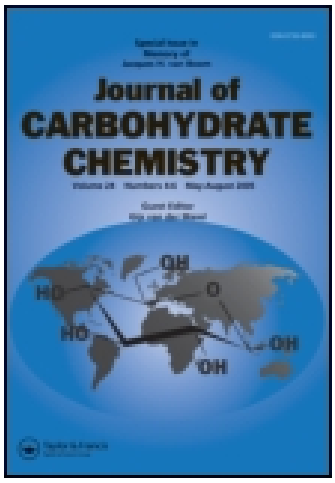

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A NEW APPROACH TO A DISACCHARIDIC HAPTEN CONTAINING A GALACTOFURANOSYL ENTITY

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A NEW APPROACH TO A DISACCHARIDIC HAPTEN CONTAINING A GALACTOFURANOSYL ENTITY[1, 2]

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ABSTRACT

A short synthetic entry into the disaccharidic hapten β-D-Gal*f*-(1→3)-α-D-Man*p*-O$(CH_2)_8CO_2$Me containing a galactofuranosyl entity at the non-reducing part is described. The synthetic scheme was designed in such a way that each required building block could be obtained by minimizing the number of chemical and purification steps. Indeed, compound **8** was obtained according to a four step–one pot preparation.

INTRODUCTION

Worldwide each year, a large number of illnesses due to parasites are reported. This can be explained by the natural outstanding diversity of parasites which carry pathogenic agents and by their high potential of adaptability to the contaminated host.[3] Generally, host and parasite are able to live in harmony. Nevertheless, *Aspergillus*, *Leishmania* and *Trypanosoma* species induce severe diseases. For instance, *T. gambiense* and *T. rhodesiense* are responsible for sleeping sickness in West and East Africa, respectively, while American or Chagas disease originates from *T. cruzi*.[3] Moreover, increasing human migrations result in exotic

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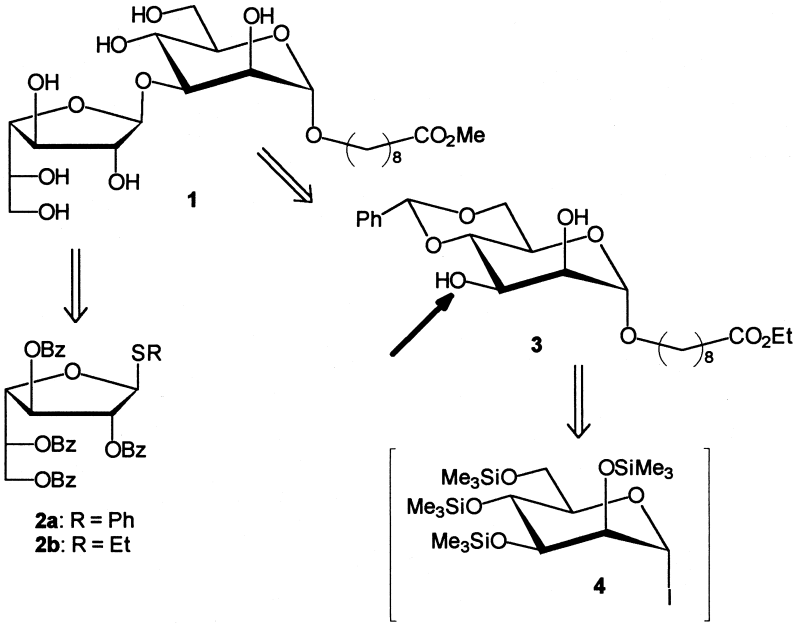

Scheme 1. Retrosynthetic scheme for the preparation of disaccharide 1.

parasitoses from African and South American continents appearing more frequently in the northern hemisphere. The clinical effects of these diseases may be caused by a number of biomolecules such as proteins, glycoproteins and/or glycolipids. Among the latter, it was established that the epitopic unit of glycoconjugates, carried by infective microorganisms, contains galacto*furanose* (Gal*f*) residues as the non-reducing end.[4]

Considering our interest in hexo*furanose* chemistry,[5] we present herein a convenient access to the disaccharidic hapten **1** (Scheme 1) characterized by a β-D-Gal*f* entity and a functionalized spacer for further connection to a carrier. Our approach relies on (i) a specific synthesis of galactofuranosyl donors **2**, (ii) a concise α-D-mannosylation of the spacer arm *via* the persilylated mannopyranosyl iodide **4** and (iii) a highly regioselective furanosylation reaction of diol **3**.

RESULTS AND DISCUSSION

The known octyl galactofuranoside **5** was obtained from D-Gal according to a procedure developed in our laboratory[6] and then benzoylated (Scheme 2). Subsequent acetolysis under conditions worked out for the preparation of per-*O*-acetyl-hexofuranoses[7] was unfortunately unsuccessful, probably because of greater electron withdrawing effects of benzoyl groups as compared to those of acetyl units. Therefore, substituting acetic anhydride by the more reactive trifluoroacetic anhydride under carefully controlled acidic conditions afforded the anomeric trifluoroacetyl furanose **7** without ring expansion. This intermediate

