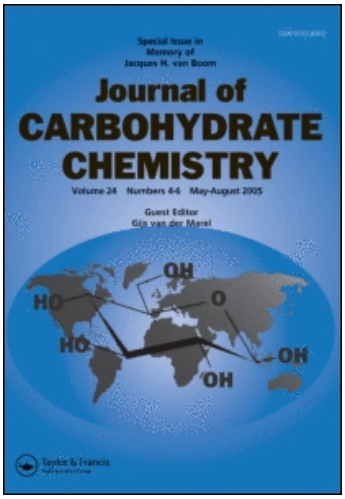

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Thierry Gourlain[a]; Anne Wadouachi[a]; R. Uzan[a]; D. Beaupère[a]
[a] Laboratoire de Chimie Organique, Université de Picardie Jules Verne, Amiens, France

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SYNTHESIS OF ETHER LINKED PSEUDO-OLIGOSACCHARIDES *VIA* 5,6-CYCLIC SULFATE DERIVATIVES OF PROTECTED MANNO AND GLUCOFURANOSE

Thierry Gourlain, Anne Wadouachi, R. Uzan and D. Beaupère *

Laboratoire de Chimie Organique, Université de Picardie Jules Verne,
33 rue Saint-Leu F-80039 Amiens, France

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ABSTRACT

C-6 ring opening of 5,6-cyclic sulfate derivatives of protected manno and glucofuranose with carbohydrate alkoxides gave ether linked pseudo-di or trisaccharides. Use of methyl 2,3-*O*-isopropylidene-5,6-*O*-sulfuryl-α-D-mannofuranoside **1** led to protected pseudo-disaccharide D-Glc*f*-(3→6)-D-Man*f*-(5→6)-D-Man*f* **4** and protected pseudo-trisaccharide D-Man*f*-(6→3)-D-Glc*f*-(6→3)-D-Glc*f* **11** derivatives in 66% and 41% overall yields, respectively.

INTRODUCTION

The key roles of oligosaccharides in many complex biological processes depends upon their specific molecular structures. Comparing the biochemical properties of natural oligosaccharides with those of analogues is a powerful way of correlating chemical

structure with biological activity.[1] Synthesis of the oligosaccharides has made considerable progress as a result of the development of glycosylation procedures[2] and elaborated strategies involving the use of protecting groups.[3]

However, only a few methodologies for the synthesis of ether linked pseudo-oligosaccharides have been developed. For example, the reaction of 2,3-dialkylstannylene acetals derived from gluco, manno or galactopyranose with aliphatic or aryl diacyl and triacyl chlorides gave glycoester derivatives which the authors named symmetric non-glycosidically linked di and trisaccharides.[4] Anhydro sugars are common precursors in the synthesis of such molecules.[5] For example reaction of 5,6-anhydro-D-glucofuranose or 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose with a partially protected hexose, pentose or alditol in basic conditions led to mixtures of ether linked di, tri and pseudo-tetrasaccharide derivatives.[6]

In a previous work, we described the synthesis of 6-*O*-alkyl and disaccharide derivatives of mannofuranose *via* a 5,6-cyclic sulfate.[7] In this paper, our methodology is extended to the synthesis of two pseudo-trisaccharides which are composed of gluco and mannofuranose units connected by ether linkages.

RESULTS AND DISCUSSION

We proposed two strategies for the synthesis of two pseudo-trisaccharides **M2 — M1— M1** and **M1— M2— M2** in which each ether linkage involves the primary carbon (Scheme 1).

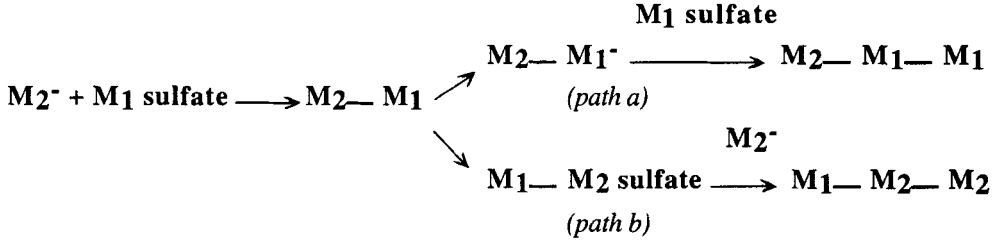
A pseudo-disaccharide (**M2 — M1**) would be first synthesized by reaction of a monosaccharide anion (**M2**$^-$) with a 5,6-*O*-sulfuryl derivative (**M1 sulfate**).

Following the *path a*, the product would be converted into a new anion (**M2 — M1**$^-$) which in turn would be coupled to a second sulfate derivative to give the pseudo-trisaccharide (**M2 — M1— M1**).

Following the *path b*, the pseudo-disaccharide (**M2 — M1**) would be partially deprotected and converted into a new cyclic sulfate (**M1 — M2 sulfate**) which would then be reacted with the anion (**M2**$^-$) to give the pseudo-trisaccharide (**M1 — M2 — M2**).

These two paths were then followed using 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**M2**) and alkyl 2,3-*O*-isopropylidene-α-D-mannofuranoside derivatives (**M1**).

