine liver, *Aspergillus niger, Aspergillus orizae*, jack beans; α-mannosidases from jack beans, almonds; β-mannosidase from *Helix pomatia*; β-D-xylosidase from *Aspergillus niger*; α-L-fucosidases from bovine epididymis, human placenta; α-N-acetylgalactosaminidase from chicken liver; β-N-acetylglucosaminidases from jack beans, bovine epididymis A, bovine epididymis B.

Except for a 43% and 27% inhibition of jack bean and almond α-mannosidases, respectively, at 1mM concentration, **2** did not inhibit the other 23 glycosidases. Compared with other polydroxypyrrolidines,[7,8] **2** is a moderate α-mannosidase inhibitor, but on the contrary to the simpler analogues it is much more specific. These results demonstrate for the first time that imino-C-disaccharides can be useful glycosidase inhibitors. Work is underway in our laboratory to prepare enantiomerically pure **2** from (+)-**4** and to generate families of analogues.

Acknowledgments : this work was supported by the *Swiss National Science Foundation.*

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18. Data for **8**: colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H : 5.87 (ddd, ^3J = 11.5, 7.4, 6.3), 5.59 (ddt, ^3J=11.5, 8.0, 0.8), 5.50 (d, ^3J=2.2), 4.71 (d, ^2J=6.8) , 4.66 (d, ^2J=6.8), 4.62 (s), 4.59 (br.s), 4.41 (dd, ^3J=8.0, 5.5), 4.27 (ddd, ^2J=13.4, ^3J=7.4, ^4J=0.8), 4.17 (ddd, ^2J=13.4, ^3J=6.3 ^4J=0.8), 3.99 (dd, ^3J=3.0, 2.2), 3.90 (dd, ^3J=8.3, 5.2), 3.79 (dd, ^3J=5.5, 4.3), 3.44 (dd, ^2J=10.0, ^3J=5.2), 3.43(s), 3.37 (dd, ^2J=10.0, ^3J=8.3), 3.36 (s), 1.90 (dd, ^3J=5.5, 3.0), 0.93, 0.15, 0.14 (3s).
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20. Data for **18**: ^{1}H-NMR (400 MHz, C_6D_6, 90°C) δ_H : 5.54 (d, 2.3), 4.79 (br.s), 4.74 (d, 6.5), 4.64 (d, 6.5), 4.49 (s, 2H), 4.48 (dd, 5.4, 4.3), 4.27 (dd, 5.4, 4. 3), 4.21 (dd. 2.8, 2.3), 4.08 (dd, 8.1, 5.0), 4.02 (dd, 8.3, 5.8), 3.59 (dd, 10.2, 5.0), 3.54 (dd, 10.2, 8.1), 3.33, 3.19 (2s), 3.05 (d, 13.1), 2.74 (dd, 5.8, 4.3), 2.45 (dd, 13.1, 4.3), 2.15 (dd, 8.3, 2.8), 1.36, 1.12 (2s); ^{13}C-NMR (100.6 MHz, C_6D_6) δ_C : 111.4 (s), 101.4 (d), 97.6, 97.3 (2t), 84.0, 82.6, 82.4, 80.7, 79.0, 72.1 (6d), 68.9 (t), 65.9 (d), 55.9, 55.5 (2q), 53.0 (t), 52.9 (d), 26.1, 24.0 (2q).
21. Data for **20**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.54 (d, 2.4), 4.81 (dd, 5.9, 2.2), 4.78, 4.75 (2d, 6.9), 4.72 (ddd, 5.9, 4.2, 1.9), 4.68 (br.s), 4.62 (s), 4.06 (dd, 2.6, 2.4), 3.99 (dd, 7.9, 5.3), 3.53 (dd, 8.0, 6.9), 3.52 (dd, 10.2, 5.3), 3.44 (s), 3.39 (dd, 10.2, 7.9), 3.36 (s), 3.15 (dd, 6.9, 2.2), 3.08 (dd, 13.2, 1.9), 3.03 (dd, 13.2, 4.2), 1.98 (dd, 8.0, 2.6), 1.48, 1.33 (2s); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 111.6 (s), 100.0 (d), 97.0, 96.6 (2t), 82.0, 81.6, 81.5, 81.2, 78.0, 70.4, 68.7 (7d), 67.7 (t), 55.8, 55.3 (2q), 52.5 (t), 50.8 (d), 26.6, 24.3 (2q).
22. Under standard conditions and optimal pH, see ref. 3.

(*Received in Belgium* 26 *December* 1996; *accepted* 4 *March* 1997)