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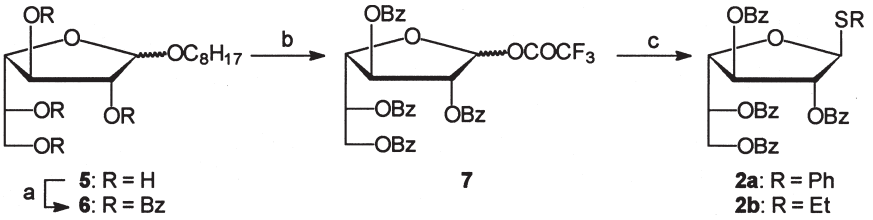
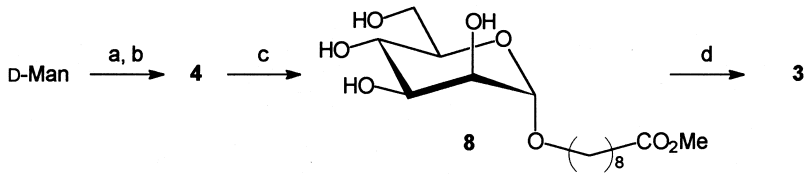


Reagents and conditions: (a) BzCl, Py (98%); (b) $(CF_3CO)_2O$, H_2SO_4, CH_2Cl_2 (80%); (c) RSH, $BF_3{\cdot}OEt_2$ (R = Ph, 91%; R = Et, 72%).

Scheme 2. Preparation of galactofuranosyl donors **2a** and **2b**.

could be isolated as a mixture of α,β -anomers (α/β = 1:4.6) but was best used for further thioglycosidation just after simple work-up. Reaction of **7** with thiophenol or ethanethiol, promoted by boron trifluoride-diethyl ether complex, resulted in the specific formation of β-thioglycofuranosides **2a** and **2b**, respectively.

Parallel to this sequence, we also focused our attention on a short entry into the mannopyranosidic acceptor **3**. Amongst various hypotheses, we considered the glycosyl iodide approach[8] in order to shorten the time consuming preparation of **3**.[9] Indeed, persilylation of free D-mannose (D-Man) occurred in pyridine in 30 min using hexamethyldisilazane (HMDS) and chlorotrimethylsilane (TMSCl) as silylating agents (Scheme 3). The resulting anomeric mixture (α/β = 1:6.7), exclusively in the pyranose form as revealed by NMR analysis, quantitatively reacted with iodotrimethylsilane (TMSI) to give the key donor **4**. Glycosylation of 8-ethoxycarbonyloctanol was then carried out in dichloromethane in the presence of sterically hindered 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) used as acid scavenger. The glycosylation step was followed by simple *in situ* methanolysis of silyl ethers. However, under these conditions, a first attempt to mannosylate the ω-functionalized alcohol yielded an anomeric mixture of mannopyranoside **8**α,β. To overcome this problem, acetylation of **8**α,β followed by anomerization under the action of ferric chloride[10] and transesterification afforded the required pure **8**α. Nevertheless, in order to shorten this multi-step sequence, we expected that a diastereospecific mannosidation would occur using the well known *in situ* anomerization approach.[11] Therefore, after optimization, best results were obtained by: (i) synthesizing the donor **4** from persilylated mannopyranose in 45 min, (ii) effecting the anomerization catalyzed by tetrabutylammonium iodide (TBAI) in 15 min, and



Reagents and conditions: (a) HMDS, TMSCl, Py; (b) TMSI, CH_2Cl_2; (c) TBAI, $HO(CH_2)_8CO_2Et$, DTBMP; MeOH (55% from D-Man); (d) $PhCH(OMe)_2$, $ZnCl_2$, AcOEt (44%).

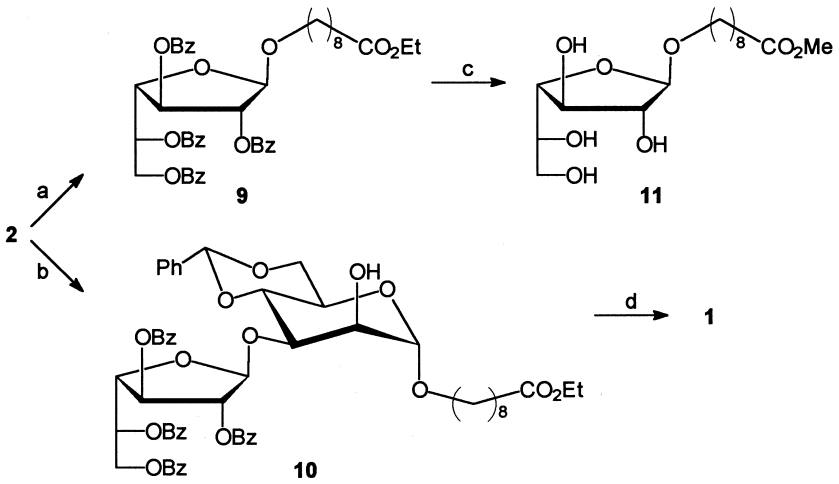
Scheme 3. Synthesis of the mannopyranosidic building block **3**.

(iii) simultaneously adding 8-ethoxycarbonyloctanol and the base. After *in situ* desilylation, this procedure gave the target α-mannopyranoside **8**α in 55% overall yield from D-Man, i.e., approximately 90% for each chemical step. Finally, selective 4,6-*O*-benzylidenation was achieved by transacetalation using benzaldehyde dimethyl acetal and affording selectively acceptor **3**.