To synthesize **4**, a derivative of D-Glc*f*-(3→6)-D-Man*f*-(5→6)-D-Man*f* (Scheme 2, *path a*), methyl *O*-(1,2:5,6-di-*O*-isopropylidene-D-glucofuranose)-(3→6)-2,3-*O*-

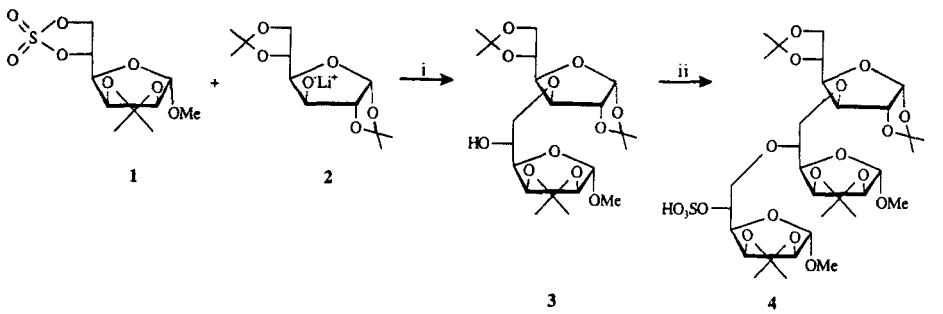


Scheme 1

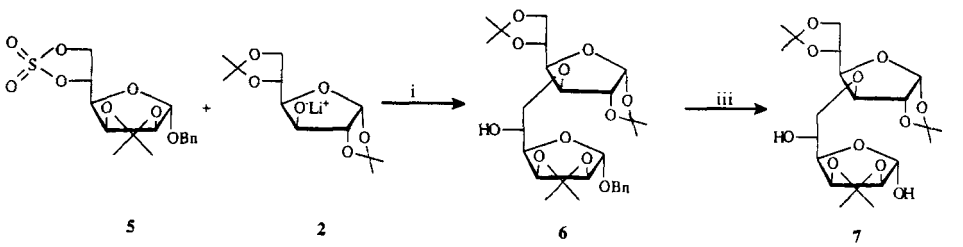
isopropylidene-α-D-mannofuranoside **3**[7] was treated with butyllithium to give the corresponding alkoxide reagent which was then condensed with the cyclic sulfate derivative **1**[8] forming the pseudo-trisaccharide **4** in 95% yield.

Using the former conditions, the disaccharide **6** was obtained from benzyl mannofuranoside derivative **5**[9] in 70% yield (Scheme 3). Removal of the benzyl group was performed with ammonium formate on Pd/C[10] to give only the α-mannofuranosyl anomer of pseudo-disaccharide **7**. The structure of compound **7** was established from its ^{1}H NMR spectrum obtained in deuterated chloroform. An anomeric proton singlet at 5.26 ppm indicating a *trans*-configuration between the hydrogens at positions 1 and 2 and typical of an α-mannofuranose ring. The ^{13}C NMR spectrum of **7** showed a chemical shift at 100.9 ppm, typical for a C-1 α furanose.[11]

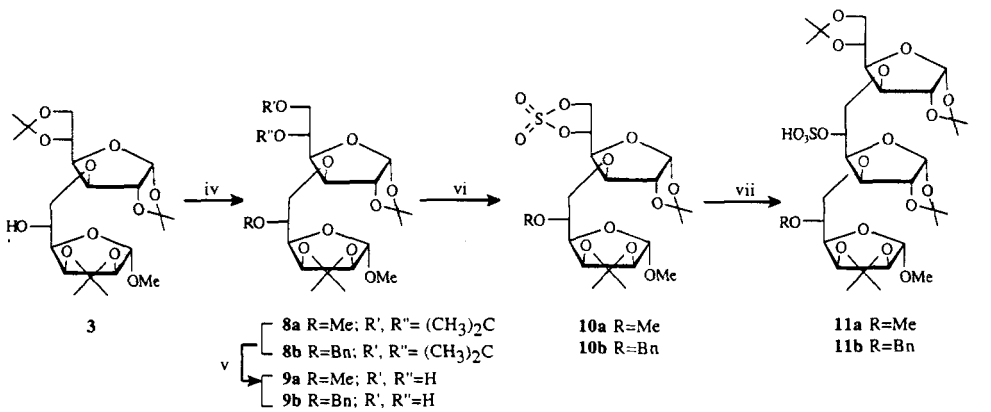
Starting from pseudo-disaccharide **3**, and following the *route b*, the pseudo-trisaccharide derivative D-Man*f*-(6→3)-D-Glc*f*-(6→3)-D-Glc*f* **11a** was prepared in 4 steps (Scheme 4). Oxidation of the cyclic sulfite derived from methyl *O*-(1,2-*O*-isopropylidene-α-D-glucofuranose)-(3→6)-2,3-*O*-isopropylidene-α-D-mannofuranoside, was carried out using the improved method of Gao and Sharpless.[12] The presence of the free 5-OH on the mannose unit might have been responsible for the loss of catalyst activity of ruthenium tetroxide,[13] so it was necessary to first protect this hydroxyl group with a methyl or benzyl group (**8a**, **8b** respectively). Selective cleavage of the 5,6-*O*-isopropylidene group of the methyl derivative **8a** was followed by transformation *via* cyclic sulfite into the cyclic sulfate **10a**. The oxidation step gave a high yield (91%) but required a longer time of reaction (2.5 h) than with monosaccharide cyclic sulfite derivatives. The reaction of the cyclic sulfate **10a** with the alkoxide **2** gave the pseudo-trisaccharide **11a** in 95% yield. As above, the pseudo-trisaccharide **11b**, in which the 5-OH group is protected with a benzyl group, was obtained from **8b** in a similar yield.



Scheme 2



Scheme 3



Scheme 4

Reagents : (i) THF/HMPA (4/1); H_2SO_4 (0.22 eq), 70%
(ii) *n*-BuLi (1 eq) THF/HMPA (4/1); **1** (1.7 eq), 95%
(iii) Pd/C 10%, MeOH, $HCOONH_4$, quant.
(iv) NaH, BnBr (1.5eq), DMF, 96% or NaH, MeI (1.5eq), 98%
(v) CH_3COOH/H_2O (7/3), 70%
(vi) **9a** or **9b**, $SOCl_2$, pyr, THF; $RuCl_3$ (cat), $NaIO_4$ (2eq), $H_2O/CH_2Cl_2/CH_3CN$ (2/1/1)
(vii) THF/HMPA (4/1), **2** (0.6 eq), 95% (R=Me)

CONCLUSION

The work described above showed that the 5,6-*O*-sulfuryl mannofuranose derivative is a good precursor for pseudo-oligosaccharide synthesis. The pseudo-trisaccharides **11a**, **11b** and **4** were prepared from D-mannose in overall yields of 31%, 21% and 48%, respectively.

