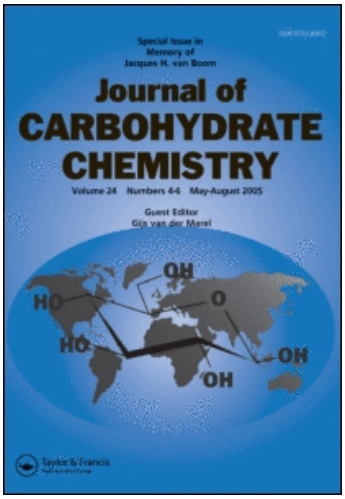

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SYNTHESIS OF D-GALACTOFURANOSYL-CONTAINING *C*-DISACCHARIDES

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ABSTRACT

The *C*-disaccharide analogue of the sequence β-D-Gal*f*-(1→3)-β-D-Glc*p*, an internal disaccharide of the capsular polysaccharide of *Klebsiella* K14 was synthesized by radical macrocyclization of temporarily tethered monosaccharides. The α-difluoro-*C*-analogue was obtained in three steps from D-galactono-1,4-lactone.

INTRODUCTION

D-Galactofuranose is a typical constituent of polysaccharides and glycoconjugates from various infectious bacteria, protozoa and fungi. It is a key component of glycoinositol phospholipids of *Trypanosoma Cruzi*.[1] The presence of D-Gal*f* in glycoproteins of *T. cruzi* may be related to the antigenicity of the glycoprotein.[2]

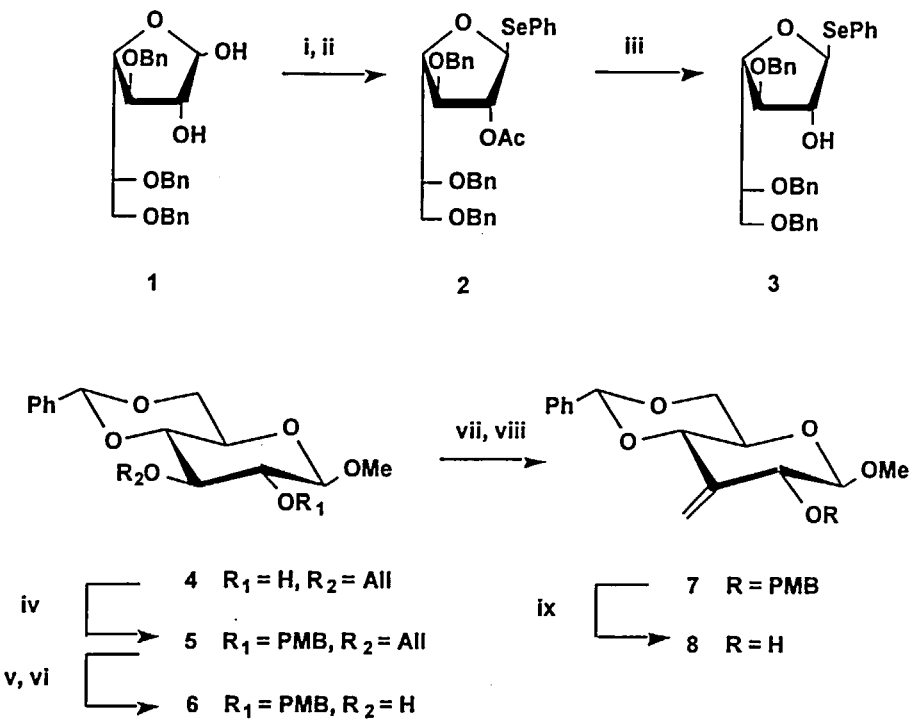
The development of new antiparasitic drugs requires the chemical synthesis of analogues that could act as enzyme inhibitors. *C*-Disaccharides, which cannot be hydrolyzed by glycosidases, may be considered as stable pharmacophores.

We would like to report on the first synthesis of D-galactofuranosyl containing *C*-disaccharides applying a methodology developed in our group[3] and involving a radical macrocyclization from two tethered sugars. A difluoromethylene *C*-disaccharide has also been prepared by a similar route.

RESULTS AND DISCUSSION

Known 3,5,6-tri-*O*-benzyl-D-galactofuranose[4] (**1**) was acetylated and converted into the selenophenyl derivative **2**, then deacetylated to give the key alcohol **3** in 65 % overall yield. On the other hand, methyl 3-*O*-allyl-4,6-*O*-benzylidene-β-D-gluco-pyranoside[5] (**4**) was reacted with *p*-methoxybenzyl chloride and sodium hydride in DMF to give crystalline **5** in 75 % yield. Deallylation was performed in two steps to give **6** in 81 % yield from **5**. Swern oxidation followed by reaction with Tebbe reagent led to **7**. The *p*-methoxybenzyl group was easily released with DDQ to give the radical acceptor **8** (Scheme **1**). The two alcohols **3** and **8** were tethered with dichlorodimethylsilane, and the resulting intermediate was directly submitted to radical cyclization conditions. The product was detethered in the presence of tetrabutylammonium fluoride, then acetylated to give, after column chromatography, a 3 to 1 mixture of two *C*-disaccharides **9a** and **9b** in 33 % overall yield (Scheme **2**). ^{1}H and ^{13}C NMR spectra of the mixture allowed assignment the major product as the β-*C*-disaccharide. Cyclization occurred preferentially on the less hindered face of the five-membered radical.[6] The two compounds could be separated by HPLC, and the major product was deprotected to give **10**. This new compound is the *C*-disaccharide analogue of the disaccharide β-D-Gal*f*-(1→3)-β-D-Glc*p*, an internal sequence of the capsular polysaccharide of *Klebsiella* K14.[7]