Having the required building blocks in hand, we next investigated the coupling reaction. Furanosylation of 8-ethoxycarbonyloctanol, yielding the protected galactofuranoside **9**, was first achieved under standard activation conditions, i.e., *N*-iodosuccinimide (NIS) and trimethylsilyl trifluoromethanesulfonate (TMSOTf), of both phenyl and ethyl thiogalactofuranosides **2a** and **2b**, respectively (Scheme 4). A better glycosylation yield was obtained from ethyl derivative **2b** (52% vs 40%), thus denoting a higher reactivity of **2b** over **2a**.[12] In this context, glycosylation of diol acceptor **3** was performed using **2b** as the furanosyl donor. Bis-glycofuranosylation of the mannosidic acceptor was avoided by carrying out the coupling reaction at 0°C. Under these conditions, the desired β-(1→3)-disaccharide **10** was obtained with high regioselectivity (no trisaccharide was identified) and isolated in 46 % yield.

Finally, deprotection of hydroxyl groups and transesterification of the ethyl ester of compound **9** were simultaneously achieved under Zemplen conditions to afford the desired galactofuranoside **11**. Moreover, a similar debenzoylation procedure was followed by hydrogenolytic removal of the 4,6-benzylidene acetal catalyzed over Pd/C that allowed the synthesis of the targeted hapten **1** in 90% yield for the last two steps.

Compounds **9**, **10**, **11** and **1** were easily characterized on the grounds of signals identified by COSY and heteronuclear ^{1}H-^{13}C 2D experiments. The β config-



Reagents and conditions: (a) $HO(CH_2)_2CO_2Et$, NIS, TMSOTf, 4Å MS, CH_2Cl_2 (40% from **2a**, 62% from **2b**); (b) **3**, NIS, TMSOTf, 4Å MS, CH_2Cl_2 (46%); (c) NaOMe, MeOH (93%); (d) NaOMe, MeOH; H_2 Pd/C (90%).

Scheme 4. Synthesis of the targeted haptens 11 and 1.

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uration of the furanosyl entities was based on a small coupling constant between H-1′ and H-2′ ($J_{1',2'} \approx 0$ Hz). Moreover, glycosylation of the equatorial hydroxyl of **3** was evidenced, for disaccharide **10**, by a typical downfield chemical shift for C-3 ($\delta_{C\text{-}3}$ = 72.6 ppm for **3** vs. $\delta_{C\text{-}3}$ = 76.8 ppm for **10**) as well as upfield shift for both adjacent carbon atoms C-2 ($\delta_{C\text{-}2}$ = 72.2 ppm for **3** vs. $\delta_{C\text{-}2}$ = 68.7 ppm for **10**) and C-4 ($\delta_{C\text{-}4}$ = 68.5 ppm for **3** vs. $\delta_{C\text{-}4}$ = 72.0 ppm for **10**).[13] A similar behaviour was observed by comparison of C-3, C-2 and C-4 chemical shifts from compounds **8** and **1**, respectively.

In summary, we have developed an efficient route toward the synthesis of a glycosidic hapten characterized by the disaccharide β-D-Gal*f*-(1→3)-α-D-Man*p* which mimics the non-reducing and epitopic part of the main lipopeptidophosphoglycan (LPPG) found in *T. cruzi*. Particular attention has been given to establishing (i) the specific formation of the furanoid ring and (ii) a short synthesis of the mannopyranosyl moiety. The key step of our strategy consisted in a four step (activation, anomerization, diastereospecific glycosidation without anchimeric assistance of participating groups, and deprotection)–one pot preparation of mannoside **8** and resulted in an important decrease in the number of purification and isolation steps required and in a significantly increased overall yield. Continuing efforts are currently under way for the chemical synthesis of natural derivatives containing hexofuranosyl residues.

EXPERIMENTAL

General Methods. While all chemicals were commercially available and used as received, octyl D-galactofuranoside (**5**) was prepared according to ref. 6. All reactions were performed under a nitrogen atmosphere. TLC analyses were carried out on precoated non-activated plates (E. Merck 60 F_{254}) with detection by UV absorption (254 nm), when applicable, and charring with 5% sulfuric acid in ethanol. For column chromatography, E. Merck 60H (5–40 μm) silica gel was used. Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 20 °C using a 1 dm cell. Melting points were determined using a Reichert microscope with heating plate and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are given in ppm (δ). $CDCl_3$ or CD_3OD and trimethylsilane were used as solvent and internal standard, respectively. Microanalyses were performed by the Service de Microanalyses de l'ICSN (Gif sur Yvette, France).

***n*-Octyl 2,3,5,6-Tetra-*O*-benzoyl-D-galactofuranoside (6).** To a solution of **5**[6] (1.53 g, 5.20 mmol,β/α=1.86:1) in dry pyridine (17 mL) cooled at 0°C was added benzoyl chloride (2.92 mL, 25.15 mmol). After stirring for 3 h and concentration under reduced pressure, the resulting crude mixture was diluted with dichloromethane. The organic layer was successively washed with 5% aqueous HCl, saturated aqueous K_2CO_3 and water, dried ($MgSO_4$), and concentrated. Flash-chromatography (9:1 light petroleum/ethyl acetate) then afforded **6** (2.70

