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Note

A new 6-*C*-alkylation from an alkyl mannofuranoside 5,6-cyclic sulfate

Thierry Gourlain, Anne Wadouachi *, Daniel Beaupère

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

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Abstract

Methyl 6-*C*-alkyl-6-deoxy-α-D-mannofuranoside derivatives have been synthesized from methyl 2,3-*O*-isopropylidene-5,6-*O*-sulfuryl-α-D-mannofuranoside (**1**). In a Path A, reaction of the 5,6-cyclic sulfate **1** with 2-lithio-1,3-dithiane afforded 2-(methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranosid-6-yl)-1,3-dithiane (**2**). Treatment of **2** with *n*-butyllithium then alkyl iodide gave the corresponding 2-(methyl 5-*O*-alkyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranosid-6-yl)-1,3-dithiane. Reaction of **2** with *n*-butyllithium and 5,6-cyclic sulfate **1** furnished 2-[methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-(methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-manno-furanosid-6-yl)-α-D-manno-furanosid-6-yl]-1,3-dithiane. 2-(Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranosid-6-yl)-1,3-dithiane was converted into the lithiated anion, which after treatment with alkyl halide afforded the corresponding 2-alkyl-*C*-(methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranosid-6-yl)-1,3-dithiane. In a Path B, 5,6-cyclic sulfate **1** reacted with 2-alkyl-2-lithio-1,3-dithiane derivatives, which led after acidic hydrolysis to 2-alkyl-2-(methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranosid-6-yl)-1,3-dithiane accompanied by methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranos-5-uloside as the by-product. This methodology was applied to synthesize 2-(methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranosid-6-yl)-2-(methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranosid-6-yl)-1,3-dithiane.

Keywords: Cyclic sulfate; Carbon–carbon bond; 1,3-Dithiane; Pseudo-*C*-disaccharide; Methyl mannofuranoside; 6-*C*-Alkyl carbohydrate

The selective functionalization of carbohydrates and their derivatives by alkyl groups is a subject of continuing interest. Introduction of fatty alkyl chains on carbohydrates leads to the formation of non-ionic surfactants [1] or liquid crystals [2]. Most of these nonionic surfactants have a heteroatom between the carbohydrate moiety and the alkyl chain [1,2]. Syntheses of non-anomeric *C*-alkyl carbohydrates currently use the Wittig reaction [3], organometallic reagents [4] or nucleophilic coupling between anhydro carbohydrate derivatives and alkyne carbanions [5]. We have previously developed a simple and efficient method of access to 6-*C*-alkynyl-6-deoxy carbohydrate derivatives and rigid pseudo-*C*-disaccharides from 5,6-cyclic sulfates derived from methyl α-D-mannofuranoside [6].

In this paper, we report on a facile route to 6-*C*-alkyl-6-deoxy carbohydrates, which are potential precursors of amphiphilic or liquid-

* Corresponding author. Fax: +33-3-2282-7561.
E-mail address: anne.wadouachi@sc.u-picardie.fr (A. Wadouachi)

