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LETTERS

Synthesis of Ester-and Amide-Linked Pseudo-Azadisaccharides via Coupling of D-Glucose with 6-Amino-6-Deoxy-2,5-Imino-D-Glucitol

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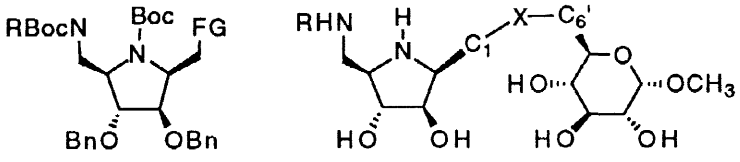
Abstract: Hydrolytically-resistant pseudodisaccharides incorporating an azafuranose have been prepared by coupling 6-amino-2,5-imino-D-glucitol derivatives with D-glucose, either through an ester or an amide bond. Synthesis of the azasugar templates was achieved by nucleophilic opening of a C_2 symmetric bis-aziridine deriving from D-mannitol. © 1998 Elsevier Science Ltd. All rights reserved.

Natural and unnatural polyhydroxylated pyrrolidines and piperidines constitute an important family of transition-state analog inhibitors of glycosidases and glycosyltransferases[1]. Analogs of a monosaccharide often act as broad spectrum inhibitors, therefore much attention is currently given to the development of new bisubstrate inhibitors which incorporate both portions of the natural substance, with the goal of increasing potency and introducing glycosidic selectivity. Hydrolytically-resistant pseudodisaccharides incorporating an azasugar which represent improved inhibitors[2] are the targets of synthetic efforts. We report here the synthesis of pseudodisaccharides in which C-1 of 6-amino-2,5-imino-D-glucitol is linked to C-6 of D-glucose either through an ester or an amide bond (scheme 1).



A

C_1-X-C_6' = CH_2-O-CO R = H **1**
C_1-X-C_6' = CH_2-O-CO R = Ac **2**
C_1-X-C_6' = CH_2-NH-CO R = H **3**
C_1-X-C_6' = CO-NH-CH_2 R = H **4**

Scheme 1

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Azasugar templates bearing a selectively free functional group are suitable intermediates for coupling to other sugars by non glycosidic bonds. We have recently carried out a divergent one-step synthesis of highly functionalized pyrrolidines **A**^{3} that resemble glucose, differently substituted at the pseudo anomeric carbon. We describe here the preparation of hydroxymethyl (**7** and **8**), carboxy (**9**) and aminomethyl (**11**) substituted pyrrolidines **A** (scheme 2), and their coupling with glucose derivatives (scheme 3).

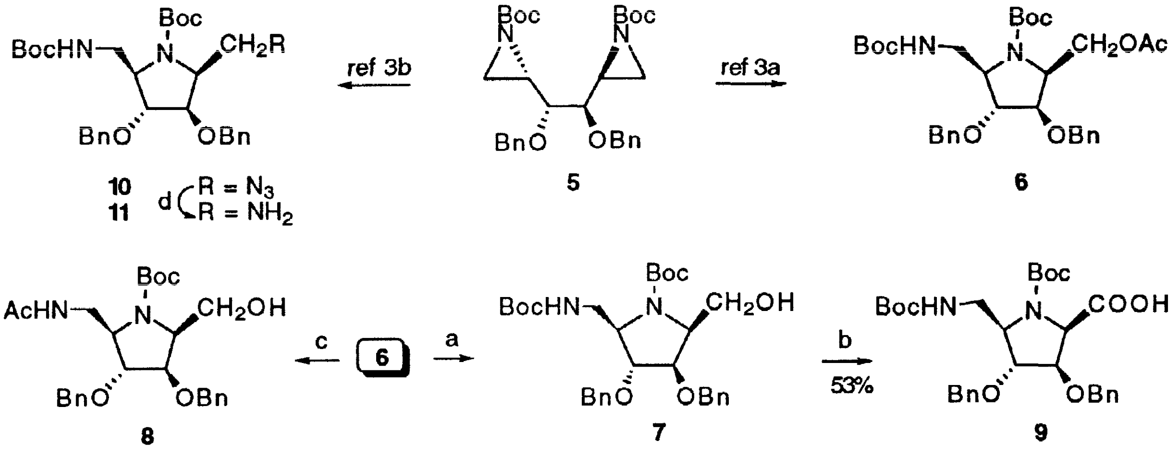
2,5-Imino-D-glucitol **6**^{3a} (**A** : FG=OAc, R=H), the common precursor in the preparation of the pyrrolidines **7**, **8**, and **9** allows the synthesis of the bisubstrates **1**, **2** and **4**^{4} respectively, while the amide linked pseudodisaccharide **3**^{4} derives from the amine **11** (FG = NH_2).

Preparation of **6** is achieved by acetic acid mediated nucleophilic opening of bis-aziridine **5**. Amine **11** results from the selective hydrogenation of the azidomethyl substituted pyrrolidine **10** (90% yield), itself prepared by sodium azide opening of **5**^{3b}.