g,β/α=1.9:1) in 73% yield as an amorphous solid. TLC (4:1 light petroleum/ethyl acetate) R*f* 0.6. **6**β: ^{1}H NMR ($CDCl_3$) δ 8.08−7.86 (m, 8 H, C_6H_5); 7.58−7.18 (m, 12 H, C_6H_5); 6.10−6.05 (m, 1 H, H-5); 5.62 (d, 1 H, H-3, $J_{3,4}$=5.1 Hz); 5.46 (s, 1 H, H-1); 5.30 (s, 1 H, H-2); 4.78 (dd, 1 H, H-6a, $J_{6a,6b}$=11.7 Hz, $J_{6a,5}$=4.6 Hz); 4.73 (dd, 1 H, H-6b, $J_{6b,5}$=6.6 Hz); 4.63 (dd, 1 H, H-4, $J_{4,5}$=3.6 Hz); 3.73 (dt, 1 H, OCH_2CH$_2$, ^2J=9.2 Hz, ^3J=7.1 Hz); 3.53 (dt, 1 H, OCH_2CH$_2$, ^3J=6.1 Hz); 1.67−1.54 (m, 2 H, OCH$_2$CH_2); 1.40−1.15 [m, 10 H, $(CH_2)_5$]; 0.86 (t, 3 H, CH_3, ^3J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 166.1, 165.7, 165.5 (CO); 133.4, 133.3, 133.2, 133.1 (C_{ipso}); 130.0−128.3 (C_6H_5); 105.6 (C-1); 82.1 (C-2); 81.2 (C-4); 77.6 (C-3); 70.3 (C-5); 67.6 (OCH_2CH$_2$); 63.5 (C-6); 31.8, 29.5, 29.4, 29.3, 26.2, 22.7 [$(CH_2)_6$]; 14.1 (CH_3). **6**α: ^{13}C NMR ($CDCl_3$) δ 166.0, 165.9, 165.7, 165.5 (CO); 133.4−128.2 (C_6H_5); 100.5 (C-1); 78.5, 77.8 (C-2, C-4); 74.9 (C-3); 71.9, 69.1 (C-5, OCH_2CH$_2$); 63.0 (C-6); 31.8, 29.3, 29.2, 29.1, 25.9, 22.6 [$(CH_2)_6$]; 14.0 (CH_3).

Anal. Calcd for $C_{42}H_{46}O_{10}$ (710.83): C, 70.97; H, 6.52. Found: C, 70.65; H, 6.50.

2,3,5,6-Tetra-*O*-benzoyl-1-*O*-trifluoroacetyl-D-galactofuranose (7). To a solution of **6** (1.585 g, 2.24 mmol) in dry dichloromethane (24 mL) were added, at 0°C, trifluoroacetic anhydride (1.27 mL, 8.95 mmol) and sulfuric acid (358 μL, 6.72 mmol). After stirring for 35 min, neutralization with triethylamine and concentration under reduced pressure, the residue was subjected to column chromatography (5:5:0.01 light petroleum/ethyl acetate/triethylamine) that afforded an anomeric mixture of **7** (1.24 g, 80%,β/α=4.6:1) as an amorphous compound. This product could be characterized by NMR analysis and thus used for subsequent reaction without further purification. TLC (5:5:0.01 light petroleum/ethyl acetate/triethylamine) R*f* 0.4. **7**β: ^{1}H NMR ($CDCl_3$) δ 8.10−7.26 (m, 20 H, C_6H_5); 6.07 (dt, 1 H, H-5, $J_{4,5}$=4.0 Hz, ^3J=6.6 Hz); 5.71 (s, 1 H, H-1); 5.64 (d, 1 H, H-3, $J_{3,4}$=5.1 Hz); 5.51 (s, 1 H, H-2); 4.86 (dd, 1 H, H-4); 4.78 (dd, 1 H, H-6a, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=12.0 Hz); 4.71 (dd, 1 H, H-6b, $J_{5,6b}$=7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 166.2, 165.8, 165.7, 165.6 (CO); 133.7−128.3 (C_6H_5); 100.9 (C-1); 82.7, 81.6 (C-4, C-2); 77.7 (C-3); 70.5 (C-5); 63.6 (C-6). ^{19}F NMR (CDCl3) δ −75.5 (CF_3). **7**α: ^{1}H NMR ($CDCl_3$) δ 8.10−7.26 (m, 20 H, C_6H_5); 6.12 (t, 1 H, H-2, $J_{1,2}$=$J_{2,3}$=4.6 Hz); 5.97 (1 H, H-5, $J_{4,5}$=6.4 Hz, ^3J=3.6 Hz); 5.84 (d, 1 H, H-1); 5.54 (t, 1 H, H-3, $J_{3,4}$=4.6 Hz); 4.84 (dd, 1 H, H-6a, $J_{6a,6b}$=12.2 Hz); 4.72 (dd, 1 H, H-6b); 4.56 (dd, 1 H, H-4). ^{13}C NMR ($CDCl_3$) δ 166.3, 166.0, 165.7, 165.5 (CO); 95.9 (C-1); 79.2, 77.6 (C-4, C-2); 75.7 (C-3); 72.2 (C-5); 63.1 (C-6). ^{19}F NMR ($CDCl_3$) δ −75.5 (CF_3).

Phenyl 2,3,5,6-Tetra-*O*-benzoyl-1-thio-β-D-galactofuranoside (2a). To a solution of **7** (1.80 g, 2.60 mmol) in dry dichloromethane (18 mL) were successively added, at 0°C, thiophenol (0.40 mL, 3.9 mmol) and BF_3.OEt_2 (0.66 mL, 5.2 mmol). The reaction was then monitored by TLC (3:2 light petroleum/ethyl acetate). After complete consumption of **7**, the mixture was diluted with dichloromethane (75 mL), washed with 5% aqueous $NaHCO_3$ and with water. The organic layer was finally dried ($MgSO_4$), concentrated, and the residue was chro-