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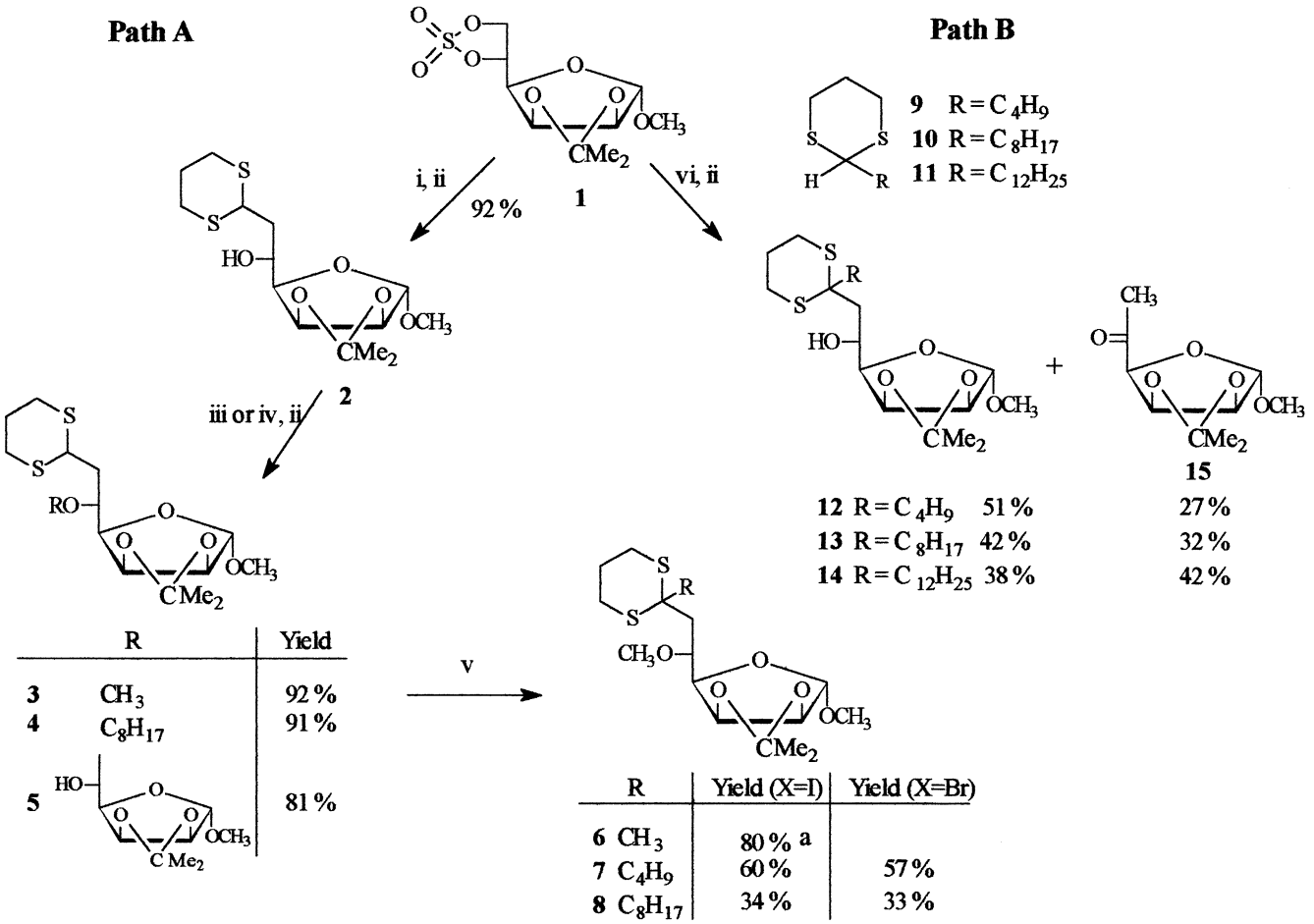
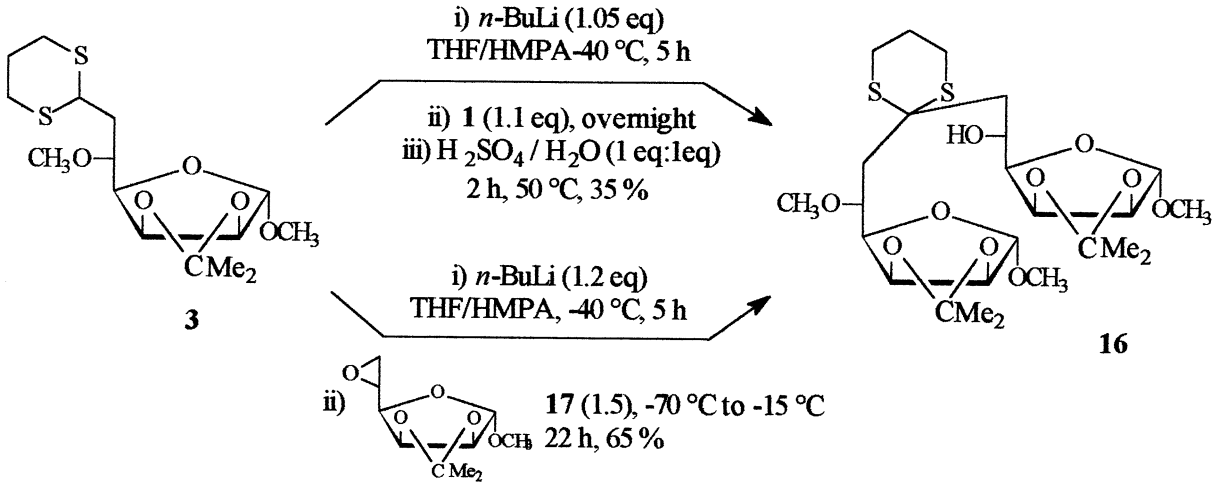


Scheme 1. (i) 1,3-Dithiane (1.5 equivalents), *n*-BuLi (1.5 equivalents), THF–HMPA (9:1), −40 °C, 2 h; (ii) H_2SO_4–H_2O (1 equivalent:1 equivalent), 40 min, 55 °C; (iii) *n*-BuLi (2 equivalents), THF–HMPA, CH_3I or C_8H_7I −40 °C, 4 h; (iv) *n*-BuLi (2 equivalents), THF–HMPA, **1** −40 °C, 17 h; (v) *n*-BuLi (1.2 equivalents), THF–HMPA, −40 °C, 1 h then RX (1.5 equivalents) −40 °C, 4 h; (vi) **9**–**11** (1.2 equivalents), *n*-BuLi (1.2 equivalents), THF, −40 °C, 2 h; [a] Compound **6** was isolated as an inseparable mixture with its precursor **3** (3:6 relative proportion 1:4 as seen from ^{1}H NMR).

crystal products from a 5,6-cyclic sulfate and 1,3-dithiane carbanion derivatives. A first application to the synthesis of a new pseudo-*C*-disaccharide is presented.

Two pathways were developed to have access to methyl 6-*C*-alkyl-6-deoxy mannofuranoside derivatives (Scheme 1). Our initial studies were carried out on methyl 2,3-*O*-isopropylidene-5,6-*O*-sulfuryl-α-D-mannofuranoside (**1**), easily prepared in three steps from D-mannose [7]. In Path A, compound **1** was reacted with 2-lithio-1,3-dithiane [8] in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) at low temperature (−40 °C) to afford the known 6-deoxy-6-*C*-substituted derivative **2** [9] in 92% yield after acidic hydrolysis and purification (Scheme 1).

First, we have attempted to generate a new 1,3-dithiane carbanion from **2** in order to create a new carbon–carbon bond. Thus, **2** was activated as a dianion with 2 equivalents of *n*-butyllithium (*n*-BuLi) in THF–HMPA at −40 °C. However, the subsequent reaction with electrophilic substrates such as alkyl iodides (step iii) or cyclic sulfate **1** (step iv) only led to the formation of the ether-linked compounds **3** and **4** or the pseudo-disaccharide **5**, respectively, in excellent yields (Scheme 1). No formation of a carbon–carbon bond involving the C-2 atom of 1,3-dithiane ring of **2** was observed. The ^{1}H NMR chemical shift values of the C-2 hydrogen for compounds **3** (δ 4.11 ppm), **4** (δ 4.20 ppm) and **5** (δ 4.23 ppm) were in agreement with the C-2 hydrogen value (δ 4.22 ppm) of the starting material **2** and con-



Scheme 2.

firmed the proposed structures. Next, the 1,3-dithiane derivative **3** was treated with a small excess of *n*-BuLi in THF–HMPA at −40 °C to afford the 2-*C*-lithiated anions, which upon reaction with alkyl halide provided the desired carbon–carbon bond (step v). However, the reaction was limited by the alkyl chain length. With short-chain alkyl halides (C_1–C_4), yields ranged from 57 to 80% (**6** and **7**), dropping to 33–34% for *n*-octyl halides. For a C_{12} chain the reaction failed. With other 5-OH protecting groups such as silyl ethers or octyl ether, we have never observed the formation of a new carbon–carbon bond. As reported in Scheme 1, alkyl iodide or bromide halide afforded the same results (step v).