EXPERIMENTAL

General procedures. Melting points were determined with a Buchi 535 apparatus and are uncorrected. TLC was performed on silica gel Merck 60 F_{254} plates with visualization by UV light (254 nm) and/or by charring with a vanillin-H_2SO_4 reagent. Preparative column chromatography was performed using 230-400 mesh Merck silica gel. Optical rotations were determined with a Jasco-DIP-370 electronic micropolarimeter. NMR spectra were recorded in $CDCl_3$, on a Bruker 300 WB spectrometer. Chemical shifts are expressed in parts per million downfield from TMS. Coupling constants, assigned by double irradiation, are in Hz and splitting pattern abbreviations are: s, singlet; d, doublet; m, multiplet. Indices a, b and c have been attributed to the monosaccharide units according to their introduction order in pseudo-di or trisaccharides. Elemental analysis were performed by the "Service Central de Microanalyse du CNRS" of Vernaison (69-Rhône-France). All solvents were distilled before use. THF was distilled from $LiAlH_4$, thionyl chloride from triphenylphosphite (10 % V/V). All reactions were performed under argon atmosphere.

Methyl 2,3-*O*-isopropylidene-6-*O*-(methyl 5-deoxy-2,3-*O*-isopropylidene-6-*O*-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl)-α-D-mannofuranosid-5-yl)-5-*O*-sulfo-α-D-mannofuranoside (4). *n*-Butyllithium 2.5 M in hexane (1.7 eq, 321 µL) was added dropwise to a solution of **3** (208 mg, 0.44 mmol) in anhydrous THF (1 mL) and HMPA (0.25 mL) cooled at -40 °C. After stirring for 1 h at -40 °C, compound **1** (1.7 eq, 238 mg) was added and the reaction mixture was allowed to reach room temperature and stirred for 4 h. After addition of a few drops of water, the mixture was concentrated. The residue was chromatographed on silica gel (CH_2Cl_2-MeOH 9:1) to give pure **4** (320 mg, 95 %; Rf 0.25, 9:1 CH_2Cl_2-MeOH). $[\alpha]_D^{27}$ +37 ° (*c* 0.95, CH_2Cl_2); ^1H NMR: δ 5.87 (d, 1H, H-1b, $J_{1,2}$ 3.6), 4.76 (m, 4H, H-1a, H-1c, H-3a, H-3c), 4.69 (m, 1H, H-5c), 4.66 (d, 1H, H-2b), 4.46 (2d, 2H, H-2a, H-2c, $J_{2,3}$ 5.8), 4.29 (m, 1H, H-5b), 4.22 (dd, 1H, H-4c, $J_{3,4}$ 3.5, $J_{4,5}$ 5.7), 4.15, 3.87

(m, 7H, H-6b, H-4b, H-4a, H-6c, H-6'c, H-6'a, H-6'b), 3.85 (d, 1H, H-3b, $J_{3,4}$ 2.7), 3.73 (m, 1H, H-5a), 3.66 (dd, 1H, H-6a, $J_{5,6}$ 3.8, $J_{6',6}$ 10.6), 3.22 (s, 6H, OCH_3), 1.39, 1.38, 1.36, 1.33, 1.25, 1.24, 1.23 (s, 24H, $C(CH_3)_2$); ^{13}C NMR: δ 112.6, 112.3, 111.6, 108.9 ($\underline{C}(CH_3)_2$), 107.3, 106.7 (C-1a, C-1c), 105.1 (C-1b), 84.7, 84.6 (C-2a, C-2c), 82.4 (C-3b), 81.8 (C-2b), 80.9 (C-4b), 79.6 (C-3a, C-3c), 78.1(C-4c), 77.7 (C-4a), 76.4 (C-5a), 76.0 (C-5c), 72.3 (C-5b), 69.2 (C-6a), 68.8 (C-6b), 66.8 (C-6c), 54.6, 54.5 (OCH_3), 26.7, 26.6, 26.1, 26.0, 25.9, 25.1, 24.8, 24.7 ($C(\underline{C}H_3)_2$).

Anal. Calcd for $C_{32}H_{52}O_{19}S$: C, 49.73; H, 6.78; O, 39.34; S, 4.15. Found: C, 49.65; H, 6.80; S, 4.20.