The same coupling was also attempted using an "inverse" approach, placing an exocyclic double bond on the furanose and a radical donor on the *gluco* moiety. Known 2,3-(bis-*O*-*tert*-butyldimethylsilyl)-5,6-*O*-isopropylidene-D-galactono-1,4-lactone[8] (**11**) was converted into the difluoroenitol **12** using dibromodifluoromethane, tris(dimethyl-amino)phosphine and zinc powder.[9] Selective desilylation of **12** in the presence of tetrabutylammonium fluoride took place at position 2, leading to **13** in 59 % yield. The two fluorine atoms were introduced in compound **13** in order to increase the electrophilic character of the reacting double bond. Compound **13** was temporarily connected to methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-β-D-allopyranoside[10] (**14**). Cyclization, desilylation, and acetylation of free hydroxyl groups gave, after silica gel chromatography, only one *C*-disaccharide product (**15**) in 29 % yield. This "inverse" approach proceeds stereo-specifically, leading to the α-difluoro-*C*-disaccharide. The α-stereochemistry indicates that hydrogen capture occurred from the less hindered face of the molecule. Similar



Reagents: i. Ac_2O, Py; ii. PhSeH, TMSOTf; iii. NaOMe, MeOH; iv. NaH, PMBCl; v. *t*-BuOK, DMSO; vi. HgO, acetone; vii. Swern oxidation; viii. Tebbe; ix. DDQ.

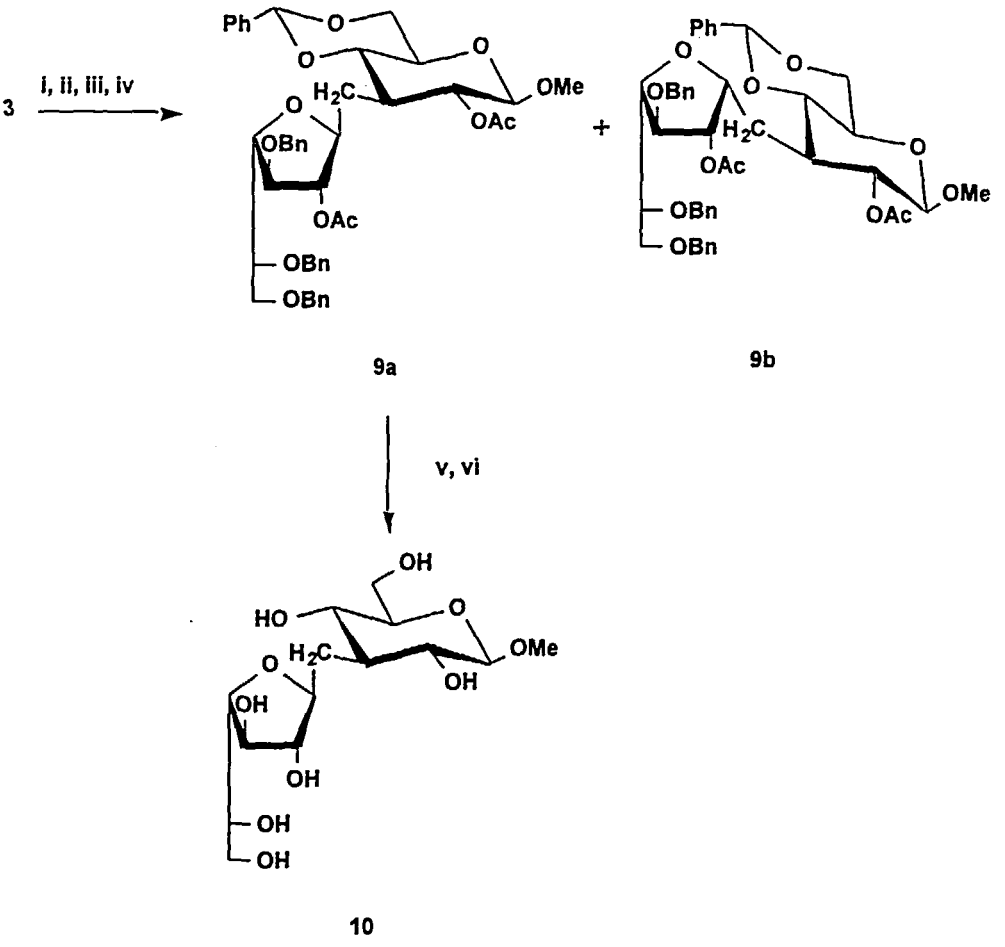
Scheme 1

results have been previously reported for CF_2-disaccharides obtained from carbohydrate *gem*-difluoroenol ethers and primary radicals in intermolecular reactions.[11, 12] De-protection of **15** gave **16** in 71 % yield (Scheme 3).

These examples show that radical macrocyclization of temporarily tethered units is a useful strategy to obtain both α- and β-*C*-disaccharides of furanoses.