Following Path B, the 5,6-cyclic sulfate **1** was reacted in THF at low temperature (−40 °C) with 2-alkyl-2-lithio-1,3-dithiane derived from **9**–**11** to lead, after acidic hydrolysis and purification on silica gel, the 6-*C*-alkyl-6-deoxy derivatives **12**–**14** in moderate yields (38–51%). These reactions gave methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranos-5-uloside (**15**) as a by-product with yield increasing with the chain length. Recently, we have shown in our laboratory that the formation of **15** was due to the reaction of basic reagents with 5,6-cyclic sulfate derivatives, this basic reagent generated an anion at the C-5 atom, which underwent an intramolecular rearrangement to lead after acidic hydrolysis the keto form [10].

From the above results, it can be concluded that Path A was a good method to accede to 6-*C*-alkyl-6-deoxy carbohydrate derivatives with a short alkyl chain, but not with a long chain. Interestingly, the latter can be obtained following Path B.

This methodology was further applied to the synthesis of the pseudo-*C*-disaccharide **16**. The cyclic sulfate **1** reacted with the carbanion derived from 1,3-dithiane **3** to give a complex mixture from which **16** was isolated in 35% yield (Scheme 2). Alternatively, we have synthesized the same pseudo-*C*-disaccharide **16** from the 5,6-anhydro derivative **17** [11], without formation of any by-product, in 65% yield (Scheme 2).

1. Experimental

General procedures.—Melting points were determined with a Büchi 535 apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (E. Merck) 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 E. Merck Silica Gel. Optical rotations were determined with a Jasco-DIP-370 electronic micropolarimeter (10 cm cell). NMR spectra were recorded in $CDCl_3$, with a Bruker 300 WB spectrometer. Elemental analysis was performed by the 'Service de Microanalyse' of Reims, France. All solvents were distilled before use. THF was distilled from $LiAlH_4$ and thionyl chloride from triphenylphosphite (10% v/v).

*2-(Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranosid-6-yl)-1,3-dithiane* (**3**).—*n*-BuLi (2.5 M) in hexane (610 mL, 1.52 mmol) was added dropwise to a stirred solution of **2** [9] (250 mg, 0.74 mmol) in anhyd THF (2 mL) and HMPA (0.25 mL) cooled to −40 °C. After stirring for 1 h at −40 °C, methyl iodide (1.1 equiv, 51 mL) was added and the reaction mixture was stirred for 4 h. After the addition of a few drops of water, the mixture was concentrated. The residue was chromatographed on silica gel (9:1 hexane–EtOAc) to give pure **3** (237 mg, 92%); R_f 0.66 (7:3 hexane–EtOAc); $[\alpha]_D^{28}$ +28.2° (*c* 1.02; CH_2Cl_2). ^{1}H NMR[1] ($CDCl_3$): δ 4.68 (s, 1 H, H-1, $J_{1,2}$ 0 Hz), 4.59 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.25 Hz, H-3), 4.38 (d, 1 H, H-2), 4.11 (dd, 1 H, $J_{2',6a}$ 5.0, $J_{2',6b}$ 9.3 Hz, H-2′), 3.70 (ddd, 1 H, $J_{5,6a}$ 3.2, $J_{5,6b}$ 7.9, $J_{4,5}$ 8.1 Hz, H-5), 3.65 (dd, 1 H, H-4), 3.33 (s, 3 H, OCH_3 at C-5), 3.15 (s, 3 H, OCH_3 at C-1), 2.73 (m, 4 H, H-6′a,b, H-4′a,b), 2.08 (ddd, 1 H, $J_{6a,6b}$ 14.6 Hz, H-6a), 1.97 (m, 1 H, H-5′a), 1.80 (ddd, 1 H, H-6b), 1.71 (m, 1 H, H-5′b), 1.31, 1.17 (2 s, 6 H, CMe_2); ^{13}C NMR[1] ($CDCl_3$): δ 112.1 (CMe_2), 106.8 (C-1), 84.8 (C-2), 80.9 (C-4), 79.8 (C-3), 74.6 (C-5), 58.4 (OCH_3 at C-5), 54.3 (OCH_3 at C-1), 41.1 (C-2′), 38.0 (C-6), 30.1 (C-4′), 29.7 (C-6′), 26.0 (CMe_2), 24.7 (C-5′), 24.9 (CMe_2). Anal. Calcd for $C_{15}H_{26}O_5S_2$: C, 51.40; H, 7.48; S, 18.30. Found: C, 51.52; H, 7.39; S, 17.63.