Benzyl 2,3-*O*-isopropylidene-5,6-*O*-sulfuryl-α-D-mannofuranoside (5) Thionyl chloride (1.5 eq, 247 µL) was added dropwise to a solution of benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (700 mg, 2.25 mmol) in anhydrous THF (30 mL) and pyridine (3 eq, 545 µL) cooled at -10 °C. This solution was stirred for 20 min at -10 °C, filtered to eliminate the pyridinium salt formed and concentrated to give a residue which was dissolved in water (25 mL) and extracted with chloroform (2x25 mL). The organic layer was successively dried, concentrated and flash chromatography on silica gel (CH_2Cl_2) gave the endo/exo mixture of benzyl 2,3-*O*-isopropylidene-5,6-*O*-sulfinyl-α-D-mannofuranoside **5'** (800 mg, 99 %; Rf_{endo} 0.59, Rf_{exo} 0.53, 8:2 hexane-ethyl acetate); ^1H NMR: δ 7.29 (m, 5H, CH (Ph)), 5.16 (m, 1H, H-5 exo), 5.10 (s, 1H, H-1, $J_{1,2}$ 0), 4.81 (dd, 1H, H-3 exo, $J_{2,3}$ 5.9, $J_{3,4}$ 3.6), 4.74 (dd, 1H, H-3 endo, $J_{2,3}$ 5.9, $J_{3,4}$ 3.7), 4.73-4.46 (m, 4H, H-5 endo, H-6, CH_2(Ph)), 4.39 (dd, 1H, H-6', $J_{5,6}$ 5.3, $J_{6,6'}$ 8.6), 4.30 (dd, 1H, H-4 endo, $J_{3,4}$ 3.7, $J_{4,5}$ 7.4), 4.10 (dd, 1H, H-4 exo, $J_{4,5}$ 5.7), 1.43, 1.28 (2s, 6H, $(C(CH_3)_2)$; ^{13}C NMR: δ 137.0 (Cipso), 128.5, 128.0 (CH (Ph)), 112.9 ($\underline{C}(CH_3)_2$), 106.0 (C-1 endo), 105.7 (C-1 exo), 84.2 (C-2), 80.1 (C-4 endo), 79.3 (C-3 endo), 79.0 (C-3 exo), 78.7 (C-5 endo), 78.3 (C-4 exo), 77.0 (C-5 exo), 69.7 (C-6 endo), 69.6 ($\underline{C}H_2$(Bn)), 68.5 (C-5 exo), 25.6, 24.4 ($C(\underline{C}H_3)_2$).

A portion of this compound **5'** (700 mg, 1.96 mmol) was dissolved in CH_2Cl_2-CH_3CN, (1:1 v/v) and stirred for 20 min at room temperature with sodium periodate (2 eq, 840 mg), a catalytic amount of ruthenium trichloride hydrate (6 mg) and water (2v). The reaction mixture was filtered on celite and washed with saturated aqueous sodium chloride (2x20 mL). The organic layer was treated as above for **5'** to give **5** (712 mg, 97 %; Rf 0.56, ethyl acetate-hexane 3:7). mp 105.8 °C; $[\alpha]_D^{30}$ +67 ° (*c* 0.9, CH_2Cl_2); ^1H NMR: δ 7.31 (m, 5H, CH (Ph)), 5.18 (m, 1H, H-5, $J_{6\text{-}5}$ 6.8, $J_{6'\text{-}5}$ 2.5, $J_{4\text{-}5}$ 4.5), 5.15 (s, 1H, H-1, $J_{1,2}$ 0), 4.76 (dd, 1H, H-3, $J_{2,3}$ 5.9, $J_{3,4}$ 3.7), 4.70 (dd, 2H, H-6, H-6'), 4.65 (d, 1H, H-2), 4.63 (d, 1H, CH_2(Ph)), 4.51 (d, 1H, CH_2(Ph)), 4.35 (t, 1H, H-4), 1.41, 1.27 (2s, 6H, $(C(CH_3)_2)$; ^{13}C NMR: δ 136.9 (Cipso), 128.5, 128.1, 128.0 (CH (Ph)), 113.1

($\underline{C}(CH_3)_2$), 105.8 (C-1), 84.8, (C-2), 79.0 (C-3), 78,5 (C-5), 77.6 (C-4), 68.9 (C-6), 69.6 ($\underline{C}H_2$(Ph)), 25.5, 23.9 (C($\underline{C}H_3)_2$).

Anal. Calcd for $C_{16}H_{20}O_8S$: C, 51.61; H, 5.41; O, 34.37; S, 8.61. Found: C, 51.70; H, 5.29; S, 8.13.

Benzyl 6-*O*-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl)-2,3-*O*-isopropylidene-α-D-mannofuranoside (6) *n*-Butyllithium (1.5 eq, 0.322 mL) was slowly added to a cooled stirred solution of **2** (210 mg, 0.81 mmol) in THF/HMPA (4/1 v/v) at -40 °C. After stirring for 1 h, **5** (200 mg, 0.54 mmol) was added and the solution was stirred for 30 min at room temperature. Sulfuric acid and water (0.3 eq/1 eq) were added to the reaction mixture which was heated at 50 °C for 1 h and poured into a cold molar solution of $NaHCO_3$ (10 -15 mL). The aqueous solution was extracted with ethyl acetate and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure and the residue was chromatographed on silica gel (4:6 ethyl acetate-hexane) to give compound **7** (208 mg, 70 %; Rf 0.82, 6:4 ethyl acetate-hexane). $[\alpha]_D^{29}$ +21 ° (*c* 0.72, CH_2Cl_2); ^{1}H NMR: δ7.26 (m, 5H, CH (Ph)), 5.84 (d, 1H, H-1b, $J_{1,2}$ 3.7), 5.02 (s, 1H, H-1a, $J_{1,2}$ 0), 4.81 (dd, 1H, H-3a, $J_{2,3}$ 5.9, $J_{3,4}$ 3.6), 4.59 (d, 1H, H-2a), 4.57 (d, 1H, CH_2(Ph)), 4.54 (d, 1H, H-2b, $J_{2,3}$ 0), 4.44 (d, 1H, CH_2(Ph)), 4.30 (m, 1H, H-5b), 4.06 (m, 3H, H-6b, H-5a, H-3b), 3.97 (m, 3H, H-6'b,, H-6a, H-4b), 3.85 (dd, 1H, H-4a, $J_{4,5}$ 8.5, $J_{3,4}$ 3.5), 3.40 (dd, 1H, H-6'a, $J_{6,5}$ 7.5, $J_{6,6'}$ 10.5), 1.44 (x2), 1.40, 1.36, 1.29, 1.27 (5s, 18H, C($CH_3)_2$); ^{13}C NMR: δ 137.4 (C_{ipso}), 128.4, 127.9, 127.8 (CH (Ph)), 112.5, 111.8, 109.2 ($\underline{C}(CH_3)_2$), 105.6 (C-1a), 105.5 (C-1b), 84.7 (C-2a), 83.9 (C-4b), 82.5 (C-2b), 81,2 (C-3b), 79.8 (C-3a), 79.4 (C-4a), 73.1 (C-6a), 72.8 (C-5b), 69.1 ($\underline{C}H_2$(Bn)), 68.7 (C-5a), 67.6 (C-6b), 26.6, 26.2, 26.0, 25.2, 24.7 (C($\underline{C}H_3)_2$).