matographically (4:1 light petroleum/ethyl acetate) purified. This procedure gave 2.00 g (89%) of desired **2a**. TLC (3:2 light petroleum/ethyl acetate) R*f* 0.7. mp =98–100 °C (ethyl acetate/light petroleum). $[\alpha]_D^{20}$ −66 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.06−7.21 (m, 25 H, C_6H_5); 6.11 (dt, 1 H, H-5, $J_{5,6b}$=6.9 Hz, $J_{5,6a}$=$J_{5,4}$=4.6 Hz); 5.84 (s, 1 H, H-1); 5.71 (d, 1 H, H-3, $J_{3,4}$=5.0 Hz); 5.67 (s, 1 H, H-2); 4.95 (t, 1 H, H-4); 4.76 (dd, 1 H, H-6a, $J_{6a,6b}$=11.8 Hz); 4.71 (dd, 1 H, H-6b). ^{13}C NMR ($CDCl_3$) δ 166.0, 165.7, 165.5, 165.3 (CO); 133.6, 133.5, 133.3, 133.1 (COC_{ipso}); 132.4 (SC_{ipso}); 130.0−127.3 (C_6H_5); 91.3 (C-1); 82.4 (C-2); 81.5 (C-4); 77.8 (C-3); 70.3 (C-5); 63.4 (C-6).

Anal. Calcd for $C_{40}H_{32}O_9S$ (688.76): C, 69.76; H, 4.68. Found C, 69.83; H, 4.69.

Ethyl 2,3,5,6-Tetra-*O*-benzoyl-1-thio-β-D-galactofuranoside (2b). Product **2b** was prepared according to the previous procedure starting with **7** (1.80 g, 2.60 mmol), ethanethiol (0.45 mL, 5.9 mmol) and $BF_3.OEt_2$ (0.66 mL, 5.2 mmol). Work-up and chromatographic (4:1 light petroleum/ethyl acetate) purification afforded **2b** (1.20 g) in 72% yield. TLC (7:3 light petroleum/ethyl acetate) R*f* 0.7. $[\alpha]_D^{20}$ −26 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.10−7.26 (m, 20 H, C_6H_5); 6.13−6.09 (m, 1 H, H-5); 5.67 (d, 1 H, H-1, $J_{1,2}$=1.0 Hz); 5.67−5.66 (m, 1 H, H-3); 5.50 (t, 1 H, H-2, $J_{2,3}$=1.0 Hz); 4.84 (t, 1 H, H-4, $J_{3,4}$=$J_{4,5}$=4.0 Hz); 4.77 (dd, 1 H, H-6a, $J_{6a,6b}$=11.7 Hz, $J_{6a,5}$=4.6 Hz); 4.74 (dd, 1 H, H-6b, $J_{6b,5}$=6.6 Hz); 2.78 (dq, 1 H, CH_2CH$_3$, ^2J=12.7 Hz, ^3J=7.6 Hz); 2.69 (dq, 1 H, CH_2CH$_3$, ^3J=7.6 Hz); 1.33 (t, 3 H, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$) δ 166.1, 165.7, 165.5, 165.4 (CO); 133.4, 133.3, 133.2, 133.1 (C_{ipso}); 130.1, 130.0, 129.9, 129.7, 128.5, 128.4, 128.3 (C_6H_5); 88.2 (C-1); 82.9 (C-2); 81.1 (C-4); 77.9 (C-3); 70.2 (C-5); 63.5 (C-6); 25.3 (CH_2CH_3); 14.9 (CH_2CH_3).

Anal Calcd for $C_{36}H_{32}O_9S$ (640.71): C, 67.49; H 5.03. Found C, 67.49; H, 5.19.

8-Ethoxycarbonyloctyl α-D-Mannopyranoside (8). To a solution of D-mannose (5.00 g, 27.8 mmol) in dry pyridine (80 mL) were successively added hexamethyldisilazane (32.2 mL, 152.8 mmol) and chlorotrimethylsilane (19.4 mL, 152.8 mmol). After stirring at room temperature for 35 min, the solvent was removed under reduced pressure. The resulting mixture was then diluted with Et_2O (100 mL) and washed with 5 % aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic layer was finally dried ($MgSO_4$) and concentrated to give an anomeric mixture of trimethylsilyl 2,3,4,6-tetra-*O*-trimethylsilyl-D-mannopyranoside (**6**) (14.87 g,α/β=6.7:1). TLC (9:1 light petroleum/diethylether) R*f* 0.8. Selected ^{1}H NMR data[14] for **6**: ($CDCl_3$) δ 4.90 (s, 0.87 H, H-1α); 4.64 (s, 0.13 H, H-1β). Selected ^{13}C NMR data[14] for **6**: ($CDCl_3$) δ 95.6 (C-1α); 95.5 (C-1β).

The crude oil (3.93 g, 7.26 mmol) was diluted in dry dichloromethane (20 mL) before adding freshly distilled iodotrimethylsilane (1.1 mL, 7.99 mmol). The mixture was stirred at room temperature for 45 min, tetrabutylammonium iodide (2.68 g, 7.26 mmol) was added and stirred for 15 min more before adding a dichloromethane (20 mL) solution of 8-ethoxycarbonyloctan-1-ol (2.93 g, 14.5