*2-(Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-octyl-α-D-mannofuranosid-6-yl)-1,3-dithiane* (**4**).—Compound **2** (250 mg, 0.74 mmol) was treated, as described above for **3**, with octyl iodide (0.147 mL, 0.82 mmol) to afford **4** (0.306 g, 91%); R_f 0.73 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ +48.2° (*c* 1.28, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 4.75 (s, 1 H, $J_{1,2}$ 0 Hz, H-1), 4.65 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.4 Hz, H-3), 4.45 (d, 1 H, H-2), 4.20 (dd, 1 H, $J_{2',6a}$ 4.9, $J_{2',6b}$ 9.6 Hz, H-2′), 3.86 (dt, 1 H, $J_{5,6a}$ 3.4, $J_{5,6b}$ 8.4, $J_{4,5}$ 8.4 Hz, H-5), 3.74 (dd, 1 H, H-4), 3.62–3.48 (m, 2 H, $CH_2\alpha$), 3.22 (s, 3 H, CH_3O), 2.88 (m, 4 H, H-6′a,b, H-4′a,b), 2.16 (ddd, 1 H, $J_{6a,6b}$ 14.5 Hz, H-6a), 2.07–1.77 (m, 3 H, H-5′a,b, H-6b), 1.48 (m, 2 H, CH_2), 1.37 (s, 3 H, CMe_2), 1.31–1.21 (m, 13 H, CMe_2, 5 CH_2), 0.81 (s, 3 H, $CH_3\omega$); ^{13}C NMR ($CDCl_3$): δ 112.2 (CMe_2), 106.9 (C-1), 84.9 (C-2), 81.3 (C-4), 79.7 (C-3), 73.1 (C-5), 70.8 ($CH_2\alpha$),54.4 (CH_3O), 43.3 (C-2′), 38.4 (C-6), 31.8 (CH_2), 30.2 (C-4′, CH_2), 29.6 (C-6′), 29.3, 29.2 (CH_2), 26.1 (CMe_2, CH_2), 25.9 (C-5′), 25.0 (CMe_2), 22.6 (CH_2), 13.6 ($CH_3\omega$). Anal. Calcd for $C_{22}H_{40}O_5S_2$: C, 58.89; H, 8.99; S, 14.29. Found: C, 58.28; H, 9.05; S, 13.23.

*2-[Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-(methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranosid-6-yl)-α-D-mannofuranosid-6-yl]-1,3-dithiane* (**5**).—Compound **2** (140 mg, 0.42 mmol) was treated, as described above for **3**, in THF (1 mL)–HMPA (0.225 mL) cooled to −40 °C with 2 equiv of *n*-BuLi (0.34 mL to a 2.5 M soln in THF, 0.84 mmol) and cyclic sulfate **1** (246 mg, 0.84 mmol). After stirring for 17 h at −40 °C, H_2SO_4 (42 μL) and water (15 μL) were added to the reaction mixture, which was heated at 50 °C for 1 h and poured into a cold molar soln of $NaHCO_3$ (1 M, 10–15 mL). The aq soln was extracted with EtOAc and the combined extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue was chromatographed on silica gel (4:1 hexane–EtOAc) to give **5** (186 mg, 81%); R_f 0.28 (7:3 hexane–EtOAc); $[\alpha]_D^{28}$ +18.8° (*c* 0.58, CH_2Cl_2). ^{1}H NMR[2] ($CDCl_3$): δ 4.81–4.70 (m, 4 H, H-1a, H-1b, H-3a, H-3b), 4.48 (2d, 2 H, $J_{1,2}$ 0, $J_{2,3}$ 5.8 Hz, H-2a, H-2b), 4.23 (dd, 1 H, $J_{2',6a}$ 5.9, $J_{2',6b}$ 7.7 Hz, H-2′), 4.01 (m, 1 H, H-5b), 3.91 (m, 2 H, H-5a, H-6b), 3.81 (m, 2 H, H-4a, H-4b), 3.64 (dd, 1 H, $J_{5,6a}$ 6.3, $J_{6a,6b}$ 9.8 Hz, H-6b′), 3.51 (m, 1 H, OH), 3.29, 3.23 (2 s, 6 H, OCH_3), 2.89–2.72 (m, 4 H, H-6′a,b, H-4′a,b), 2.21–1.78 (m, 4 H, H-6a, H-6a′, H-5′a,b), 1.40, 1.39, 1.26, 1.24 (4s, 12 H, CMe_2); ^{13}C NMR[2] ($CDCl_3$): δ 112.4 (2 CMe_2), 107.1, 106.7 (C-1a, C-1b), 84.7, 84.6 (C-2a, C-2b), 80.8 (C-4b), 79.8, 79.6 (C-3a, C-3b), 79.0 (C-4a), 75.1 (C-5a), 73.0 (C-6b), 68.7 (C-5b), 54.4, 54.3 (OCH_3), 43.1 (C-2′), 38.1 (C-6a), 30.3, 30.2 (C-4′, C-6′), 25.9 (2 CMe_2), 25.7 (C-5′), 24.9, 24.6 (CMe_2). Anal.

[1] For NMR notations, unprimed numbers refer to the carbohydrate moiety and primed numbers to the 1,3-dithiane ring.

[2] For NMR notations, unit 'a' refers to the *O*-5-substituted mannose moiety and unit 'b' to the *O*-5 unsubstituted one.

Calcd for $C_{24}H_{40}O_{10}S_2$: C, 52.16; H, 7.29; S, 11.60. Found: C, 52.07; H, 7.32; S, 10.86.