EXPERIMENTAL

General methods. Melting points (mp) were determined with a Fisher-Johns mp apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C with a Perkin Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Elemental analyses were

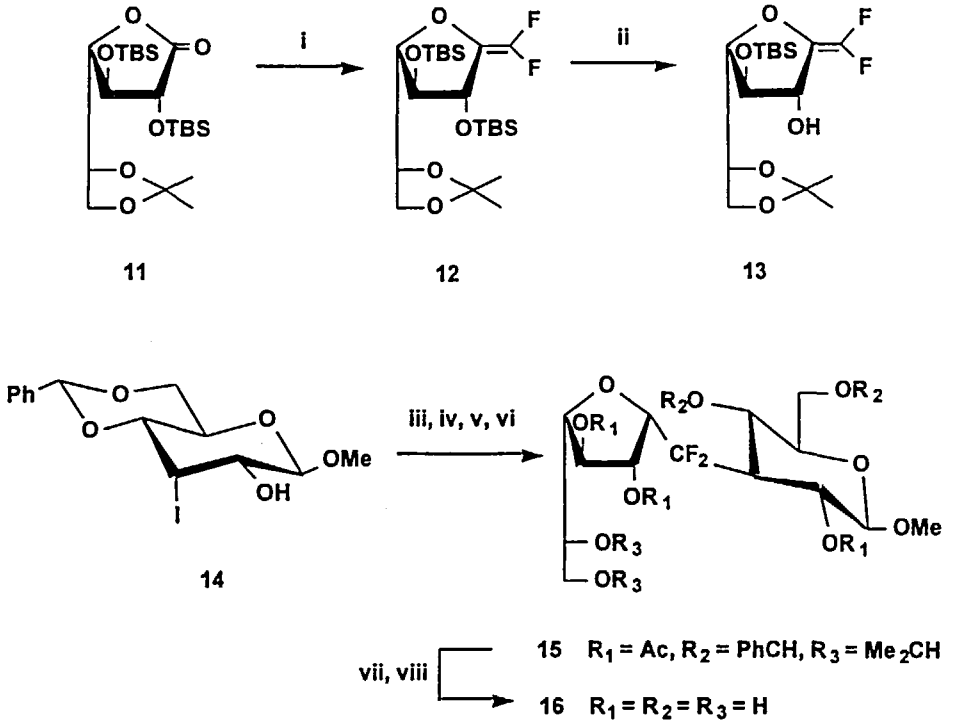


Reagents: i. BuLi, Me_2SiCl_2 then **8**, DMAP; ii. Bu_3SnH, AIBN, toluene, 110 °C; iii. TBAF; iv. Ac_2O, Py; v. MeOH-H_2O-Et_3N; vi. H_2 (Pd/C).

Scheme 2

performed by UMYMFOR (CONICET) or by Service de Microanalyse (Paris VI). ^1H NMR spectra were recorded with a Bruker AC 200, AC 250 or AM 400, for solutions in $CDCl_3$ (internal Me_4Si, δ 0) or D_2O (internal acetone, δ 2.225) at ambient temperature. Mass spectra were obtained with a JMS-700 spectrometer.

Phenyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-seleno-β-D-galactofuranoside (2). 3,5,6-Tri-*O*-benzyl-D-galactofuranose[4] (**1**, 337.8 mg, 0.75 mmol) was acetylated in 2:1



Reagents: i. CF_2Br_2, Zn, $P(NMe_2)_3$; TBAF (1 equiv); iii. BuLi, Me_2SiCl_2 then **13**, DMAP; iv. Bu_3SnH, AIBN; v. TBAF; vi. Ac_2O, Py; vii. TFA-H_2O; viii. MeOH-H_2O-Et_3N.

Scheme 3

pyridine-acetic anhydride. After solvent evaporation, the crude product was dried over P_2O_5 and dissolved in dry dichloromethane (15 mL). Benzeneselenol (0.096 mL, 0.9 mmol) and trimethylsilyl trifluoromethanesulfonate (0.136 mL, 0.75 mmol) were added at 0 °C. After 1 h, triethylamine (0.14 mL) was added, and the mixture was diluted with dichloromethane. The solution was washed with satd aqueous $NaHCO_3$, and water, then dried ($MgSO_4$), filtered and concentrated. Flash chromatography on silica gel, (30:1 to 10:1 cyclohexane-ethyl acetate) yielded pure **2**, syrup (326.2 mg, 69 % yield): $[\alpha]_D$ -148 (*c* 1.17, chloroform): ^{1}H NMR (200 MHz) δ 7.61-7.56 and 7.35-7.17 (20 H, arom.), 5.84 (s, 1 H, H-1), 5.30 (s, 1 H, H-2), 4.72-4.32 (m, 7 H, C*H*$_2$Ph, H-6a), 3.96 (d, 1H, J = 5.5 Hz, H-3), 3.82-3.73 (m, 1 H, H-5), 3.68-3.59 (m, 2 H, H-4, H-6b), 1.89 (s, 3 H, acetyl); ^{13}C NMR (50 MHz) δ 169.85 (CO), 138.11-127.56 (Ph), 86.97 (C-1), 83.30 (C-3), 82.50 (C-2, C-4) , 76.35 (*C*H$_2$Ph), 73.53 (2 *C*H$_2$Ph), 72.08 (C-5), 70.63 (C-6), 20.38 (acetyl).

Anal. Calcd for $C_{35}H_{36}O_6Se$: C, 66.56; H, 5.74. Found: C, 66.33; H, 5.92.

Phenyl 3,5,6-tri-*O*-benzyl-1-seleno-β-D-galactofuranoside (3). 272 mg (0.43 mmol) of **2** were dissolved in methanol (8 mL) and sodium was added at 0 °C. After stirring overnight at room temperature, the solution was neutralized with Dowex 50X8 (H^+) resin, then filtered and concentrated. Flash chromatography on silica gel, (10:1 cyclohexane-ethyl acetate) yielded pure **3**, syrup (241.9 mg, 95 % yield): $[\alpha]_D$ -169 (*c* 1.06, chloroform): ^{1}H NMR (200 MHz) δ 7.61-7.56 and 7.33-7.20 (20 H, arom.), 5.73 (s, 1 H, H-1), 4.80-4.41 (m, 8 H, C*H*$_2$Ph, H-2, H-6a), 4.05-3.66 (m, 5 H, H-3, H-4, H-5, H-6b, O*H*); ^{13}C NMR (50 MHz) δ 138.01-127.10 (Ph), 92.02 (C-1), 85.29 (C-3), 84.54 (C-4), 79.25 (C-2), 76.69 (*C*H$_2$Ph), 73.60 (*C*H$_2$Ph), 73.47 (*C*H$_2$Ph), 71.97 (C-5), 70.42 (C-6).