Anal. Calcd for $C_{28}H_{40}O_{11}$: C, 60.86; H, 7.30; O, 31.85. Found: C, 60.90; H, 7.39.

6-*O*-(3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl)-2,3-*O*-isopropylidene-α-D-mannofuranose (7) A solution of **6** (129 mg, 0.23 mmol) in 10.5 mL of methanol in the presence of ammonium formate (35 mg, 2.4 eq) and palladium on activated carbon 10 % (82.8 mg) was stirred at 70 °C for 95 min and then the reaction mixture was filtered and washed with hot methanol (50 mL). The filtrate was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane-ethyl acetate) to give compound **7** quantitatively pure $[\alpha]_D^{29}$ -11 ° (*c* 0.5, CH_2Cl_2); ^{1}H NMR: δ 5.82 (d, 1H,H-1b, $J_{1,2}$ 3.6), 5.26 (s, 1H, H-1a, $J_{1,2}$ 0), 4.79 (dd, 1H, H-3a, $J_{2,3}$ 5.8, $J_{3,4}$ 3.2), 4.52 (2d, 2H, H-2b, H-2a, $J_{2b,3b}$ 0), 4.28 (m, 1H, H-5b), 4.05 (m, 4H, H-4a, H-5a, H-3b, H-6b), 3.95 (m, 3H, H-6'a, H-4b, H-6'b), 3.49 (dd, 1H, H-6a,

$J_{6,6'}$ 10.4, $J_{1,2}$ 6.1), 1.42; 1.39; 1.36; 1.29; 1.26; 1.24 (6s, 18H, C($\underline{C}H_3$)$_2$); ^{13}C NMR: δ 112.4; 111.8; 109.3 ($\underline{C}$(CH$_3$)$_2$), 105.3 (C-1b), 100.9 (C-1a), 85.3 (C-2a), 83.6 (C-4b), 82.2 (C-2b), 81.0 (C-3b), 79.8 (C-3a), 79.3 (C-4a), 72.8 (C-6a), 72.5 (C-5b), 68.9 (C-5a), 67.5 (C-6b), 26.7; 26.; 25.9; 25.2; 24.6 (C($\underline{C}H_3$)$_2$).

Anal. Calcd for $C_{21}H_{34}O_{11}$: C, 54.54; H, 7.41; O, 38.05. Found: C, 54.60; H, 7.46.

Methyl 6-*O*-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl)-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside (8a) Sodium hydride (1.5 eq, 107 mg) was slowly added to a stirred solution at room temperature of **3** (1.42 g, 2.98 mmol) in DMF (10 mL) . After stirring for 1 h, methyl iodide (1.5 eq, 279 μL) was added dropwise and the solution was stirred overnight. Methanol (10 mL) was then added to destroy the excess of sodium hydride and the solution was concentrated to give a residue which was dissolved in water (20 mL) and extracted with ether (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure and the residue was chromatographed on silica gel (1:9 ethyl acetate-hexane) to give compound **8a** (1.43 g, 98 %; Rf 0.25, 1:9 ethyl acetate-hexane). $[\alpha]_D^{26}$ +17 ° (*c* 2.25, CH_2Cl_2); ^{1}H NMR: δ 5.70 (s, 1H, H-1b, $J_{1,2}$ 3.7), 4.67 (d, 1H, H-1a, $J_{1,2}$ 0), 4.58 (dd, 1H, H-3a, $J_{2,3}$ 5.8, $J_{3,4}$ 3.5), 4.43 (d, 1H, H-2a), 4.36 (d, 1H, H-2b, $J_{2,3}$ 0), 4.19 (m, 1H, H-5b), 3.91 (dd, 1H, H-4b, $J_{3,4}$ 2.5, $J_{4,5}$ 7.9), 3.93 (dd, 1H, H-6b, $J_{5,6}$ 6.1, $J_{6',6}$ 8.3), 3.79 (m, 3H, H-3b, H-6'a, H-6'b), 3.74 (dd, 1H, H-4a, $J_{4,5}$ 8.9), 3.54 (dd, 1H, H-6a, $J_{5,6}$ 5.2, $J_{6',6}$ 10.6), 3.45 (m, 1H, H-5a), 3.31 (s, 3H, OCH$_3$ (C-5a)), 3.13 (s, 3H, OCH$_3$ (C-1a)), 1.32, 1.28, 1.24, 1.16 (x2), 1.15 (5s, 18H, C($\underline{C}H_3$)$_2$); ^{13}C NMR: δ 111.5, 111.4, 108.6 ($\underline{C}$(CH$_3$)$_2$), 107.1 (C-1a), 105.0 (C-1b), 84.5 (C-2a), 82.8 (C-3b), 82.3 (C-2b), 81,1 (C-4b), 79.6 (C-3a), 78.0 (C-4a), 77.5 (C-5a), 72.2 (C-5b), 70.4 (C-6a), 67.1 (C-6b), 58.1 (OCH$_3$ (C-5a)), 54.3 (OCH$_3$ (C-1a)), 26.6, 26.5, 26.1, 25.9, 25.2, 24.7 (C($\underline{C}H_3$)$_2$).