2-Methyl-2-(methyl 6-deoxy-2,3-O-isopropylidene-5-O-methyl-α-D-mannofuranosid-6-yl)-1,3-dithiane (**6**).—*n*-BuLi (2.5 M) in hexane (126 μL, 0.31 mmol) was added dropwise to a soln of **3** (92 mg, 0.26 mmol) in anhyd THF (0.7 mL) and HMPA (0.07 mL) cooled to −40 °C. After stirring for 1 h at −40 °C, methyl iodide (25 μL, 0.4 mmol) was added and the mixture was stirred for 4 h. After the addition of a few drops of water the mixture was concentrated. The residue was chromatographed on silica gel (19:1 hexane–EtOAc) to give an inseparable mixture in 1:4 relative proportion (^{1}NMR) of **3** and **6**; R_f 0.46 (4:1 hexane–EtOAc). ^{1}H NMR ($CDCl_3$): δ 4.77 (s, 1 H, H-1, $J_{1,2}$ 0 Hz), 4.66 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.2 Hz, H-3), 4.49 (d, 1 H, H-2), 3.84 (m, 1 H, H-5), 3.72 (dd, 1 H, $J_{4,5}$ 7.4 Hz, H-4), 3.40 (s, 3 H, OCH_3 at C-5), 3.24 (s, 3 H, OCH_3 at C-1), 2.96–2.61 (m, 4 H, H-6′a,b, H-4′a,b), 2.52 (dd, 1 H, $J_{5,6a}$ 1.2, $J_{6a,6b}$ 15.2 Hz, H-6a), 2.00 (dd, 1 H, $J_{5,6b}$ 8.7 Hz, H-6b), 2.00–1.76 (m, 2 H, H-5′a,b), 1.58 (s, 3 H, CH_3), 1.39, 1.25 (2 s, 6 H, CMe_2); ^{13}C NMR ($CDCl_3$): δ 112.3 (CMe_2), 106.7 (C-1), 85.2 (C-2), 80.8 (C-4), 79.7 (C-3), 76.3 (C-5), 57.7 (OCH_3 at C-5), 54.4 (OCH_3 at C-1), 48.4 (C-2′), 43.2 (C-6), 28.7 (CH_3), 30.1, 29.7 (C-4′, C-6′), 26.1, 25.1 (CMe_2), 24.9 (C-5′).

2-Butyl-2-(methyl 6-deoxy-2,3-O-isopropylidene-5-O-methyl-α-D-mannofuranosid-6-yl)-1,3-dithiane (**7**).—The same protocol used to obtain **6** starting from **3** (82.3 mg, 0.23 mmol) and iodobutane (40 μL, 0.35 mmol) afforded pure **7** (60%, 57.3 mg) after chromatography on silica gel (97.5:2.5 hexane–EtOAc); R_f 0.47 (4:1 hexane–EtOAc); $[\alpha]_D^{27}$ +61.9° (*c* 0.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 4.76 (s, 1 H, $J_{1,2}$ 0 Hz, H-1), 4.67 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.1 Hz, H-3), 4.50 (d, 1 H, H-2), 3.86 (m, 1 H, H-5), 3.69 (dd, 1 H, $J_{4,5}$ 7.9 Hz, H-4), 3.41 (s, 3 H, OCH_3 at C-5), 3.25 (s, 3 H, OCH_3 at C-1), 2.87 (m, 2 H, H-6′a, H-4′a), 2.66 (m, 2 H, H-6′b, H-4′b), 2.47 (dd, 1 H, $J_{5,6a}$ 1.2, $J_{6a,6b}$ 15.4 Hz, H-6a), 2.06 (dd, 1 H, $J_{5,6b}$ 8.7 Hz, H-6b), 2.00–1.77 (m, 4 H, H-5′a,b, H-8a,b), 1.47 (m, 2 H, H-9a,b), 1.39 (s, 3 H, CMe_2), 1.26 (m, 2 H, H-10a,b), 1.23 (s, 3 H, CMe_2), 0.86 (t, 3 H, H-11a,b,c); ^{13}C NMR ($CDCl_3$): δ 112.3 (CMe_2), 106.7 (C-1), 85.3 (C-2), 81.1 (C-4), 79.7 (C-3), 76.1 (C-5), 58.1 (OCH_3 at C-5), 54.4 (OCH_3 at C-1), 52.9 (C-2′), 40.4 (C-6), 39.4 (C-8), 26.2 (CMe_2), 26.1, 25.8 (C-6′, C-4′), 25.9 (C-9), 25.3 (C-5′), 25.2 (CMe_2), 22.9 (C-10), 13.9 (C-11). Anal. Calcd for $C_{19}H_{34}O_5S_2$: C, 56.13; H, 8.43; S, 15.77. Found: C, 56.25; H, 8.37; S, 15.92.

2-(Methyl 6-deoxy-2,3-O-isopropylidene-5-O-methyl-α-D-mannofuranosid-6-yl)-2-octyl-1,3-dithiane (**8**).—The same protocol used to obtain **6** starting from **3** (129.4 mg, 0.37 mmol) and iodooctane (100 μL, 0.55 mmol) afforded pure **8** (35%, 60 mg) after chromatography on silica gel (9:1 hexane–EtOAc); R_f 0.55 (4:1 hexane–EtOAc); $[\alpha]_D^{26}$ +101.7° (*c* 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 4.77 (s, 1 H, $J_{1,2}$ 0 Hz, H-1), 4.68 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.2 Hz, H-3), 4.51 (d, 1 H, H-2), 3.85 (m, 1 H, H-5), 3.70 (dd, 1 H, $J_{4,5}$ 7.9 Hz, H-4), 3.41 (s, 3 H, OCH_3 at C-5), 3.25 (s, 3 H, OCH_3 at C-1), 2.88 (m, 2 H, H-6′a, H-4′a), 2.67 (m, 2 H, H-6′b, H-4′b), 2.47 (d, 1 H, $J_{5,6a} \sim 0$, $J_{6a,6b}$ 15.4 Hz, H-6a), 2.09 (dd, 1 H, $J_{5,6b}$ 8.7 Hz, H-6b), 1.98–1.82 (m, 4 H, H-5′a,b, H-8a,b), 1.50 (m, 2 H, H-9a,b), 1.40 (s, 3 H, CH_3), 1.27 (s, 3 H, CMe_2), 1.23 (m, 10 H, CH_2), 0.82 (t, 3 H, H-15a,b,c); ^{13}C NMR ($CDCl_3$): δ 112.3 (CMe_2), 106.7 (C-1), 85.4 (C-2), 81.1 (C-4), 79.7 (C-3), 76.1 (C-5), 58.1 (OCH_3 at C-5), 54.4 (OCH_3 at C-1), 53.0 (C-2′), 40.4 (C-6), 39.7 (C-8), 31.8, 29.9, 29.3, 29.2 (CH_2), 26.3 (CMe_2), 26.1, 25.3 (C-4′, C-6′), 25.9 (C-5′), 25.2 (CMe_2), 23.8, 22.6 (CH_2), 14 (C-15). Anal. Calcd for $C_{23}H_{42}O_5S_2$: C, 59.70; H, 9.15; S, 13.86. Found: C, 59.81; H, 9.18; S, 12.91.