Anal. Calcd for $C_{33}H_{34}O_5Se$: C, 67.10; H, 5.81. Found: C, 67.30; H, 6.03.

Methyl 3-*O*-allyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (5). To a solution of methyl 3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranoside[5] (**4**, 12.66 g, 39.3 mmol) in DMF (110 mL), *p*-methoxybenzyl chloride (6.4 mL, 47.1 mmol) and sodium hydride (60 % in oil, 2.04 g, 51.1 mmol) were added at 0 °C. After 12 h, methanol was added, and the solvent was evaporated under vacuum. The residue was dissolved in dichloromethane, and the solution was washed with water, then dried ($MgSO_4$), filtered and concentrated. Flash chromatography on silica gel, (7:1 to 5:1 cyclohexane-ethyl acetate) yielded pure **5**, as a white solid, which crystallized from 2-propanol (13.06 g, 75 % yield): mp 92-93 °C; $[\alpha]_D$ -28 (*c* 1.2, chloroform): ^{1}H NMR (250 MHz) δ 7.38-7.10 and 6.77-6.70 (9 H, arom.), 5.81 (m, 1 H, C*H*=), 5.64 (s, 1 H, PhC*H*), 5. 40 and 5.28 (two m, 2 H, =C*H*$_2$), 5.15 and 5.03 (two d, 2 H, J = 10.5 Hz, C*H*$_2$PMB), 4.29-4.07 (m, 3 H, C*H*$_2$C=C, H-6a), 4.25 (d, 1 H, J = 7.7 Hz, H-1), 3.66 (s, 3 H, OC*H*$_3$ PMB), 3.61 (d, 1 H, J = 10.3 Hz, H-6b), 3.49-3.43 (m, 2 H, H-3, H-4), 3.45 (s, 3 H, OC*H*$_3$), 3.29-3.18 (m, 2 H, H-2, H-5). CIMS: 443 (M^+ + 1), 460 (M^+ + 18).

Anal. Calcd for $C_{25}H_{30}O_7$: C, 67.88; H, 6.83. Found: C, 67.90; H, 6.92.

Methyl 4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (6). To a solution of **5** (13.06 g, 29.5 mmol) in dry DMSO (520 mL), potassium *tert*-butoxide (19.54 g, 174.1 mmol) was added. The mixture was heated 1 h at 60 °C, then cooled and stirred 15 min with saturated aqueous $NaHCO_3$. The solution was extracted with ether, and the organic layer was dried ($MgSO_4$), filtered and concentrated. To the residue, mercuric oxide (10.0 g, 46.17 mmol), acetone (500 mL) and water (50 mL) were added. At the end of the reaction, the mixture was filtered through celite and concentrated. The residue was taken with dichloromethane, and the organic layer was washed with 10 % potassium iodide, and water, dried ($MgSO_4$), filtered and concentrated. Flash chromatography on silica gel, (4:1 cyclohexane-ethyl acetate) yielded crystalline **6**, (9.62 g, 81 % yield): mp 130-131 °C; $[\alpha]_D$ -19 (*c* 1.9, chloroform): ^{1}H NMR (250 MHz) δ 7.38-7.13 and 6.79-6.72 (9 H, arom.), 5.39 (s, 1 H, PhC*H*), 4.72 and 4.61 (two d, 2 H, J = 11.1

Hz, C*H*$_2$PMB), 4.28 (d, 1 H, J = 7.7 Hz, H-1), 4.22 (dd, 1 H, J = 10.5, 4.9 Hz, H-6a), 3.68 (ddd, 1 H, J = 9.2, 8.7, 2.1, H-3), 3.67 (s, 3 H, OC*H*$_3$ PMB), 3.62 (d, 1 H, J = 10.5 Hz, H-6b), 3.47 (s, 3 H, OC*H*$_3$), 3.40 (dd, 1 H, J = 9.2 Hz, H-4), 3.30 (dd, 1 H, J = 9.2, 4.9 Hz, H-5), 3.27 (dd, 1 H, J = 8.7, 7.7 Hz, H-2), 2.32 (d, 1 H, J = 2.1 Hz, O*H*). CIMS: 403 (M^+ + 1), 420 (M^+ + 18).

Anal. Calcd for $C_{22}H_{27}O_7$: C, 65.66; H, 6.76. Found: C, 65.60; H, 6.51.

Methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-*p*-methoxybenzyl-3-*C*-methylene-β-D-*ribo*-hexopyranoside (7). To a solution of oxalyl chloride (3.95 mL, 45.3 mmol) in dry dichloromethane, a solution of DMSO (3.53 mL, 49.8 mmol) in dichloromethane (40 mL) was added at -78 °C. After 30 min, a solution of **6** (9.11 g, 22.6 mmol) in dichloromethane (100 mL) was added. After 30 min at -78 °C, triethylamine (15.78 mL, 113.2 mmol) was added and the mixture was slowly warmed at room temperature. The solution was washed with saturated aqueous ammonium chloride, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in THF (250 mL) and pyridine (3.66 mL, 45.3 mmol) then Tebbe reagent (90.56 mL, 0.5 M in toluene) was added at -78 °C. The mixture was warmed to room temperature in 2 h, then 20 % NaOH (30 mL) was added at -20 °C. The mixture was filtered through celite using ethyl acetate as eluent, and the solvent was evaporated under vacuum. Flash chromatography on silica gel, (3:1 cyclohexane-ethyl acetate) yielded **7**, which was recrystallized from methanol (7.49 g, 83 % yield): mp 157-158 °C; $[\alpha]_D$ -38 (*c* 1.7, chloroform): ^{1}H NMR (250 MHz) δ 7.49-7.21 and 6.85-6.78 (9 H, arom.), 5.54 (s, 1 H, PhC*H*), 5.30 (ddd, 1 H, J = 1.9 Hz, C*H*=), 5.20 (ddd, 1 H, J = 1.9 Hz, C*H*=), 4.74 and 4.61 (two d, 2 H, J =11.4 Hz, C*H*$_2$PMB), 4.27 (dd, 1 H, J = 10.5, 4.9 Hz, H-6a), 4.24 (d, 1 H, J = 7.5 Hz, H-1), 3.87 (ddd, 1 H, J = 9.3, 1.9 Hz, H-4), 3.78-3.66 (m, 2 H, H-2, H-6b), 3.67 (s, 3 H, OC*H*$_3$ PMB), 3.53 (s, 3 H, OC*H*$_3$), 3.26 (ddd, 1 H, *J*= 9.3, 6.0, 4.9 Hz, H-5). CIMS: 399 (M^+ + 1), 416 (M^+ + 18).

Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.56. Found: C, 69.47; H, 6.55.

Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methylene-β-D-*ribo*hexopyranoside (8). To a solution of **7** (606.6 mg, 1.52 mmol), in dichloromethane (33 mL), water (1.7 mL) and DDQ (518 mg, 2.28 mmol) were added at 0 °C. After stirring for 3.5 h at room temperature, saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with dichloromethane. The organic layer was washed with satd aqueous $NaHCO_3$, and satd aqueous NaCl, then dried ($MgSO_4$), filtered and concentrated to a yellow oil, which after recrystallization from ethyl acetate gave **8** (385.4 mg, 91 % yield): mp 232 °C; $[\alpha]_D$ -33 (*c* 0.5, dichloromethane): ^{1}H NMR (250 MHz) δ 7.60-7.50 and 7.45-7.35 (5 H, arom.), 5.64 (s, 1 H, PhC*H*), 5.32 (m, 2 H, =C*H*$_2$), 4.36 (dd, 1 H, J = 4.8, J = 10.2 Hz, H-6a), 4.20 (d, 1 H, J = 7.6 Hz, H-1), 4.05-3.95 (m, 2 H, H-2, H-4), 3.84 (dd, 1 H, J = 10.2 Hz, H-6b), 3.60 (s, 3 H, OMe), 3.40 (ddd, 1 H, J = 10.2 Hz, H-5), 2.45 (d, 1 H, J = 3.1 Hz, O*H*); ^{13}C

NMR: δ 142.00-126.24 (Ph, C-3), 106.73 (=CH_2), 105.29 (C-1), 101.44 (*C*HPh), 78.29 (C-4), 72.20 (C-2), 70.54 (C-5), 69.15 (C-6), 57.50 (OCH_3). CIMS: 279 (M^+ + 1), 296 (M^+ + 18).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.70; H, 6.52.

Methyl 2-*O*-acetyl-3-*C*-(2,5-anhydro-1-deoxy-3-*O*-acetyl-4,6,7-tri-*O*-benzyl-D-*glycero*-L-*manno*-heptit-1-yl)-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside (9a) and methyl 2-*O*-acetyl-3-*C*-(2,5-anhydro-1-deoxy-3-*O*-acetyl-4,6,7-tri-*O*-benzyl-D-*glycero*-L-*gluco*-heptit-1-yl)-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside (9b). To a solution of **3** (74.4 mg, 0.126 mmol) in dry THF (3.0 mL), butyllithium (1.6 M in hexanes, 0.11 mL) and dimethyldichlorosilane (0.077 mL, 0.63 mmol) were added at -78 °C. The mixture was allowed to reach room temperature within 3 h, then concentrated to dryness under vacuum. The residue was taken in THF (3.0 mL), and **8** (35.1 mg, 0.126 mmol), DMAP (15.7 mg) were added. After stirring overnight at room temperature, the solvent was evaporated, and the residue was dissolved in degassed toluene (12.0 mL). To this boiling mixture, a solution of *n*-Bu_3SnH (0.074 mL, 0.277 mmol) and AIBN (6.2 mg) in toluene (2.0 mL) was added over 18 h by means of syringe pump. Then the solvent was evaporated, the residue was dissolved in THF (3 mL) and tetrabutylammonium fluoride (108 mg, 0.34 mmol) was added. After 2 h at room temperature, triethylamine (0.2 mL) was added and the mixture was concentrated to a syrup. Flash chromatography on silica gel (9:1 to 3:1 cyclohexane-ethyl acetate) yielded a *C*-disaccharide fraction, which was acetylated (2:1 pyridine-acetic anhydride) and purified by flash chromatography (5:1 cyclohexane-ethyl acetate) to give a 3:1 mixture of **9a** and **9b** (33.0 mg, 33 % yield).

FAB MS (LiCl): Calcd for $C_{46}H_{52}O_{12}$ + Li: 803.3620. Found: 803.3627.