Anal. Calcd for $C_{23}H_{38}O_{11}$: C, 56.32; H, 7.81; O, 35.88. Found: C, 56.42; H, 7.90.

Methyl 6-*O*-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl)-5-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannofuranoside (8b) Sodium hydride (1.5 eq, 91 mg) was slowly added to a stirred solution of **3** (1.2 g, 2.52 mmol) in DMF (10 mL). After 1 h, benzyl bromide (1.5 eq, 0.449 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. The reaction mixture was treated as described above for **8a** and gave **8b** (1.36 g, 96 %; Rf 0.2, 9:1 hexane- ethyl acetate). $[\alpha]_D^{25}$ +10 ° (*c* 0.69, CH_2Cl_2); ^{1}H NMR: δ 7.29 (m, 5H, CH$_2$ (Ph)), 5.82 (d, 1H, H-1b, $J_{1,2}$ 3.7), 4.82 (s, 1H, H-1a, $J_{1,2}$ 0), 4.75 (dd, 1H, H-3a, $J_{2,3}$ 5.9, $J_{3,4}$ 3.3),

4.74, 4.64 (2xd, 2H, CH_2(Bn)), 4.54 (d, 1H, H-2b), 4.50 (d, 1H, H-2a), 4.34 (m, 1H, H-5b, $J_{4,5}$ 7.8, $J_{5,6}$ 4.0, $J_{5,6'}$ 5.9), 4.08 (dd, 1H, H-4b, $J_{3,4}$ 3.0), 3.99 (m, 2H, H-6b, H-6'b), 3.89 (m, 4H, H-3b, H-4a, H-5a, H-6a), 3.73 (dd, H-6a, $J_{5,6}$ 5.05, $J_{6,6'}$ 10.3), 3.26 (s, 3H, OCH_3), 1.46, 1.43, 1.37, 1.29, 1.25, 1.25 (6s, 18H, $C(CH_3)_2$); ^{13}C NMR: δ 128.1, 127.9, 127.5 (CH (Ph)), 138.8 (Cipso), 112.2, 111.6, 108.9 ($\underline{C}(CH_3)_2$), 107.4 (C-1a), 105.1 (C-1b), 84.6 (C-2a), 82.8 (C-3b), 82.3 (C-2b), 81.2 (C-4b), 79.7 (C-3a), 79.3 (C-4a), 76.4 (C-5a), 73.1 (C-6a), 72.3 (C-5b), 67.2 (C-6b), 54.5 (OCH_3), 26.8, 26.2, 26.1, 25.3, 24.8 ($C(\underline{C}H_3)_2$).

Anal. Calcd for $C_{29}H_{42}O_{11}$: C, 61.47; H, 7.47; O, 31.06. Found: C, 61.48; H, 7.41.

Methyl 6-*O*-(3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranos-3-yl)-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside (9a) A solution of **8a** (1.33 g, 2.71 mmol) in acetic acid-water 7:3 (v/v), was stirred at room temperature for 18 h. The reaction mixture was concentrated to give a residue which was dissolved in water (20 mL) and extracted with diethyl ether (4x20 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the residue was chromatographed on silica gel (8:2 ethyl acetate-hexane) to yield **9a** as syrup (855 mg, 70 %; Rf 0.41, 9:1 ethyl acetate-hexane). $[\alpha]_D^{28}$ +12 ° (*c* 2.47, CH_2Cl_2); ^1H NMR: δ 5.85 (d, 1H, H-1b, $J_{1,2}$ 3.8), 4.76 (s, 1H, H-1a, $J_{1,2}$ 0), 4.68 (dd, 1H, H-3a, $J_{2,3}$ 5.9, $J_{3,4}$ 3.5), 4.51 (d, 1H, H-2b, $J_{2,3}$ 0), 4.46 (d, 1H, H-2a), 4.07 (dd, 1H, H-4b, $J_{3,4}$ 3.4, $J_{4,5}$ 8.2), 3.98 (dd, 1H, H-6'a, $J_{5,6'}$ 2.8, $J_{6',6}$ 10.6), 3.93 (d, 1H, H-3b), 3.90 (m, 1H, H-5b), 3.81 (dd, 1H, H-4a, $J_{4,5}$ 8.5), 6.79 (m, 1H, H-6'b), 3.61 (m, 2H, H-5a, H-6b), 3.49 (dd, 1H, H-6a, $J_{5,6}$ 6.4), 3.42 (s, 3H, OCH_3 (C-5a)), 3.23 (s, 3H, OCH_3 (C-1a)), 1.40, 1.37, 1.24, 1.23 (4s, 12H, $C(CH_3)_2$); ^{13}C NMR: δ 112.3, 111.6 ($\underline{C}(CH_3)_2$), 107.3 (C-1a), 105.3 (C-1b), 84.4 (C-2a), 83.9 (C-3b), 82.1 (C-2b), 80,1 (C-4b), 79.6 (C-3a), 78.8 (C-4a), 77.2 (C-5a), 70.5 (C-6a), 69.4 (C-5b), 64.4 (C-6b), 58.6 (OCH_3 (C-5a)), 54.7 (OCH_3 (C-1a)), 26.7, 26.2, 26.0, 24.7 ($C(\underline{C}H_3)_2$).

Anal. Calcd for $C_{20}H_{34}O_{11}$: C, 56.32; H, 7.81; O, 35.88. Found: C, 56.42; H, 7.88.