2-Butyl-1,3-dithiane (**9**).—To a cold soln (−40 °C) of 1,3-dithiane (500 mg, 4.16 mmol) in THF was added dropwise *n*-BuLi (1.66 mL, 5 mmol). After 2 h at −40 °C iodobutane (0.57 mL, 5 mmol) was added and the reaction mixture was stirred for 3 h. After addition of a few drop of water the mixture was concentrated under reduced pressure and chromatographed on silica gel (pure hexane) to give pure **9** (660 mg, 90%); R_f 0.54 (19:1 hexane–EtOAc). ^{1}H NMR ($CDCl_3$): δ 3.92 (t, 1 H, H-2′), 2.73 (m, 4 H, H-4′a,b, H-6′a,b), 1.99 (m, 1 H, H-5′a), 1.74 (m, 1 H, H-5′b), 1.62 (m, 2 H, $CH_2\alpha$), 1.36 (m, 2 H, $CH_2\alpha+1$), 1.24 (m, 2 H, CH_2, $CH_2\omega-1$), 0.78 (t, 3 H,

$CH_3\omega$); ^{13}C NMR ($CDCl_3$): δ 47.5 (C-2′), 35.0 ($CH_2\alpha$), 30.4 (C-4′, C-6′), 28.6 ($CH_2\alpha+1$), 26.0 (C-5′), 22.2 ($CH_2\omega-1$), 13.8 ($CH_3\omega$). Anal. Calcd for $C_8H_{16}S_2$: C, 54.48; H, 9.14; S, 36.37. Found: C, 54.63; H, 8.98; S, 36.21.

2-Octyl-1,3-dithiane (**10**).—The same protocol used to obtain **9** with iodooctane (0.864 mL, 5 mmol) to give pure **10** (880 mg, 91%); R_f 0.6 (19:1 hexane–EtOAc). ^1H NMR ($CDCl_3$): δ 3.92 (t, 1 H, H-2′), 2.73 (m, 4 H, H-4′a,b, H-6′a,b), 1.99 (m, 1 H, H-5′a), 1.74 (m, 1 H, H-5′b), 1.62 (m, 2 H, $CH_2\alpha$), 1.38 (m, 2 H, $CH_2\alpha+1$), 1.15 (m, 10 H, $(CH_2)_4$, $CH_2\omega-1$), 0.76 (t, 3 H, $CH_3\omega$); ^{13}C NMR ($CDCl_3$): δ 47.5 (C-2′), 35.4 ($CH_2\alpha$), 31.7 (CH_2), 30.4 (C-4′, C-6′), 29.2, 29.1 (3 CH_2), 26.5 ($CH_2\alpha+1$), 26.0 (C-5′), 22.5 ($CH_2\omega-1$), 14.0 ($CH_3\omega$). Anal. Calcd for $C_{12}H_{24}S_2$: C, 62.00; H, 10.40; S, 27.59. Found: C, 62.18; H, 10.29; S, 27.82.

2-Dodecanyl-1,3-dithiane (**11**).—The same protocol used to obtain **9** with iododododecane (1.23 mL, 5 mmol) to give pure **11** (1.1 mg, 92%); R_f 0.62 (19:1 hexane–EtOAc). ^1H NMR ($CDCl_3$): δ 3.97 (t, 1 H, H-2′), 2.77 (m, 4 H, H-4′a,b, H-6′a,b), 2.04 (m, 1 H, H-5′a), 1.78 (m, 1 H, H-5′b), 1.66 (m, 2 H, $CH_2\alpha$), 1.42 (m, 2 H, $CH_2\alpha+1$), 1.18 (m, 18 H, $(CH_2)_8$, $CH_2\omega-1$), 0.81 (t, 3 H, $CH_3\omega$); ^{13}C NMR ($CDCl_3$): δ 47.6 (C-2′), 35.4 ($CH_2\alpha$), 31.8 (CH_2), 30.4 (C-4′, C-6′), 29.6, 29.57, 29.3, 29.2 (CH_2), 26.5 ($CH_2\alpha+1$), 26.0 (C-5′), 22.6 ($CH_2\omega-1$), 14.0 ($CH_3\omega$). Anal. Calcd for $C_{16}H_{32}S_2$: C, 66.60; H, 11.17; S, 22.22. Found: C, 66.53; H, 11.26; S, 22.01.