Separation of **9a** and **9b** was performed on a fraction (9 mg) of the *C*-disaccharide mixture by HPLC using a Ultrasphere ODS (dp 5 μ, 4.6 mm x 25 cm) RP 18 column, 85:15 methanol-water, flow 1 mL/min, UV detection at 254 nm.

Major isomer: β-*C*-disaccharide **9a** (6.1 mg): Retention time 17.2 min, syrup, $[\alpha]_D$ -59 (*c* 0.55, chloroform): ^{1}H NMR (400 MHz) δ 7.43-7.23 (20 H, arom.), 5.48 (s, 1 H, PhC*H*), 4.93 (t, 1 H, J = 1.4 Hz, H-3'), 4.85 (dd, 1 H, J = 7.6, J = 10.5 Hz, H-2), 4.71 (d, 1 H, J = 11.5 Hz, PhCH_2), 4.64-4.22 (m, 9 H, H-1, H-6a, H-2', H-7'a, PhCH_2), 4.05 (dd, 1 H, J = 4.9, J = 2.9 Hz, H-5'), 3.91 (dd, 1 H, J = 4.9, J = 2 Hz, H-4'), 3.80-3.56 (m, 4 H, H-5, H-6b, H-6', H-7'b), 3.47 (s, 3 H, O*Me*), 3.50-3.40 (m, 1 H, H-4), 2.16 (m, 1 H, H-3), 1.94 and 1.82 (two s, 6 H, O*Ac*), 1.82 (m, 2 H, H-1'a, H-1'b); ^{13}C NMR: δ 170.36, 169.51 (*C*=O), 138.40-126.13 (Ph), 103.54 (C-1), 101.46 (*C*HPh), 84.12 (C-4'), 82.71 (C-5'), 81.35 (C-2'), 79.61 (C-4), 78.73 (C-3'), 78.01 (C-2), 76.37, 73.48 and 73.41 (*C*H_2Ph), 72.82 (C-6'), 70.99 (C-7'), 69.46 (C-5), 68.87 (C-6), 56.79 (OCH_3), 40.06 (C-3), 29.81 (C-1'), 20.75 and 20.86 (O*A*

Minor isomer: α-*C*-disaccharide **9b** (2.7 mg): Retention time 18.7 min, syrup, $[\alpha]_D$ -79 (*c* 0.25, chloroform): ^{1}H NMR (400 MHz) δ 7.46-7.20 (20 H, arom.), 5.47 (s, 1 H, PhC*H*), 5.09 (d, 1 H, J = 3.3 Hz, H-3'), 4.84 (dd, 1 H, J = 7.4, J = 10.5 Hz, H-2), 4.80-4.25 (m, 9 H, H-1, H-6a, H-7'a, PhCH_2), 4.17 (td, 1 H, J = 3.3, J = 6.5 Hz, H-2'), 3.89-3.80 (m, 2 H, H-4', H-5'), 3.75-3.55 (m, 4 H, H-5, H-6b, H-6', H-7'b), 3.49 (s, 3 H, O*Me*), 3.52-3.41 (m, 1 H, H-4), 2.07 (m, 1 H, H-3), 2.05 and 1.77 (two s, 6 H, O*Ac*), 1.86 (m, 2 H, H-1'a, H-1'b); ^{13}C NMR: δ 170.41, 169.39 (*C*=O), 138.43-126.09 (Ph), 103.31 (C-1), 101.62 (*C*HPh), 84.23 (C-4'), 82.82 (C-5'), 81.32 (C-2'), 79.96 (C-4), 79.21 (C-3'), 77.68 (C-2), 73.37, 72.53 and 73.22 (*C*H_2Ph), 72.53 (C-6'), 70.83 (C-7'), 69.30 (C-5), 69.10 (C-6), 56.90 (O*C*H_3), 39.95 (C-3), 29.66 (C-1'), 20.98 and 20.59 (OAc).

Methyl 3-*C*-(2,5-anhydro-1-deoxy-D-*glycero*-L-*manno*-heptit-1-yl)-3-deoxy-β-D-glucopyranoside (10). Major *C*-disaccharide **9a** (6.1 mg) was deacetylated in 1.0:0.4:0.2 methanol-water-triethylamine (1.6 mL) overnight at room temperature. After repeated evaporation with water, the residue was dissolved in 10:5:0.2 methanol-ethyl acetate-acetic acid (15.2 mL) and hydrogenated over 10% Pd-C at 50 psi for 8 h. Solvent evaporation gave **10** (2.7 mg, quantitative) as a syrup: $[\alpha]_D$ -29 (*c* 0.32, water); ^{1}H NMR (400 MHz) δ 4.75-4.60 (m, 1 H, H-2'), 4.42 (d, 1 H, J = 6.5 Hz, H-3'), 4.18 (d, 1 H, J = 7.9 Hz, H-1), 3.99 (t, 1 H, J = 6.4 Hz, H-4'), 3.90-3.05 (m, 9 H, H-2, H-4, H-5, H-6a, H-6b, H-5', H-6', H-7'a, H-7'b), 3.41 (s, 3 H, O*Me*), 2.28-2.22 (m, 1 H, H-3), 1.87-1.61 (m, 2 H, H-1'a, H-1'b); ^{13}C NMR: δ 105.56 (C-1), 81.79 (C-5'), 81.44 (C-2'), 81.20 (C-4'), 79.54 (C-4), 77.50 (C-3'), 72.89 (C-2), 71.76 (C-5), 68.61 (C-6'), 63.42 (C-7'), 61.90 (C-6), 57.72 (O*C*H_3), 45.53 (C-3), 32.66 (C-1'). No destructive analysis was performed on this material.