Methyl 6-*O*-(3-deoxy-1,2-*O*-isopropylidene-5,6-*O*-sulfuryl-α-D-glucofuranos-3-yl)-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside (10a) Thionyl chloride (1.3 eq, 38 μL) was added dropwise to a solution of compound **9a** (179 mg, 0.4 mmol) in anhydrous THF (15 mL) and pyridine (2.7 eq, 86 μL) was cooled at -10 °C. The solution was stirred for 20 min at -10 °C, filtered to eliminate the pyridinium salt formed and concentrated to give a residue which was dissolved in water (20 mL) and extracted with chloroform (2x20 mL). The organic layer was dried,

concentrated and flash column chromatography on silica gel (CH_2Cl_2) gave the endo/exo mixture of methyl 6-*O*-(3-deoxy-1,2-*O*-isopropylidene-5,6-*O*-sulfinyl-α-D-glucofuranos-3-yl)-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside **9a'** (191 mg, 97 %; Rf 0.78, 8:2 hexane-ethyl acetate); ^{1}H NMR: δ 5.83 (2xd, 2H, H-1b, $J_{1,2}$ 3.5), 5.10 (m, 1H, H-5b exo), 4.76 (s, 2H, H-1a, $J_{1,2}$ 0), 4.69-4.53 (m, 9H, H-3a, H-6b, H-6'b, H-2b, H-5b endo), 4.47 (m, 2H, H-2a, $J_{2,3}$ 5.8), 4.39 (dd, 1H, H-4b endo, $J_{3,4}$ 3.3, $J_{4,5}$ 8.2), 4.18 (dd, H-4b exo, $J_{3,5}$ 3.3, $J_{4,5}$ 6.3), 3.99 (d, 1H, H-3b endo), 3.90 (m, 3H, H-3b exo, H-6a), 3.82 (dd, 2H, H-4a, $J_{3,4}$ 3.5, $J_{4,5}$ 8.5), 3.57 (m, 4H, H-5a, H-6'a), 3.39 (s, 6H, OCH_3 (C-5a)), 3.23 (s, 6H, OCH_3 (C-1a)), 1.41, 1.38, 1.25 (3s, 24H, ($C(CH_3)_2$); ^{13}C NMR: δ 112.2, 112.1 ($\underline{C}(CH_3)_2$), 107.3 (C-1a), 105.3 (C-1b), 84.6 (C-2a), 82.6 (C-3b), 82.2 (C-2b endo), 82.0 (C-2b exo), 81.2 (C-4b exo), 79.6 (C-3a), 78.9 (C-4b endo), 78.1 (C-4a), 77.8 (C-5b endo), 77.4 (C-5b exo), 76.7 (C-5a), 70.2 (C-6b), 68.6 (C-6a), 58.2 (OCH_3 (C-5a)), 54.7 (OCH_3 (C-1a)), 26.8, 26.1, 26.0, 24.8 ($C(\underline{C}H_3)_2$).

This compound **9a'** was dissolved in CH_2Cl_2-CH_3CN, (1:1 v/v) and stirred for 2.5 h at room temperature with sodium periodate (3.15 eq, 260 mg), a catalytic amount of ruthenium trichloride hydrate and water (2v). The reaction mixture was filtered on celite and washed with saturated aqueous sodium chloride (2x20 mL). The organic layer was treated as described above for **9a** to give **10a** (185 g, 94 %; Rf 0.62, CH_2Cl_2-Acetone 94:4). $[\alpha]_D^{29}$ +1.5 ° (*c* 0.7, CH_2Cl_2); ^{1}H NMR: δ 5.87 (d, 1H, H-1b, $J_{1,2}$ 3.5), 5.14 (m, 1H, H-5b), 4.80 (s, 1H, H-1a, $J_{1,2}$ 0), 4.75-4.71 (m, 3H, H-6b, H-6'b, H-3a), 4.60 (d, 1H, H-2b), 4.51 (m, 2H, H-2a, H-4b, $J_{2,3}$ 5.8), 4.02 (d, 1H, H-3b, $J_{2,3}$ 3.3), 3.92 (m, 1H, H-6a), 3.82 (dd, 1H, H-4a, $J_{3,4}$ 3.4, $J_{4,5}$ 8.4), 3.59 (m, 2H, H-5a, H-6'a), 3.38 (s, 3H, OCH_3 (C-5a), 3.24 (s, 3H, OCH_3 (C-1a), 1.44, 1.39, 1.26 (x2) (3s, 12H, ($C(CH_3)_2$); ^{13}C NMR: δ 112.5, 112.3 ($\underline{C}(CH_3)_2$), 107.4 (C-1a), 105.4 (C-1b), 84.6, (C-2a), 82.7 (C-3b), 81.8 (C-2b), 79.6 (C-3a), 78.3 (C-4b), 78.1 (C-4a), 77,9 (C-5b), 77.3 (C-5a), 70.6 (C-6b), 60.9 (C-6a), 58.1 (OCH_3 (C-5a)), 54.8 (OCH_3 (C-1a)), 26.8, 26.1, 26.0, 24.7 ($C(\underline{C}H_3)_2$).

Anal. Calcd for $C_{20}H_{32}O_{13}S$: C, 46.87; H, 6.29; O, 40.58; S, 6.26. Found: C, 46.99; H, 6.22; S, 6.33.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(6-deoxy-1,2-*O*-isopropylidene-3-*O*-(methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranosid-6-yl)-5-*O*-sulfo-α-D-glucofuranos-6-yl)-α-D-glucofuranose (11a) *n*-Butyllithium 2.5 M in hexane (1 eq, 178 µL) was added dropwise to a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (116 mg, 0.446 mmol) in THF/HMPA (4/1 v/v) cooled at -20 °C. The reaction mixture was stirred for 1 h 15 min at -20 °C and **10a** (114 mg, 2,23 mmol) was added. The solution was allowed to warm to room temperature, for