*2-Butyl-2-(methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-mannofuranosid-6-yl)-1,3-dithiane* (**12**).—*n*-BuLi (2.5 M) in hexane (405 μL, 1.01 mmol) was added dropwise to a soln of **9** (179 mg, 1.01 mmol) in anhyd THF (2.5 mL) cooled to −40 °C. After stirring for 1 h at −40 °C, the cyclic sulfate **1** (250 mg, 0.84 mmol) was added and the reaction mixture was stirred for 2 h. Sulfuric acid (42 μL) and water (15 μL) were added to the reaction mixture, which was heated at 50 °C for 2 h and poured into a cold molar soln of $NaHCO_3$ (10 mL). The aq soln was extracted with EtOAc and the combined extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue was chromatographed on silica gel (pure hexane) to afford **12** (170 mg, 51%) and **15** (42 mg, 27%). Compound **12** had: R_f 0.10 (hexane); $[\alpha]_D^{23}$ +63.7° (*c* 0.5, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 4.78 (s, 1 H, $J_{1,2}$ 0 Hz, H-1), 4.73 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.5 Hz, H-3), 4.47 (d, 1 H, H-2), 4.16 (m, 1 H, H-5), 3.66 (dd, 1 H, $J_{4,5}$ 8.5 Hz, H-4), 3.43 (m, 1 H, OH), 3.22 (s, 3 H, OCH_3), 2.99–2.83 (m, 2 H, H-6′a, H-4′a), 2.63 (m, 2 H, H-6′b, H-4′b), 2.33–2.16 (m, 2 H, H-6a,b), 2.00–1.77 (m, 4 H, H-5′a,b, $CH_2\alpha$), 1.47–1.37 (m, 2 H, $CH_2\alpha+1$), 1.37 (s, 3 H, $C(CH_3)_2$), 1.30–1.18 (m, 2 H, $CH_2\omega-1$), 1.24 (s, 3 H, CMe_2), 0.82 (t, 3 H, $CH_3\omega$); ^{13}C NMR ($CDCl_3$): δ 112.4 (CMe_2), 107.0 (C-1), 84.8 (C-2), 81.7 (C-4), 79.7 (C-3), 67.0 (C-5), 54.4 (OCH_3), 52.1 (C-2′), 41.0 (C-6), 39.3 ($CH_2\alpha$), 26.3, 25.8 (C-4′, C-6′), 26.0 (CMe_2), 25.6 ($CH_2\alpha+1$), 25.0 (C-5′), 24.9 (CMe_2), 22.8 ($CH_2\omega-1$), 14.0 ($CH_3\omega$). Anal. Calcd for $C_{18}H_{32}O_5S_2$: C, 55.07; H, 8.22; S, 16.34. Found: C, 55.21; H, 8.13; S, 15.29.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-lyxo-hexofuranos-5-uloside* (**15**).—R_f 0.65 (4:1 hexane–EtOAc); $[\alpha]_D^{25}$ +36° (*c* 0.3, CH_2Cl_2); IR: 1719 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.98 (s, 1 H, $J_{1,2}$ 0 Hz, H-1), 4.94 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 4.1 Hz, H-3), 4.50 (d, 1 H, H-2), 4.37 (d, 1 H, H-4), 3.28 (s, 3 H, OCH_3), 2.19 (s, 3 H, H-6a,b,c), 1.35 (s, 3 H, CMe_2), 1.21 (s, 3 H, CMe_2); ^{13}C NMR ($CDCl_3$): δ 204.2 (C-5), 113.0 (CMe_2), 107.4 (C-1), 84.8 (C-4), 84.2 (C-2), 80.7 (C-3), 54.8 (OCH_3), 27.7 (C-6), 25.7, 24.5 (CMe_2). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.42; H, 7.52.

*2-(Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-mannofuranosid-6-yl)-2-octyl-1,3-dithiane* (**13**).—The same protocol used to obtain **12** starting from **10** (92.5 mg, 0.4 mmol) and **1** (100 mg, 0.34 mmol) gave pure **13** (64.2 mg, 42%); R_f 0.63 (7:3 hexane–EtOAc); $[\alpha]_D^{23}$ +61.3° (*c* 0.54, CH_2Cl_2) and **15** (23 mg, 32%). ^1H NMR ($CDCl_3$): δ 4.78 (s, 1 H, $J_{1,2}$ 0 Hz, H-1), 4.73 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.6, H-3), 4.48 (d, 1 H, H-2), 4.17 (m, 1 H, H-5), 3.66 (dd, 1 H, $J_{4,5}$ 8.5 Hz, H-4), 3.44 (m, 1 H, OH), 3.23 (s, 3 H, OCH_3), 3.00-2.84 (m, 2 H, H-6′a, H-4′a), 2.66 (m, 2 H, H-6′b, H-4′b), 2.35–2.17 (m, 2 H, H-6a,b), 2.01–1.75 (m, 4 H, H-5′a,b, $CH_2\alpha$), 1.53–1.31 (m, 2 H, CH_2), 1.38 (s, 3 H,

CMe_2), 1.25 (s, 3 H, CMe_2), 1.17 (m, 10 H, 5 CH_2), 0.79 (t, 3 H, $CH_3\omega$); ^{13}C NMR ($CDCl_3$): δ 112.5 (CMe_2), 107.0 (C-1), 84.8 (C-2), 81.7 (C-4), 79.7 (C-3), 67.1 (C-5), 54.4 (OCH_3), 52.2 (C-2′), 41.1 (C-6), 39.6 ($CH_2\alpha$), 31.7, 29.7, 29.3, 29.1 (CH_2), 26.3, 25.9 (C-4′, C-6′), 26.0 (CMe_2), 25.0 (C-5′), 24.9 (CMe_2), 23.4, 22.5 (CH_2), 14.0 ($CH_3\omega$). Anal. Calcd for $C_{22}H_{40}O_5S_2$: C, 58.89; H, 8.99; S, 14.29. Found: C, 58.82; H, 8.90; S, 14.42.