2,5-Anhydro-1-deoxy-1,1-difluoro-3,4-(bis-*O*-*tert*-butyldimethylsilyl)-6,7-*O*-isopropylidene-D-galacto-hept-1-enitol (12). To a solution of 2,3-(bis-*O*-*tert*-butyldimethylsilyl)-5,6-*O*-isopropylidene-D-galactono-1,4-lactone[8] (**11**, 2 g, 4.48 mmol) and dibromodifluoromethane (2.0 mL, 22.8 mmol) in anhydrous THF (35 mL), tris(dimethylamino)phosphine (8.3 mL, 45.7 mmol) dissolved in THF (20 mL) was added at -20 °C, and the mixture was stirred at room temperature for 30 min. Zinc powder (1.5 g, 22.8 mmol) and tris(dimethylamino)phosphine (0.8 mL) were added and the mixture heated to reflux for 15 h. The mixture was cooled to room temperature and diethyl ether (50 mL) was added. The ether layer was decanted and the residue washed with ether (50 mL). The combined ether extracts were washed with saturated copper sulfate solution until it remained blue, water, and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Flash chromatography on silica gel (99:1, then 95:5 cyclohexane-ethyl acetate) afforded **12** (1.34 g, 62 % yield) as a pale yellow oil: $[\alpha]_D$ -26 (*c* 1.0, chloroform); MS (CI, NH_3): 498 (M + NH_4^+), 481 (M + 1). ^{1}H NMR

(250 MHz) δ 4.50-4.34 (m, 2 H, H-4, H-7a), 4.15 (d, 1 H, J = 8.5 Hz, H-3), 4.01 (dd, 1 H, J = 6.9 Hz, J' = 8.0 Hz, H-6), 3.80 (broad s, 1 H, H-5), 3.75 (dd, 1 H, J = 8.0 Hz, H-7b), 1.45 and 1.37 (two s, 6 H, Me), 0.90 (s, 18 H, *t*-BuSi), 0.10 and 0.09 (two s, 12 H, MeSi); ^{13}C-NMR (62.5 MHz) δ 150.11 (dd, J = 267, J' = 289 Hz, C-1), 121.02 (dd, J = 13, J' = 50 Hz, C-2), 110.12 (*C*Me$_2$), 91.83 (C-3), 79.41 (d, J = 2 Hz, C-4), 75.59 (d, J = 4 Hz, C-5), 75.44 (d, J = 7 Hz, C-6), 65.62 (C-7), 26.94, 26.66, 25.61, 25.56, 25.19 (*t*-Bu), 17.69, 17.64 (*C*H$_3$), -459, -4.69, -5.01, -5.04, -5.28, -5.29 (*C*Si); ^{19}F NMR δ -104.4 (d, 1 F, J = 91 Hz), -119.3 (d, 1 F, J = 91 Hz).

Anal. Calcd for $C_{22}H_{42}F_2O_5Si_2$: C, 54.96; H, 8.81. Found: C, 54.89; H, 8.77.

2,5-Anhydro-1-deoxy-1,1-difluoro-4-*O*-*tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-D-*galacto*-hept-1-enitol (13). To a solution of **12** (300 mg, 0.62 mmol) in dry THF (5.0 mL), tetrabutylammonium fluoride (174 mg, 0.62 mmol) was added at -10 °C. After 1 h, satd aqueous $NaHCO_3$ was added, and the mixture was extracted with dichloromethane. The organic layer was washed with satd aqueous $NaHCO_3$, and satd aqueous NaCl, then dried ($MgSO_4$), filtered and concentrated. Flash chromatography on silica gel (9:1 to 6:1 cyclohexane-ethyl acetate) gave **13** (144.7 mg, 59 % yield) as a syrup: $[\alpha]_D$ -35 (*c* 0.82, chloroform); ^{1}H NMR (200 MHz) δ 4.69 (d, 1 H, J = 2.8 Hz, H-3), 4.42 (q, 1 H, J = 6.8 Hz, H-6), 4.12 (dd, 1 H, J = 3.1, J = 6.8 Hz, H-5), 4.05 (dd, 1 H, J = 6.8 Hz, J' = 8.4 Hz, H-7a), 4.00 (m, 1 H, H-4), 3.87 (dd, 1 H, J = 6.8, J' = 8.4 Hz, H-7b), 1.97 (broad s, 1 H, O*H*), 1.47 and 1.39 (two s, 6 H, Me), 0.90 (s, 9 H, t-BuSi), 0.14 and 0.12 (two s, 6 H, MeSi); ^{13}C NMR (62.5 MHz) δ 110.17 (*C*Me$_2$), 88.31 (C-3), 78.59 (C-4), 75.40 (C-5), 75.04 (C-6), 65.27 (C-7), 26.51, 25.57, 25.15 (*t*-Bu), 17.89 (*C*H$_3$).

Methyl 2-*O*-acetyl-3-*C*-(2,5-anhydro-1-deoxy-1,1-difluoro-3,4-di-*O*-acetyl-6,7-*O*-isopropylidene-D-*glycero*-L-*gluco*-heptit-1-yl)-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside (15). To a solution of methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-β-D-allopyranoside[10] (**14**, 75.0 mg, 0.191 mmol) in dry THF (2.2 mL), butyllithium (1.6 M in hexanes, 0.165 mL) and dimethyldichlorosilane (0.116 mL, 0.95 mmol) were added at -78 °C. The mixture was allowed to reach room temperature in 3 h, then concentrated to dryness under vacuum. The residue was taken in THF (1.5 mL), and **13** (70.0 mg, 0.191 mmol), DMAP (26 mg) were added. After stirring overnight at room temperature, the solvent was evaporated, and the residue was dissolved in degassed toluene (19 mL). To this boiling mixture, a solution of *n*-Bu_3SnH (0.57 mL, 0.21 mmol) and AIBN (7 mg) in toluene (1.25 mL) was added over 18 h by means of syringe pump. Then the solvent was evaporated, the residue was dissolved in THF (1.5 mL) and tetrabutylammonium fluoride (54 mg, 0.17 mmol) was added. After 2 h at room temperature, triethylamine (0.1 mL) was added and the mixture concentrated to a syrup.