mmol) and 1.49 g (7.26 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine. The reaction mixture was stirred at room temperature for 6 h, and final desilylation was performed in 30 min with methanol (60 mL). The resulting solution was made neutral (triethylamine), concentrated, and purification by column chromatography (9:1 dichloromethane/methanol) afforded the target compound **8** (1.45g) in 55% global yield. TLC (8:1 dichloromethane/methanol) R*f* 0.3. $[\alpha]_D^{20}$ +28 (*c* 1.0, methanol) [lit.[15] $[\alpha]_D^{25}$ +48 (*c* 0.75, water)]. ^{1}H NMR ($CDCl_3$) δ 4.70 (s, 1 H, H-1); 4.10−4.05 (m, 2 H, $CO_2CH_2CH_3$); 3.79−3.72 (m, 2 H, H-2, H-6a); 3.70−3.62 (m, 3 H, H-3, H-6b, OCH_2CH_2); 3.58 (t, 1 H, H-4, $J_{3,4}=J_{4,5}=9.5$ Hz); 3.50−3.43 (m, 1 H, H-5); 3.40−3.35 (m, 1 H, OCH_2CH_2); 2.27 (t, 2 H, $CH_2CH_2CO_2Et$, $^3J=7.4$ Hz); 1.62−1.50 [m, 4 H, $(CH_2)_2$]; 1.38−1.24 [m, 8 H, $(CH_2)_4$]; 1.21 (t, 3 H, $CO_2CH_2CH_3$, $^3J=7.1$ Hz). ^{13}C NMR (CD_3OD) δ 175.5 (CO); 101.4 (C-1); 74.4 (C-5); 72.6 (C-3); 72.2 (C-2); 68.5 (C-4, OCH_2CH_2); 62.8 (C-6); 61.3 ($CO_2CH_2CH_3$); 35.0 ($CH_2CH_2CO_2Et$); 30.5, 30.3, 30.2, 30.0, 27.2, 26.0 [$(CH_2)_6$]; 14.6 ($CO_2CH_2CH_3$).

8-Ethoxycarbonyloctyl 4,6-*O*-Benzylidene-α-D-mannopyranoside (3). To a solution of **8** (0.90 g, 2.47 mmol) in ethyl acetate (5 mL) were successively added $ZnCl_2$ (0.36 g, 2.64 mmol) and benzaldehyde dimethyl acetal (408 μL, 2.64 mmol). After stirring at 50 °C for 1.5 h, the reaction mixture was cooled and then washed with 10% aqueous $Na_2S_2O_4$, saturated aqueous $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The target compound **3** was finally purified by column chromatography (3:2 light petroleum/ethyl acetate) and isolated in 44% yield (488 mg) as a colorless oil. TLC (1:1 light petroleum/ethyl acetate) R*f* 0.4. $[\alpha]_D^{20}$ +37 (*c* 1.2, $CHCl_3$) [lit.[9] $[\alpha]_D^{20}$ +37 (*c* 1.2, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$) δ 7.51−7.48 (m, 2 H, C_6H_5); 7.39−7.35 (m, 3 H, C_6H_5); 5.56 (s, 1 H, PhC*H*); 4.82 (s, 1 H, H-1); 4.29−4.23 (m, 1 H, H-6a); 4.14−4.09 (m, 2 H, $CO_2CH_2CH_3$); 4.10−4.04 (m, 1 H, H-3); 4.01−3.98 (m, 1 H, H-2); 3.91 (t, 1 H, H-4, $J_{3,4}=J_{4,5}=9.1$ Hz); 3.83−3.79 (m, 2 H, H-6b, H-5); 3.68 (dt, 1 H, OCH_2CH_2, $^2J=9.6$ Hz, $^3J=6.6$ Hz); 3.40 (dt, 1 H, OCH_2CH_2, $^3J=6.6$ Hz); 2.29 (t, 2 H, $CH_2CH_2CO_2Et$, $^3J=7.6$ Hz); 1.64−1.56 [m, 4 H, $(CH_2)_2$]; 1.38−1.29 [m, 8 H, $(CH_2)_4$]; 1.25 (t, 3 H, $CO_2CH_2CH_3$, $^3J=7.1$ Hz). ^{13}C NMR ($CDCl_3$) δ 174.0 (CO); 137.2 (C_{ipso}); 129.2, 128.3, 126.2 (C_6H_5); 102.2 (PhCH); 100.1 (C-1); 77.0 (C-4); 71.1 (C-3); 68.8 (C-6); 68.6 (C-3); 68.0 (OCH_2CH_2); 63.0 (C-5); 60.2 ($CO_2CH_2CH_3$); 34.3 ($CH_2CH_2CO_2Et$); 29.3, 29.1, 29.0, 26.0, 24.9 [$(CH_2)_6$]; 14.2 ($CO_2CH_2CH_3$).

8-Ethoxycarbonyloctyl 2,3,5,6-Tetra-*O*-benzoyl-β-D-galactofuranoside (9). To a solution of donor **2b** (0.093 g, 0.145 mmol) and 8-ethoxycarbonyloctanol (0.024 g, 0.212 mmol) in dry dichloromethane (1 mL) in the presence of molecular sieves (4 Å, 0.20 g), cooled at 0°C and protected from light, were successively added *N*-iodosuccinimide (26 mg, 0.145 mmol) and trimethylsilyl triflate (2 μL, 0.012 mmol). After stirring for 3 h at 0°C and 4 h at room temperature, the reaction mixture was made neutral by a few drops of triethylamine, filtered over a bed of celite, concentrated and finally purified by column chromatography (7:2:1