*2-Dodecyl-2-(methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-mannofuranosid-6-yl)-1,3-dithiane* (**14**).—The same protocol used to obtain **12** with **11** (234 mg, 0.81 mmol) and **1** (200 mg, 0.67 mmol) gave pure **14** (129.5 mg, 38%); R_f 0.79 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ + 59.3° (*c* 0.76, CH_2Cl_2) and **15** (31 mg, 42%). ^1H NMR ($CDCl_3$): δ 4.80 (s, 1 H, $J_{1,2}$ 0, H-1), 4.75 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.4, H-3), 4.49 (d, 1 H, H-2), 4.18 (m, 1 H, H-5), 3.68 (dd, 1 H, $J_{4,5}$ 8.5, H-4), 3.46 (m, 1 H, OH), 3.24 (s, 3 H, OCH_3), 3.01–2.86 (m, 2 H, H-6′a, H-4′a), 2.68 (m, 2 H, H-6′b, H-4′b), 2.35–2.18 (m, 2 H, H-6a,b), 2.06–1.80 (m, 4 H, H-5′a,b, $CH_2\alpha$), 1.59–1.36 (m, 2 H, CH_2), 1.39 (s, 3 H, $C(CH_3)_2$), 1.26 (s, 3 H, $C(CH_3)_2$), 1.18 (m, 18 H, (9 CH_2)), 0.80 (t, 3 H, $CH_3\omega$); ^{13}C NMR ($CDCl_3$): δ 112.5 ($C(CH_3)_2$), 107.0 (C-1), 84.8 (C-2), 81.7 (C-4), 79.7 (C-3), 67.1 (C-5), 54.4 (OCH_3), 52.2 (C-2′), 41.1 (C-6), 39.6 ($CH_2\alpha$), 31.8, 29.78, 29.5, 29.3, 29.2 (CH_2), 26.3, 25.8 (C-4′, C-6′), 26.0 ($C(CH_3)_2$), 25.0 (C-5′), 24.9 ($C(CH_3)_2$), 23.5, 22.6 (CH_2), 14.0 ($CH_3\omega$). Anal. Calcd for $C_{26}H_{48}O_5S_2$: C, 61.86; H, 9.58; S, 12.70. Found: C, 61.73; H, 9.63; S, 12.39.

*2-(Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-mannofuranosid-6-yl)-2-(methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-α-*D*-mannofuranosid-6-yl)-1,3-dithiane* (**16**).—To a stirred soln of **3** (320 mg, 0.91 mmol) in THF (2.5 mL)–HMPA (0.25 mL) cooled to −40 °C was added dropwise a soln of *n*-BuLi in hexane (0.365 mL, 0.91 mmol). After 5 h at −40 °C, the cyclic sulfate **1** (297 mg, 1 mmol) was added and the mixture was stirred overnight. Sulfuric acid (50 μL) and water (20 μL) were added to the reaction mixture, which was heated at 50 °C for 2 h and poured into a cold molar soln of $NaHCO_3$ (10 mL).

The aq soln was extracted with EtOAc and the combined extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue was chromatographed on silica gel (17:3 hexane–EtOAc) to give pure **16** (181 mg, 35%); R_f 0.53 (7:3 hexane–EtOAc); $[\alpha]_D^{28}$ + 9.6° (*c* 0.31, CH_2Cl_2). ^1H NMR[3] ($CDCl_3$): δ 4.80 (s, 1 H, $J_{1,2}$ 0 Hz, H-1a or b), 4.75 (m, 2 H, H-3a, $J_{2,3}$ 5.8, $J_{3,4}$ 3.5 Hz, H-1a or b), 4.64 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.2 Hz, H-3b), 4.48 (d, 1 H, H-2a), 4.47 (d, 1 H, H-2b), 4.27 (m, 1 H, H-5a), 4.04 (m, 1 H, H-5b), 3.66 (dd, 1 H, $J_{4,5}$ 7.4 Hz, H-4b), 3.60 (dd, 1 H, $J_{4,5}$ 7.4 Hz, H-4a), 3.47 (s, 3H, OCH_3 at C-5), 3.24, 3.22 (s, 6 H, OCH_3 at C-1a,b), 2.75 (m, 4 H, H-6′a,b, H-4′a,b), 2.60 (m, 2 H, H-6a, H-6b), 2.29 (dd, 1 H, $J_{5,6b'}$ 2.9, $J_{6b,6b'}$ 15.7 Hz, H-6b′), 2.04 (dd, 1 H, $J_{5,6a'}$ 9.4, $J_{6a,6a'}$ 15.4 Hz, H-6a′), 2.00–1.76 (m, 2 H, H-5′a,b), 1.41, 1.38, 1.26, 1.24 (s, 12 H, CMe_2); ^{13}C NMR[3] ($CDCl_3$): δ 112.4 (2 CMe_2), 107.1, 106.5 (C-1a,b), 85.2 (C-2a), 84.9 (C-2b), 82.3 (C-4a), 82.9 (C-4b), 79.7 (C-3a), 79.6 (C-3b), 76.4 (C-5b), 65.5 (C-5a), 58.5 (OCH_3 at C-5), 54.4 (OCH_3 at C-1a,b), 51.3 (C-2′), 43.5 (C-6a), 39.7 (C-6b), 26.2, 26.1 (CMe_2), 26.0, 25.8 (C-4′, C-6′), 25.1 (C-5′), 24.9, 24.6 (CMe_2). Anal. Calcd for $C_{25}H_{42}O_{10}S_2$: C, 52.98; H, 7.47; S, 11.32. Found: C, 52.91; H, 7.44; S, 11.43. When the reaction started from **3** (250 mg, 0.71 mmol) and methyl 5,6-anhydro-2,3-*O*-isopropylidene-α-D-mannofuranoside (**17**) [11] (231 mg, 1.07 mmol) at −15 °C for 22 h, compound **16** was obtained in 65% yield.

[3] For NMR notations, unit 'a' refers to the *O*-5-unsubstituted mannose moiety and unit 'b' to the 5-*O*-methyl mannose residue.

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