Compound **6**, which bears orthogonally protected substituents, is easily converted into the alcohols **7** and **8**, while the oxydation of **7** gives the functionalized proline **9**.

Sodium methoxide mediated transesterification carried out on 1-*O*-acetyl pyrrolidine **6** yields quantitatively the 2-hydroxymethyl pyrrolidine **7** [$[\alpha]_D$ +8 (c 0.50, CH_2Cl_2)] which oxidation towards **9**^{4}, achieved with $H_2Cr_2O_7$ under mild phase transfer conditions^5 (53% yield) proved consistent with the Boc protection of the amines.

Preparation of the *N*-acetylated alcohol **8** [$[\alpha]_D$ +11.5 (c 3.50, MeOH)] has been carried out in 65% overall yield from compound **6**. Trifluoracetic acid deprotection was followed by selective acylation of the primary amine at C-6, and carbamoylation of the intracyclic nitrogen before freeing of the hydroxyl group at C-1.



(a) MeONa/ MeOH, 20°C,15h, 100% (b) $Na_2Cr_2O_7$, 4 H_2SO_4, 4eq, H_2O/ Et_2O, 0°C, 4h, 53%

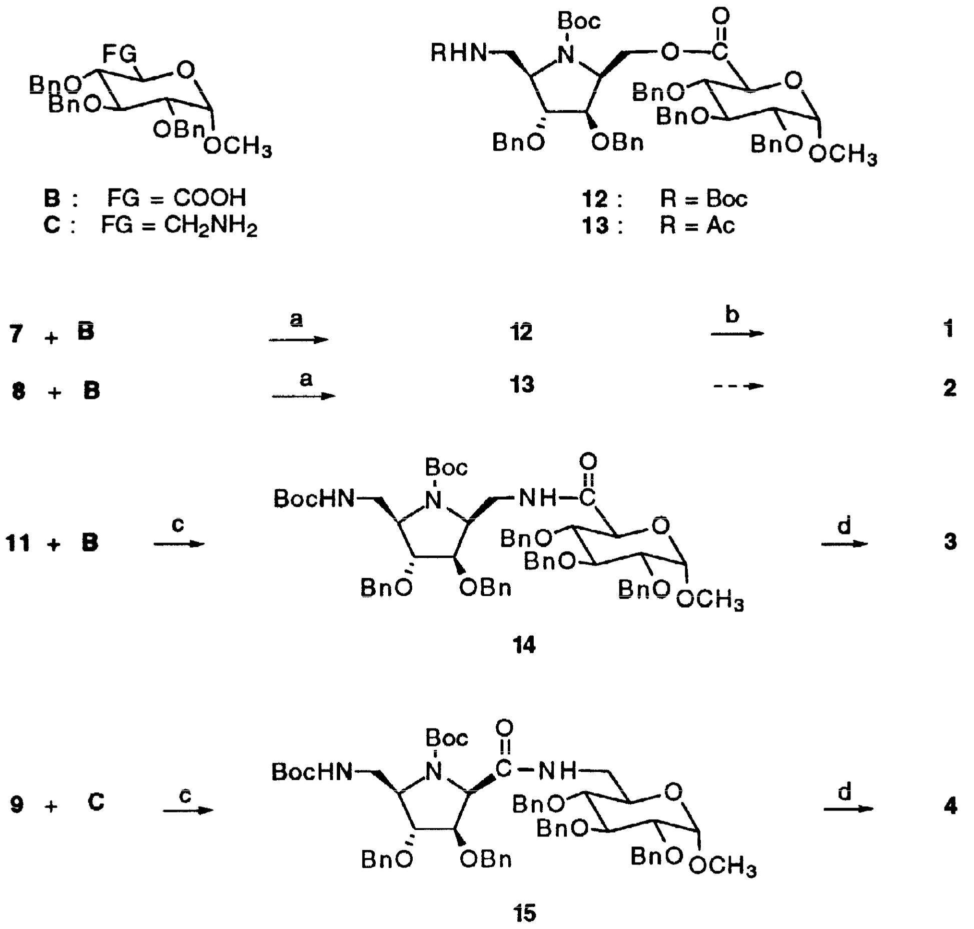
(c) i) TFA/CH_2Cl_2, 0 to 20°C; ii) $(CH_3CO)_2O/Et_3N$, CH_2Cl_2, -10°C, 4h; iii) $(Boc)_2O/Et_3N$; iv) (a), 65%

(d) H_2/Pd black, EtOAc, 3h, 90%

Scheme 2

Coupling of **7** with 2,3,4-tri-*O*-benzyl-D-glucuronic acid **B**^{6a} in the presence of DCC under reported conditions^7, leads to the protected ester **12** [$[\alpha]_D$ +19 (c 1.0, CH_2Cl_2)] in 58% yield. Hydrogenolysis of **12**, followed by acid treatment gives the pseudo disaccharide **1**^{4} which was isolated as its TFA salt. Coupling of **8** with **B** under the same conditions gives **13** in about 60% yield (spectral evaluation). As a matter of facts the protected disaccharide **13** remains contaminated with DCU which chromatograhic separation proved difficult. On the other hand direct acylation at C-6 of the diamine derived from **12** proved unsuccessfull due to the poor selectivity of the reaction.