light petroleum/ethyl acetate/dichloromethane). Product **9** (0.059 g) was thus isolated in 52% yield. TLC (7:2:1 light petroleum/ethyl acetate/dichloromethane) R*f* 0.4. ^{1}H NMR ($CDCl_3$) δ 8.09−7.89 (m, 8 H, C_6H_5); 7.59−7.26 (m, 12 H, C_6H_5); 6.10−6.06 (m, 1 H, H-5); 5.63 (d, 1 H, H-3, $J_{3,4}$=5.1 Hz); 5.47 (s, 1 H, H-1); 5.30 (s, 1 H, H-2); 4.79 (dd, 1 H, H-6a, $J_{6a,6b}$=11.7 Hz, $J_{6a,5}$=4.6 Hz); 4.74 (dd, 1 H, H-6b, $J_{6b,5}$=7.1 Hz); 4.64 (dd, 1 H, H-4, $J_{4,5}$=3.6 Hz); 4.15−4.09 (m, 2 H, $CO_2CH_2CH_3$); 3.75 (dt, 1 H, OCH_2CH_2, ^2J=9.6 Hz, ^3J=6.6 Hz); 3.53 (dt, 1 H, OCH_2CH_2, ^3J=6.1 Hz); 2.26 (t, 2 H, $CH_2CH_2CO_2Et$, ^3J=7.4 Hz); 1.67−1.56 [m, 4 H, $(CH_2)_2$]; 1.41−1.21 [m, 8 H, $(CH_2)_4$]; 1.25 (t, 3 H, $CO_2CH_2CH_3$, ^3J=7,1 Hz). ^{13}C NMR ($CDCl_3$) δ 173.8 (*C*OOEt); 166.1, 165.7, 165.6, 165.4 (O*C*OPh); 133.5, 133.3, 133.2, 133.1 (C_{ipso}); 129.9−128.3 (C_6H_5); 105.5 (C-1); 82.0 (C-2); 81.2 (C-4); 77.6 (C-3); 70.3 (C-5); 67.6 (OCH_2CH_2); 63.5 (C-6); 60.1 ($CO_2CH_2CH_3$); 34.3 ($CH_2CH_2CO_2Et$); 29.4, 29.3, 29.2, 29.1, 26.1, 24.9 [$(CH_2)_6$]; 14.2 ($CO_2CH_2CH_3$).

Anal Calcd for $C_{45}H_{48}O_{12}$ (780.87): C, 69.22; H, 6.20. Found C, 69.15; H, 6.25.

8-Ethoxycarbonyloctyl 2,3,5,6-Tetra-*O*-benzoyl-β-D-galactofuranosyl-(1(3)-4,6-*O*-benzylidene-α-D-mannopyranoside (10). Galactofuranosyl donor **2b** (0.17 g, 0.27 mmol) and glycosyl acceptor **3** (0.10 g, 0.22 mmol) were dissolved in anhydrous dichloromethane (4 mL) containing molecular sieves (4 Å, 0.20 g). The reaction mixture was then protected from light and cooled to 0°C before adding *N*-iodosuccinimide (60 mg, 0.27 mmol) and trimethylsilyl triflate (9 μL, 0.04 mmol) and stirring for 15 min. After completion of the reaction, the media was quenched with several drops of triethylamine until it turned into a yellow solution. The resulting mixture was filtered over a bed of celite, concentrated under reduced pressure and finally subjected to column chromatography (4:1 toluene/ethyl acetate). This procedure provided the required disaccharide **10** (0.103 g) in 46% yield. TLC (4:1 toluene/ethyl acetate) R*f* 0.3. $[\alpha]_D^{20}$ +61 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.04−7.81 (m, 8 H, C_6H_5); 7.59−7.16 (m, 17 H, C_6H_5); 5.90 (ddd, 1 H, H-5′, $J_{5',6'a}$=8.6 Hz,, $J_{5',6'b}$=5.6 Hz, $J_{5',4'}$=3.0 Hz); 5.56 (dd, 1 H, H-3′, $J_{3',4'=}$5.6 Hz, $J_{3',2'}$=1.5 Hz); 5.49 (s, 1 H, H-1′); 5.46 (s, 1 H, PhC*H*); 5.44 (d, 1 H, H-2′); 4.93 (s, 1 H, H-1); 4.74 (dd, 1 H, H-4′); 4.59 (dd, 1 H, H-6′a, $J_{6'a,6'b}$=12.2 Hz,); 4.31−4.26 (m, 2 H, H-4, H-5); 4.16−4.02 (m, 5 H, H-2, H-3, H-6′b, $CO_2CH_2CH_3$); 3.92 (dd, 1 H, H-6a, $J_{6a,6b}$=10.2 Hz, $J_{6a,5}$=4.6 Hz); 3.90 (dd, 1H, H-6b, $J_{6b,5}$=5.1 Hz); 3.71 (dt, 1 H, OCH_2CH_2, ^2J=9.6 Hz, ^3J=6.6 Hz); 3.41 (dt, 1 H, OCH_2CH_2, ^3J=6.6 Hz); 2.28 (t, 2 H, $CH_2CH_2CO_2Et$, ^3J=7.1 Hz); 1.62−1.58 [m, 4 H, $(CH_2)_2$]; 1.36−1.21 [m, 8 H, $(CH_2)_4$]; 1.23 (t, 3 H, $CO_2CH_2CH_3$, ^3J=7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 166.0, 165.9, 165.7, 165.5 (CO); 137.3 (CHC_{ipso}); 135.5, 133.5, 133.1, 132.3 (COC_{ipso}); 130.0−125.9 (C_6H_5); 102.4 (C-1′); 102.0 (Ph*C*H); 100.1 (C-1); 82.4 (C-2′); 81.3 (C-4′); 77.2 (C-3′); 76.8 (C-3); 72.0 (C-4); 70.1 (C-5′); 68.9 (C-5); 68.7 (C-2); 68.1 (OCH_2CH_2); 64.2 (C-6′); 63.6 (C-6); 60.1 ($CO_2CH_2CH_3$); 34.3 ($CH_2CH_2CO_2Et$); 30.3, 29.7, 29.2, 29.1, 26.0, 24.9 [$(CH_2)_6$]; 14.2 ($CO_2CH_2CH_3$).