Acetylation was performed with pyridine-acetic anhydride (2:1). Flash chromatography on silica gel, (9:1 to 1:1 cyclohexane-ethyl acetate) yielded only one *C*-

disaccharide product **15** (37.0 mg, 29 % yield) which crystallized from dichloromethane-*n*-hexane: mp 84 °C; $[\alpha]_D$ -47 (*c* 0.34, chloroform); ^{1}H NMR (400 MHz) δ 7.46-7.33 (5 H, arom.), 5.58 (t, 1 H, J = 3.5 Hz, H-3'), 5.52 (s, 1 H, PhC*H*), 5.33 (dd, 1 H, J = 7.1 Hz, J' = 9.6 Hz, H-2), 5.24 (dd, 1 H, J = 3.4 Hz, J' = 6.2 Hz, H-4'), 4.54 (td, 1 H, J = 3.8, J' = 14.8 Hz, H-2'), 4.44 (d, 1 H, J = 7.1 Hz, H-1), 4.37 (dd, 1 H, J = 4.7 Hz, J' = 10.5 Hz, H-6a), 4.25 (td, 1 H, J = 4.2 Hz, J' = 6.6 Hz, H-6'), 4.13 (dd, 1H, J = 4.2 Hz, J' = 6.0 Hz, H-5'), 4.01 (dd, 1 H, J = 6.6 Hz, J' = 8.2 Hz, H-7'a), 3.90 (dd, 1 H, J = 6.6 Hz, J' = 8.2 Hz, H-7'b), 3.89 (t, 1 H, J = 10.5 Hz, H-4), 3.77 (t, 1 H, J = 10.5 Hz, H-6b), 3.55 (td, 1 H, J = 4.7 Hz, J' = 10.2 Hz, H-5), 3.49 (s, 3 H, O*Me*), 2.83 (dq, 1 H, J = 10.2 Hz, J' = 14.2 Hz, H-3), 2.09 and 2.07 (two s, 6 H, O*Ac*), 1.86 (s, 3 H, O*Ac*), 1.38 and 1.35 (two s, 6 H, *Me*); ^{13}C NMR: δ 169.97, 169.71, 168.98 (*C*=O), 136.86-125.94 (Ph), 121.00 (dd, J = 239, J' = 264 Hz, C-1'), 109.72 (*C*Me$_2$), 102.83 (C-1), 101.24 (*C*HPh), 82.99 (C-4'), 82.92 (dd, J = 29, J' = 22 Hz, C-2'), 78.54 (C-2, C-4), 75.18 (C-5'), 75.07 (C-3'), 74.97 (C-6'), 68.89 (C-6), 68.09 (C-5), 65.25 (C-7'), 56.73 (O*C*H$_3$), 46.98 (t, J = 23 Hz, C-3), 26.11, 25.36 (*C*H$_3$), 20.87, 20.69 and 20.47 (O*Ac*).

FAB-MS (CH_4): Calcd for $C_{30}H_{38}O_{13}F_2 + H^+$: 645.2359. Found: 645.2348.

Methyl 3-*C*-(2,5-anhydro-1-deoxy-1,1-difluoro-D-*glycero*-L-*gluco*-heptit-1-yl)-3-deoxy-β-D-glucopyranoside (16). To a solution of **15** (9.8 mg, 0.015 mmol) in dichloromethane (1 mL), trifluoroacetic acid (0.040 mL) and water (0.015 mL) were added. After stirring for 2 h at room temperature, triethylamine (0.2 mL) was added and the mixture was concentrated to dryness. The residue was dissolved in methanol (1.0 mL), and water (0.4 mL) and triethylamine (0.2 mL) were added and the solution stirred overnight at room temperature. Evaporation at reduced pressure, followed by repeated addition of water and evaporation, and lyophilization yielded **16** (4.2 mg, 71 %): $[\alpha]_D$ -16 (*c* 0.34, water); ^{1}H NMR (400 MHz) δ 4.45-4.19 (m, 2 H, H-2', H-3'), 4.32 (d, 1 H, J = 8.0 Hz, H-1), 4.11 (t, 1 H, J = 7.5 Hz, H-4'), 3.89-3.33 (m, 9 H, H-2, H-4, H-5, H-6a, H-6b, H-5', H-6', H-7'a, H-7'b), 3.50 (s, 3 H, O*Me*), 2.44 (m, 1 H, H-3); ^{13}C NMR: δ 122.01 (dd, J = 240, J' = 262 Hz, C-1'), 104.49 (C-1), 81.86 (C-5'), 81.50 (dd, J = 30, J' = 21 Hz, C-2'), 78.07 (C-4'), 76.87 (C-3'), 76.10 (C-2, C-4), 70.58 (C-5), 63.78 (C-6'), 62.91 (C-7'), 61.14 (C-6), 57.33 (O*C*H$_3$), 50.61 (t, J = 23 Hz, C-3). No destructive analysis was performed on this material.

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