Peptide coupling in the presence of DCC and HOBt of glucuronic acid **B** and 1-aminomethyl pyrrolidine **11** gives the amide linked pseudodisaccharide **14** in 62% yield [$[\alpha]_D$ +6 (c 1.0, CH_2Cl_2)], while the coupling of **C** with acid **9** yields **15** which present the reverse peptide bond [67%, $[\alpha]_D$ +16 (c 1.0, CH_2Cl_2)]. Removing of the Bn and Boc protecting groups effected by Pd catalyzed hydrogenation of **14** and **15** followed by acid treatment led to disaccharides **3**[4] and **4**[4] respectively, in 85% yield.



(a) DCC, DMAP cat, CH_2Cl_2, 20°C, 24h (b) i) H_2, Pd/C, EtOH/AcOH, 40h, 85%
ii) TFA/CH_2Cl_2 2:8, 0 to 20°C, 2h,100% (c) DCC, HOBt, Et_3N, THF, 0 to 20°C overnight
(d) i) H_2, Pd/C, EtOH/AcOH, 40h, 85% ii) TFA/CH_2Cl_2 1:1, 0 to 20°C, 2h,100%

Scheme 3

Preliminary investigations of the effect of the unprotected pyrrolidines and of the new pseudo disaccharides on different glycosidases are currently in progress and will be reported elsewhere later.

References and Notes

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4. Physical and spectral data of selected products (primed numbers refer to glucose carbons) :
   9: mp 66-67°C; $[\alpha]_D$ -26 (c 0.70, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.40 (s, 18H), 3.18 (m, 1H), 3.49 (s, 1H), 3.71 (m, 1H), 3.90 (m, 1H), 4.24 (m, 1H), 4.30-4.90 (m, 5H), 5.40-5.45 (brs, 1H), 7.10-7.60 (m, 10H). CIMS, m/z : 557 (MH^+).
   1 (TFA salt): $[\alpha]_D$ +43 (c 1.0, CH_3OH); ^{1}H NMR (250 MHz, CD_3OD) δ: 3.34 (s, 3H, OCH_3), 3.38-3.75 (m, 6H, H-2', H-3', H-4', H-5, H-6), 3.98 (m, 1H, H-2), 4.10 (d, 1H, J=9Hz, H-5'), 4.12 (brs, 1H, H-4), 4.18 (m, 1H, H-3), 4.43 (dd, 1H, J=8.5, 12Hz, H-1a), 4.59 (dd, 1H, J=4.5, 12Hz, H-1b), 4.71 (d, 1H, J=3.5Hz, H-1'); ^{13}C NMR (63 MHz, CD_3OD) δ: 41.71 (C-6), 56.22 (OCH_3), 62.34 (C-2), 62.70, (C-1), 64.99 (C-5), 72.70 (C-5'), 73.11 (C-2'), 73.45,(C-4'), 74.49 (C-3'), 76.68 (C-4), 79.44 (C-3), 102.01 (C-1'), 175.35 (CO); FAB HRMS exact mass calcd for MH^+ $C_{13}H_{25}N_2O_9$ 353. 1560, found 353. 1560.
   3 (TFA salt) : $[\alpha]_D$ +36 (c 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ: 3.40-3.55 (m, 4H), 3.42 (s, 3H), 3.66 (dd, 1H, J=9Hz), 3.68 (dd, 1H, J=8, 15Hz), 3.72 (dd, 1H, J=9.5, 15Hz), 3.76 (dd, 1H, J=6.5Hz), 3.99 (d, 1H, J=10Hz), 4.02 (m, 1H), 4.14 (brs, 1H), 4.21 (brs, 1H), 4.75 (d, 1H, J=3.5Hz); ^{13}C NMR (63 MHz, CD_3OD) δ: 37.32 (C-1), 40.94 (C-6), 56.26 (OCH_3), 64.44 (C-2), 66.06 (C-5), 72.19 (C-5'), 72.93 (C-2'), 73.83 (C-4'), 74.44 (C-3'), 76.34 (C-3), 78.68 (C-4), 101.75 (C-1'), 173.95 (CO).
   4 (TFA salt) : $[\alpha]_D$ +70 (c 1.0, MeOH); ^{1}H NMR (250 MHz, CD_3OD) δ: 3.20 (dd, 1H, J=9Hz), 3.26-3.80 (m, 7H), 3.39 (s, 3H), 4.17 (dd, 1H, J=1.5Hz), 4.39 (dd, 1H, J=1.5, 4.5Hz), 4.51 (d, 1H, J=4.5Hz), 4.65 (d, 1H, J=3.5Hz).
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