Anal. Calcd for $C_{58}H_{62}O_{16}$ (1015.13): C, 68.62; H, 6.16. Found C, 68.45; H, 6.20.

8-Methoxycarbonyloctyl β-D-Galactofuranoside (11). To a solution of **9** (0.050 g, 64 μmol) in anhydrous methanol (2 mL) was added sodium (0.1 mg). After stirring at room temperature for 24 h, the reaction was made neutral with IR120-H^+-form resin, filtered and concentrated under reduced pressure. After removal of the solvent, the desired product **11** was purified by flash-chromatography (9:1 dichloromethane/methanol) and isolated (0.021 g) in 93% yield. TLC (9:1 dichloromethane/methanol) R*f* 0.3. $[\alpha]_D^{20}$ −66 (*c* 1.0, MeOH) [lit[9] $[\alpha]_D^{20}$ −73 (*c* 0.6, EtOH)]. ^{1}H NMR (CD_3OD) δ 4.75 (d, 1 H, H-1, $J_{1,2}$=1.8 Hz); 3.90 (dd, 1 H, H-3, $J_{2,3}$=4.0 Hz, $J_{3,4}$=6.6 Hz); 3.83 (dd, 1 H, H-2); 3.81 (dd, 1 H, H-4, $J_{4,5}$=3.0 Hz); 3.65−3.50 (m, 7 H, H-5, H-6, H-6′, H-α, CH_3); 3.37−3.28 (m, 1 H, H-α′); 2.22 (t, 2 H, CH_2CO, ^3J=7.5 Hz); 1.52−1.47 (m, 2 H, CH_2β); 1.25−1.21 [m, 8 H, $(CH_2)_4$]. ^{13}C NMR (CD_3OD) δ 176.0 (CO); 109.4 (C-1); 84.0 (C-4); 83.4 (C-2); 78.7 (C-3); 72.4 (C-5); 68.9 (CH_2α); 64.6 (C-6); 52.0 (CH_3); 34.8 (CH_2β); 30.7, 30.3, 30.1, 27.2, 26.0 [$(CH_2)_6$)].

8-Methoxycarbonyloctyl β-D-Galactofuranosyl-(1→3)-α-D-mannopyranoside (1). To a solution of disaccharide **10** (0.10 g, 0.097 mmol) in anhydrous methanol (2 mL) was added a 0.1 M methanolic solution of sodium methoxide (0.97 mL). After stirring at room temperature for 16 h, the reaction mixture was made neutral with IR120-H^+-form resin, filtered and concentrated under reduced pressure: TLC (9:1 dichloromethane/methanol) R*f* 0.4. The resulting crude product was then subjected to hydrogenolysis in absolute ethanol (2 mL) using 10% palladium activated on charcoal as catalyst. No transesterification was observed under these conditions. After 48 h at room temperature, the catalyst was removed by filtration, and the solvent was evaporated. A chromatographic purification (4:1 dichloromethane/methanol) provided **1** (45 mg, 90% over two steps): TLC (4:1 CH_2Cl_2/MeOH) R*f* 0.4. $[\alpha]_D^{20}$ +61 (*c* 1.0, $CHCl_3$). ^{1}H NMR (CD_3OD) δ 4.99 (s, 1 H, H-1′); 4.69 (d, 1 H, H-1, $J_{1,2}$=1.5 Hz); 4.02−3.98 (m, 1 H, H-3′); 3.97−3.94 (m, 2 H, H-2′, H-4′); 3.89−3.87 (m, 1 H, H-2); 3.79−3.73 (m, 2 H, H-3, H-6a); 3.67−3.46 (m, 7 H, H-5′, H-6′a, H-4, H-5, OCH_2CH_2); 3.57 (s, 3 H, CO_2CH_3); 3.35 (dt, 1 H, OCH_2CH_2, ^2J=9.6 Hz, ^3J=6.6 Hz); 2.24 (t, 2 H, $CH_2CH_2CO_2$Me, ^3J=7.1 Hz); 1.57−1.49 [m, 4 H, $(CH_2)_2$]; 1.34−1.22 [m, 8 H, $(CH_2)_4$]. ^{13}C NMR (CD_3OD) δ 176.1 (CO); 106.5 (C-1′); 101.4 (C-1); 85.4 (C-4′); 82.8 (C-2′); 79.0 (C-3′); 77.5 (C-3); 74.5 (C-5); 72.5 (C-5′); 68.8 (C-2); 68.7 (OCH_2CH_2); 66.8 (C-4); 64.4 (C-6′); 62.9 (C-6); 52.0 (CO_2CH_3); 34.8 ($CH_2CH_2CO_2$Me); 30.6, 30.4, 30.3, 30.1, 27.3, 26.0 [$(CH_2)_6$]. $[\alpha]_D^{20}$ (of peracetylated disaccharide) +12 (*c* 1.0, $CHCl_3$) [lit.[9] $[\alpha]_D^{20}$ +37 (*c* 1.2, $CHCl_3$)].

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