1.5 h, and treated as described above for **4** to give pure **11a** (163 mg, 94.5 %; Rf 0.42, CH_2Cl_2-methanol 9:1). mp 165 °C; $[\alpha]_D^{29}$ +14.5 ° (*c* 0.76, CH_2Cl_2); ^1H NMR: δ 5.82 (t, 2H, H-1b, H-1c, $J_{1b,2b}$ 3.7, $J_{1c,2c}$ 3.7), 4.79 (s, 1H, H-1a, $J_{1,2}$ 0), 4.74 (m, 2H, H-3a, H-5b, $J_{2a,3a}$ 5.8, $J_{3a,4a}$ 3.5), 4.63 (d, 1H, H-2c), 4.54 (d, 1H, H-2b), 4.48 (d, 1H, H-2a), 4.35 (m, 2H, H-5c, H-4b), 4.13 (dd, 1H, H-4c, $J_{3,4}$ 2.8, $J_{4,5}$ 6.3), 4.06 (dd, 1H, H-6'c, $J_{5,6}$ 6.2, $J_{6,6'}$ 8.3), 3.97-3.83 (m, 6H, H-3b, H-3c, H-6c, H-4a, H-6b, H-6'a), 3.78 (dd, 1H, H-6'b, $J_{5,6}$ 4.2, $J_{6,6'}$ 11.3), 3.69 (dd, 1H, H-6a, $J_{5,6}$ 6.5, $J_{6,6'}$ 10.5), 3.47 (s, 3H, OCH_3 (C-5a)), 3.25 (s, 3H, OCH_3 (C-1a)), 1.41, 1.40, 1.35, 1.30, 1.26, 1.25 (6s, 24H, $(C(CH_3)_2)$; ^{13}C NMR: δ 112.2, 111.7, 111.5, 108.7 ($\underline{C}(CH_3)_2$), 107.2 (C-1a), 105.1, 104.7 (C-1b, C-1c), 84.5 (C-2a), 82.7 (C-3c), 82.6 (C-3b), 82.2 (C-2c), 81.8 (C-2b), 80.8 (C-4c), 79.6 (C-3a), 78.1 (C-4b, C-4a, C-5a), 75.2 (C-5b), 72.6 (C-5c), 70.5 (C-6b), 69.1 (C-6a), 66.4 (C-6c), 59.1 (OCH_3 (C-5a)), 54.7 (OCH_3 (C-1a)), 26.7, 26.6, 26.5, 26.2, 26.0, 25.3, 24.7 ($C(\underline{C}H_3)_2$).

Anal. Calcd for $C_{32}H_{52}O_{19}S$: C, 49.73; H, 6.78; O, 39.34; S, 4.15. Found: C, 49.66; H, 6.85; S, 3.34.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(6-deoxy-1,2-*O*-isopropylidene-3-*O*-(methyl 5-*O*-benyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranosid-6-yl)-5-*O*-sulfo-α-D-glucofuranos-6-yl)-α-D-glucofuranose (11b) Compound **8b** (135.6 mg, 0.24 mmol) was treated as **8a** to give **11b** (83 mg, 41 % (in overall yield from **8b**); Rf 0.4, 9:1 CH_2Cl_2-MeOH). $[\alpha]_D^{30}$ +1 ° (*c* 0.727, CH_2Cl_2); ^1H NMR: δ 7.29 (m, 5H, $C\underline{H}$ (Ph)), 5.77 (d, 2H, H-1b, H-1c, $J_{1,2}$ 3.6), 4.80 (s, 1H, H-1a, $J_{1,2}$ 0), 4.78 (m, 1H, H-5b), 4.72 (dd, 1H, H-3a, $J_{2,3}$ 5.7, $J_{3,4}$ 3.3), 4.71, 4.62 (2xd, 2H, $C\underline{H}_2$(Bn)), 4.61 (d, 1H, H-2c, $J_{2,3}$ 0), 4.49 (d, 1H, H-2b, $J_{2,3}$ 0), 4.48 (d, 1H, H-2a, $J_{2,3}$ 5.7), 4.40 (dd, 1H, H-4b, $J_{3,4}$ 3.0, $J_{4,5}$ 6.1), 4.35 (m, 1H, H-5c), 4.14 (dd, 1H, H-4c, $J_{3,4}$ 2.9, $J_{4,5}$ 6.2), 4.06 (m, 2H, H-6b, H-6c), 3.96 (d, 1H, H-3b), 3.91 (m, 3H, H-3c, H-4a, H-6'c), 3.82 (m, 1H, H-5a), 3.79 (m, 3H, H-6a, H-6'b, H-6'c), 3.25 (s, 3H, OCH_3), 1.40, 1.39, 1.35, 1.30, 1.27, 1.21, 1.20 (7s, 24H, $C(\underline{C}H_3)_2$); ^{13}C NMR: δ 138.2 (Cipso), 128.4, 128.2, 127.7 (CH (Ph)), 112.1, 111.7, 111.5, 108.6 ($\underline{C}(CH_3)_2$), 107.2 (C-1a), 105.0 (C-1b), 104.7 (C-1c), 84.5 (C-2a), 82.8 (C-3b), 82.7 (C-3c), 82.2 (C-2c), 81.3 (C-2b), 80.8 (C-4c), 79.6 (C-3c), 78.5 (C-4b), 78.2 (C-4a), 76.2 (C-5a), 75.0 (C-5b), 73.1 ($\underline{C}H_2$(Bn)), 72.7 (C-5c), 70.7 (C-6b), 69.3 (C-6a), 66.4 (C-6c), 54.6 (OCH_3), 26.7, 26.6, 26.5, 26.1, 25.3, 24.7 ($C(\underline{C}H_3)_2$).

Anal. Calcd for $C_{38}H_{56}O_{19}S$: C, 53.76; H, 6.65; O, 35.81; S, 3.78. Found: C, 53.68; H, 6.72; S, 3.54.

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